Session 09: EMF Therapeutics

9-1 A PROPOSED ELECTROCHEMICAL MECHANISM FOR EMF MODULATION OF TISSUE REPAIR

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Summary of Abstract. This study proposes PEMF accelerates tissue repair by directly affecting the kinetics of Ca^{2+} binding to calmodulin (CaM), via which further molecular signaling is modulated. This work shows how effective EMF signals may be configured a priori to be first messengers by evaluation of signal to thermal noise ratio (SNR) in a two step pathway involving Ca^{2+} binding to CaM, followed by Ca^{2+}/CaM binding to epithelial or neuronal nitric oxide synthase (eNOS and nNOS, respectively),which modulates nitric oxide (NO) release. A scheme for PEMF acceleration of tissue healing is proposed.

Objectives. The activation of calmodulin (CaM) by Ca^{2+} has been found to be the initial stimulus for many biochemical cascades involved in tissue repair, starting with the inflammatory phase. The initial steps of the Ca/CaM-dependent cascades often start with activation of eNOS which causes an immediate release of NO . This causes an immediate vasodilation which is subsequently followed by increased , e.g., cGMP formation which can enhance growth factor release. It is shown here how PEMF signals may be configured to modulate Ca/CaM binding leading to increased tissue repair.

Methods. The EMF target is considered to be Ca^{2+} binding to CaM followed by CaM binding to eNOS or nNOS, both of which control the CaM-dependent release of the signaling molecule nitric oxide (NO). Analysis of the kinetic equations describing this two step process yields a two time constant electrical equivalent circuit analog, as shown in figure 1. Here $R_A C_A$ and $R_B C_B$ are the time constants for Ca^{2+} binding to CaM, and CaM binding to, e.g., NOS, respectively; and C_d and R_M are the membrane capacitance and leak resistance, respectively. Knowledge of the actual time constants, allows any EMF signal to be assessed in the frequency domain with respect to its ability to produce a detectable (i.e. SNR≈1) voltage in the target. This has been reported for pulsed radio frequency (PRF) signals which confirmed the correct pulse modulation of a 27.12 MHz sinusoidal RF signal to modulate the Ca/CaM pathway significantly accelerated tendon repair in a rat model. A PEMF bone repair signal was predicted ineffective in the same study.

Results. A PRF signal configured a priori for the Ca/CaM pathway was tested clinically in a randomized double-blind study for its effect on pain reduction immediately post breast augmentation. Active patients received the PRF signal every 4 hours, days 1-3, every 8 hours, days 4-6, and every 12 hours thereafter. Pain was assessed twice daily using a validated VAS. The results are shown in figure 2. Bars represent the mean VAS pain score at Day 1 for all breasts and at Day 7 for both the active and sham groups. Mean (± SD) VAS score was 54 ± 9 mm for all groups on Day 1. Mean VAS decreased to 17 ± 4.4 mm in the treated group (218%, $P<0.001$ vs Day 1) and to 31 ± 5.6 mm in the sham group (74%, $P<0.001$ vs Day 1). The difference in mean pain between the active and sham cohorts was

also statistically significant ($P<0.001$), suggesting post surgical use of PRF therapy could produce a clinically meaningful reduction in pain by nearly a factor of 3. Active patients also exhibited a concomitant decrease in pain medication by a factor of 2.5.

Conclusions. It is proposed EMF signals configured via SNR analysis to match the bandpass of a second messenger target can act as a first messenger to modulate biochemical cascades related to tissue growth and repair. The likely second messenger is Ca^{2+} binding to CaM which activates eNOS or nNOS. The result is PEMF acts to reduce the inflammatory phase of tissue repair and then acts to accelerate the remaining phases of repair by directly modulating the appropriate growth factor release at the appropriate time and with the correct kinetics. A scheme for PEMF acceleration of tissue healing based upon the model presented here is proposed in figure 3.

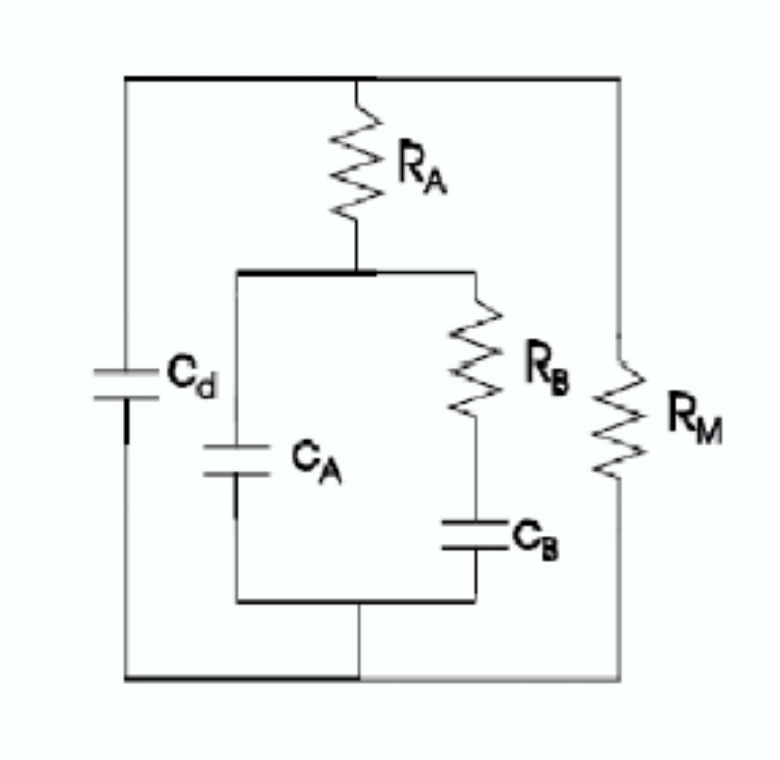

FIGURE 1.

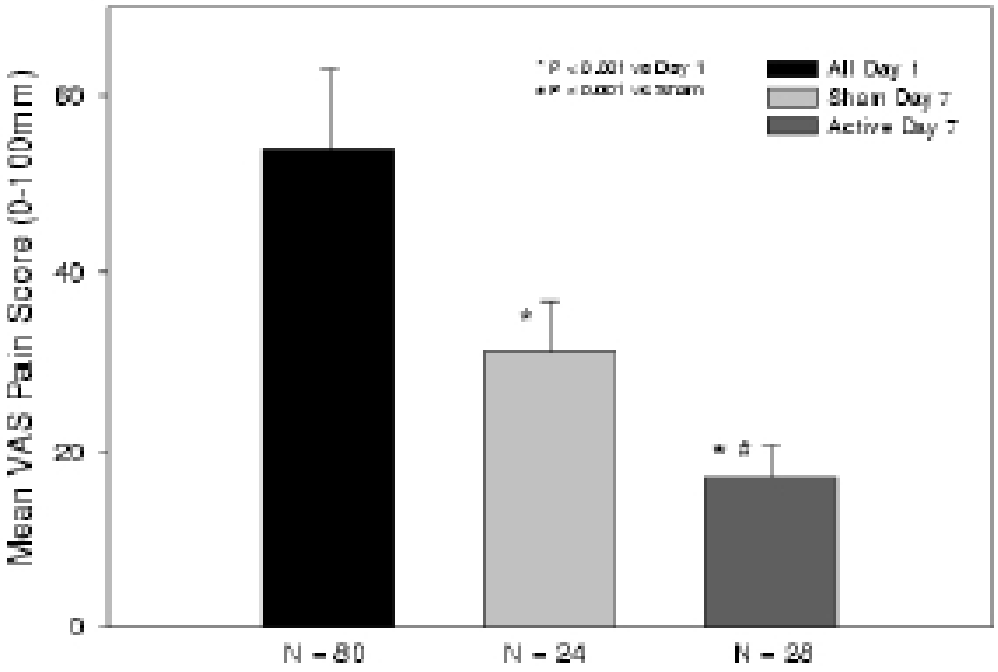

FIGURE 2.

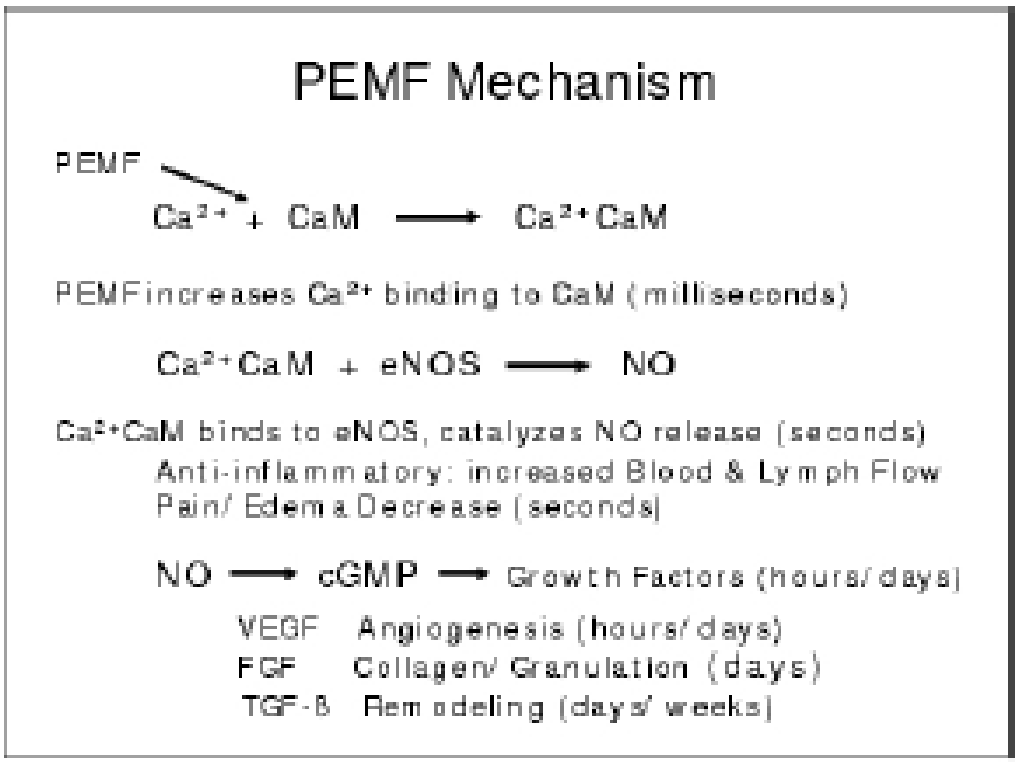

FIGURE 3.