Pulsed Magnetic Field Therapy Increases Tensile Strength in a Rat Achilles' Tendon Repair Model

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Purpose: To examine the effect of pulsing electromagnetic fields on the biomechanic strength of rat Achilles' tendons at 3 weeks after transection and repair.

Methods: This noninvasive modality was tested in a prospective, randomized, double-blinded, placebo-controlled study to evaluate the effect of a specific noninvasive radiofrequency pulsed electromagnetic field signal on tendon tensile strength at 21 days post transection in a rat model.

Results: In the animals receiving PMF exposure, an increase in tensile strength of up to 69% was noted at the repair site of the rat Achilles' tendon at 3 weeks after transection and repair compared with nonstimulated control animals.

Conclusions: The application of electromagnetic fields, configured to enhance Ca^{2+} binding in the growth factor cascades involved in tissue healing, achieved a marked increase of tensile strength at the repair site in this animal model. If similar effects occur in humans, rehabilitation could begin earlier and the risk of developing adhesions or rupturing the tendon in the early postoperative period could be reduced. (J Hand Surg 2006;31A: 1131–1135. Copyright © 2006 by the American Society for Surgery of the Hand.)

Key words: Pulsed electromagnetic fields, tendon repair, rat model.

Tendon injuries account for a large proportion of all occupational and sports-related injuries in the United States each year.[1] Following tendon repair a rapid increase in tensile strength would be advantageous. A more rapid healing phase allows for earlier mobilization, which could decrease the incidence of adhesions at the repair site. Although pulsed electromagnetic fields (PMFs) have shown clinical value in the adjunctive treatment of fractures, spinal fusions, and chronic wounds,[2–5] surprisingly few, sometimes conflicting, studies of the effect of PMFs on tendon or ligament repair have been reported.[6–9] In a manner similar to bone and wound repair, tendon repair involves an inflammatory phase, angiogenesis, cell proliferation, collagen production, and remodeling stages, whether the tendon is located in an epitenon or in a synovial sheath.[1]

Recently we tested a specifically configured PMF signal in a rat wound model and observed a more rapid increase in skin tensile strength.[10] We performed a prospective, randomized, double-blinded, placebo-controlled study of this signal configuration on the primary repair of rat Achilles' tendons, as measured by tensile strength at 21 days post transection.

Materials and Methods

All procedures and protocols were approved by the institutional Animal Care and Use committee. Forty young-adult male Sprague-Dawley rats (mean weight, 350 g) were anesthetized with an intraperitoneal injection of a ketamine/medetomidine 75 mg/kg/0.5 mg/kg mixture. All surgical procedures were performed under sterile conditions with the aid of an operating microscope (Zeiss Opni I, Carl Zeiss, Oberkochen, Germany).

Surgical Procedure

Laceration and repair of the Achilles' tendons were accomplished using the model established by Murrell

et al.[11] The right hind leg was shaved and prepared with Betadine and alcohol. Under sterile conditions, a 2-cm midline longitudinal incision was made. The tendon was separated from the surrounding tissue, and then transected using a scalpel. The tendon then was immediately repaired with a single 6-0 nylon suture using a modified Kessler stitch. The plantaris tendon was divided but was not repaired. The skin was sutured with interrupted 5-0 sutures (Ethilon, Ethicon, Inc., Somerville, NJ). The limb was not immobilized. After surgery the animals received ketoprofen for pain control. They were returned to their cages and fed standard rat chow and water *ad libitum*.

Pulsed Electromagnetic Field Treatment

On the first postoperative day all animals were randomly assigned to 4 treatment groups (groups 1–4, 10 animals/group). Randomization followed the parallel group protocol wherein each animal was randomly assigned to one of the treatment groups until there were 10 in each group.[12] Animals remained in their assigned group until they were killed. Three active groups received specific PMF treatments for two 30-minute sessions per day over a period of 3 weeks and a single control group was treated identically except that no PMF was applied. Before the surgeries the PMF units were calibrated to the desired signals by the manufacturer (Ivivi Technologies, Inc., Northvale, NJ) with all investigators blinded to signal assignment. The PMF signal used in this study was a pulsed radio frequency (PRF) waveform consisting of a repetitive burst of 27.12-MHz sinusoidal waves emitted by a PMF-generating coil. This modality has been approved by the Food and Drug Administration for the reduction of postoperative pain and edema and is reimbursed by the federal Centers for Medicare and Medicaid Services (CMS) for wound repair.

Two configurations were used. The first PRF waveform, assigned to group 1, consisted of a burst duration of 65 microseconds (μsec), repeating at 600 bursts/s with an amplitude at the tendon target of 1 G. The second PRF waveform consisted of a burst duration of 2,000 μsec, repeating at 5 bursts/s, with an amplitude at the tendon target of 0.05 G (group 2), and the third PRF waveform was configured identically to the second, except with amplitude at the tendon target of 0.1 G (group 3). Control animals (no signal) were assigned to group 4.

The PRF signal was delivered with a single-loop coil (14 $\times$ 21 inches) that was mounted on a plastic support which allowed a standard rat plastic cage with all metal portions removed to positioned entirely within its boundaries. Specifically, the coil loop was located 1 inch outside each wall of the cage and 3.5 inches above and horizontal to the floor of the cage. Five freely roaming animals were treated with each coil. The PMF signal amplitude was checked by a third party (AAP) throughout the study with a calibrated field probe (NIST traceable calibrated field probe model FCC-301-1-MR1; Fischer Custom Communications, Torrance, CA) connected to a calibrated 100-MHz oscilloscope (model 2358; Tektronix, Beaverton, OR). Signal amplitude within the rat treatment cage over the normal range of rat movement was uniform to $\pm$10%. Signal consistency was verified weekly by a third party (AAP) who was not involved with the surgical, treatment, or testing phases of this study. There were 2 cages each for the control and active groups, and each cage had its individual coded PMF exposure system. The PMF treatment was performed twice daily for 30-minute sessions until the animals were killed. Control animals were treated in identical cages equipped with identical coils but inactivated. All PMF exposure systems were set to active or control by a third party (AAP) at the start of the experiment, thereby enabling the investigators who were handling the animals throughout all phases of this study to remain blinded.

Biomechanic Test

At the end of the 3-week treatment period animals were killed by a pentobarbital solution. The Achilles' tendon was harvested by proximally severing the muscle bellies arising from the tendon and distally disarticulating the ankle, keeping the calcaneous and foot attached. All extraneous soft and hard tissues were removed from the calcaneous–Achilles' tendon complex. Tensile strength testing was performed immediately after harvest on a tensiometer (Com-ten 922MTC; Com-Ten Industries, Pinelles Park, FL) equipped with a 9-kg load cell. The tendon, in continuity with the calcaneal bone, was fixed between 2 metal clamps so as to maintain a physiologically appropriate foot extension compared with the vertically oriented Achilles' tendon. The tendons then were pulled apart at a constant speed of 0.45 mm/s until failure and the peak tensile strength was recorded. The investigator performing the mechanical test had no knowledge of whether the tendon being tested was from the active or control group.

Table 1. Comparison of PMF Effects on Achilles' Tendon Repair in the Rat

PMF Treatment	Tensile Strength (kg/cm^2 ± SD)	Percentage Increase Over Control	Analysis of Variance
Sham	80.6 ± 16.6	—	—
65 μsec, 1 G	99.4 ± 14.6	24	p = .055
2,000 μsec, 0.05 G	129.4 ± 27.8	60	p < .001*
2,000 μsec, 0.1 G	136.4 ± 31.6	69	p < .001*

*Denotes statistical significance.

Statistical Analysis

The mean tensile strength was compared for each group at 3 weeks after tendon transection. Data were analyzed using statistical software (SigmaStat 3.0; SPSS, Chicago, IL). All data passed the Kolmogorov-Smirnov normality test, which allowed a parametric statistical analysis to be used. One-way analysis of variance was used for all comparisons. Significance was accepted at a p value of .05 or less. Unblinding occurred after data analysis.

Results

Tensile strength was calculated as the maximum breaking strength (in kg) per cross-sectional area (in cm^2). All analyzable tendons failed at the original transection site. One tendon from group 2 pulled apart at the clamp site, indicating faulty mounting, and the result from 1 tendon in group 4 was not usable because of a load-cell malfunction during testing. The tensile strengths from a total of 38 tendons were available for analysis. The results are shown in Table 1. Tendons treated with the 65-microsecond (μsec) signal (group 1) had a mean breaking strength of 99.4 ± 14.6 kg/cm^2 compared with 80.6 ± 16.6 kg/cm^2 for the control group (group 4). This represented a 24% increase in breaking strength versus the control group at 21 days, which was not statistically significant (p = .055). Tendons from groups 2 and 3, treated with the 2,000-microsecond (μsec) signals, had markedly higher mean breaking strengths of 129.4 ± 27.8 kg/cm^2 and 136.4 ± 31.6 kg/cm^2 for the 0.05-G and 0.1-G signals, respectively, versus the control group (80.6 ± 16.6 kg/cm^2). The mean strengths for both groups 2 and 3 were 60% and 69% higher, respectively, at the end of 3 weeks of treatment compared with the control group. This increase in strength was statistically significant (p < .001); however, the difference in the mean tensile strength between groups 2 and 3 was not statistically significant (p = .541). The differences in mean tensile strength between group 1 (65-microsecond (μsec) burst) and groups 2 and 3 (2,000-μsec burst) were statistically significant (p < .05).

Discussion

The results presented here show that noninvasive PMFs can produce up to a 69% increase in rat Achilles' tendon breaking strength versus control tendons at 21 days after transection. Although all signals used in this study accelerated tendon repair, the greatest acceleration was obtained with waveforms configured to target a signaling mechanism involving Ca^{2+} binding.

In a manner similar to bone and wound repair, tendon repair for both epitenon and synovial-sheathed tendons begins with an inflammatory stage that involves infiltration of inflammatory cells such as macrophages, neutrophils, and T lymphocytes.[1] This stage is followed by angiogenesis, fibroblast proliferation, and collagen (mainly type III) production. Finally, cells and collagen fibrils orient to achieve maximum mechanical strength. These phases all occur in bone and wound repair, in which PMF has shown effectiveness, particularly in the inflammatory, angiogenesis, and cell proliferation stages.[4,13]

The most commonly accepted PMF transduction pathway involves ion binding in regulatory pathways involving growth factor release.[13–17] There is abundant evidence suggesting that production of many of the growth factors and cytokines involved in tissue growth and repair is dependent on Ca/calmodulin (CaM).[13,15] Pulsed electromagnetic fields have been shown to accelerate Ca^{2+} binding to calmodulin.[16–18] The 0.05- and 0.1-G signals used in this study were configured *a priori*, targeting a Ca/CaM transduction pathway.[19,20] The objective was to produce sufficient electric field amplitude (dose) within the frequency response of Ca^{2+} binding. This would allow a lower-power, more-effective signal. The model predicted that millisecond range burst durations would satisfy these objectives at amplitudes in the 0.05-G range. The 0.1-G signal was added to ensure that the small size of the rat tendon target did not limit the induced current pathway or reduce the expected dose. The model also predicted that the 65-μsec burst clinical signal would produce

lower amplitude in the Ca/CaM pathway, rendering it less effective, but not ineffective, in this tendon model, in accord with the experimental results. Although this provides some support for the Ca/CaM-based model, it by no means suggests that this is the only transduction pathway. For example, Ca^{2+}-dependent nitric oxide synthase, which modulates the signaling molecule nitric oxide, also has been reported to affect tendon repair as well.[21]

Regardless of the exact mechanism by which the PMF signals used in this study accelerated tendon repair, it is important to place these results in the context of those from other PMF waveforms and from growth factors. Other reports[6–9] have not shown the same degree of PMF-accelerated healing with other waveforms. In addition, the use of selective growth factors, such as insulin-like growth factor-1 to modulate inflammation or vascular endothelial growth factor to augment angiogenesis, does not seem to affect the mechanical outcome of tendon repair if no fixation or immobilization is used.[16] The results obtained in our study were achieved with no fixation or immobilization of the Achilles' tendon.

It is not clear whether the comparative increase in strength is a function of qualitative or of temporal improvements in the tendon's healing. Our previous experiments with this radiofrequency PMF signal on angiogenesis[22,23] showed that the improved vessel formation of the treatment group was a temporal phenomenon. The control groups in these studies eventually developed comparable neovascularization, given more time. This is characteristic of all reported PMF effects on normal tissue repair. Thus PMF accelerates bone repair by accelerating the return to intact breaking strength and therefore to normal function.[24] The sham-treated fractures eventually reach the same biomechanic end point, but with increased morbidity. We have observed similar biomechanic acceleration in a linear full-thickness cutaneous wound in the rat.[10] Pulsed electromagnetic fields identical to those used in this study accelerated wound repair by approximately 60% at 21 days compared to the sham-treated group, with intact breaking strength achieved about 50% sooner than the untreated wounds (approximately 30 vs. 45 days post surgery). This result implies that the improvements in healing achieved with PMF result from an increase in the speed and efficiency of the cellular response to primary injury.

If prior experience in the development of PMF therapies for human bone and soft tissue is any indication,[3,4] the improvement in tendon healing in the present experiment could have clinical application in the management of patients after tendon repair at any site. This is possible because PMFs in theory can modulate repair directly at the cellular level in all phases of repair, independent of anatomic differences in the repairing tendon.

After tendon injury and repair marked morbidity results from immobilization of the involved extremity; however, immobilization is necessary to ensure the development of adequate tendon strength before the initiation of active rehabilitation. If the application of PMF allows for the achievement of adequate tendon strength in a shorter time frame, the risk of developing adhesions or rupturing the repaired tendon in the early postoperative period, when this risk is highest, becomes less. The accelerated recovery may decrease the immobilization time required and allow rehabilitation to begin earlier.

This study investigated the effect of a particular PMF signal on the biomechanic strength of repaired paratenon-covered Achilles' tendons and not on synovial fluid-bathed tendons within the digital sheath. Although the 2 tendons have different healing characteristics, the basic cellular processes that PMFs can modulate are identical. Nonetheless the applicability of the information in this study to flexor tendons within the digital sheath will require further study.

The use of electromagnetic fields in tissue healing is still a relatively recent application and much research remains to be performed. Areas that need greater explanation include the interplay between wound healing, contributing growth factors, and angiogenesis. Pulsed electromagnetic fields hold promise as a safe, easily administered, noninvasive modality to accelerate and improve the body's healing mechanisms.

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