Bone Growth Adjuncts: Electrical Stimulation and Ultrasound

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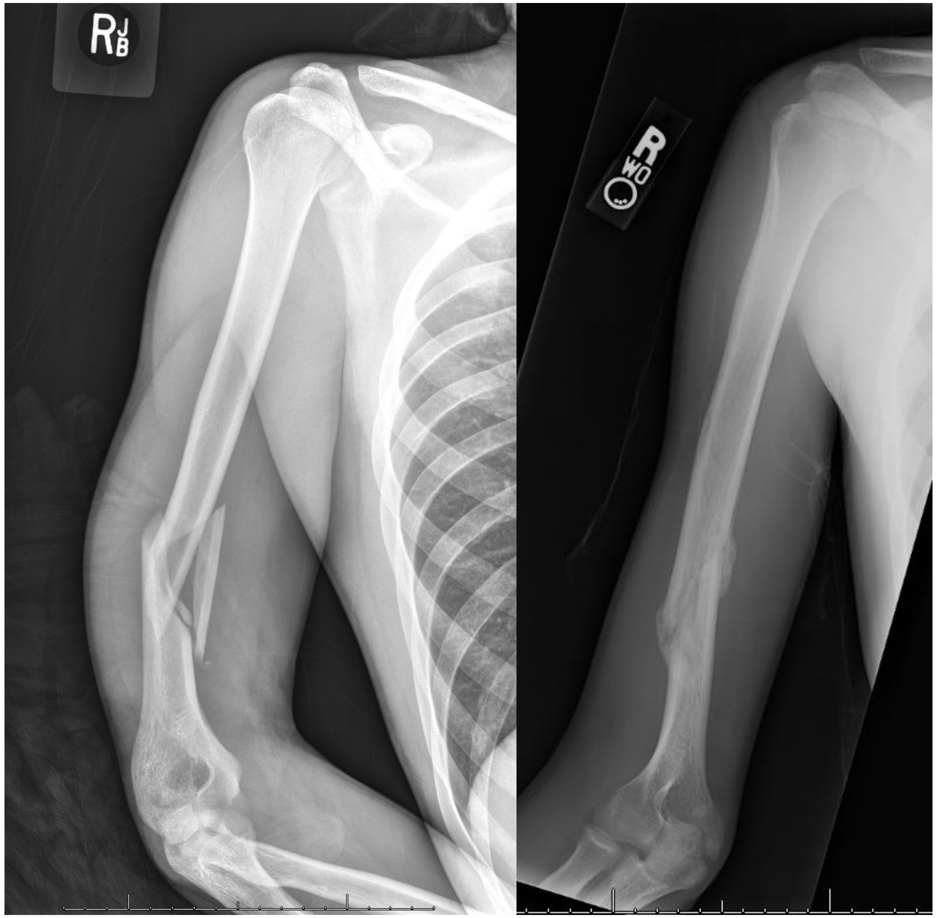
Objectives

- Review the mechanisms through which biophysical bone stimulation may act.
- Review clinic studies of electrical stimulation to ultrasound.
- Attempt to highlight recent research (of which there is very little) and identify gaps in current knowledge.

Normal Fracture Healing

- Depends on a complex set of well-defined spatial and temporal events:
  - Cells
  - Cytokines/Growth Factors
  - Mechanical environment
  - Vascularity



Impaired Fracture Healing

- Smoking
- Drugs
  - NSAIDs
  - Antiangiogenesis drugs (Cancer Chemo)
- Infection (FRI)
- Diabetes
- Glucocorticoid therapy

The Clinical Problem

- How to obtain more rapid healing of acute fractures for more rapid return to function?

- Treatment of nonunions

Electrical Stimulation

Electrical Stimulation

History

FIG. 1. Iwao Yasuda, 1909–present. (Courtesy of E. Fukada, D.Sc.).

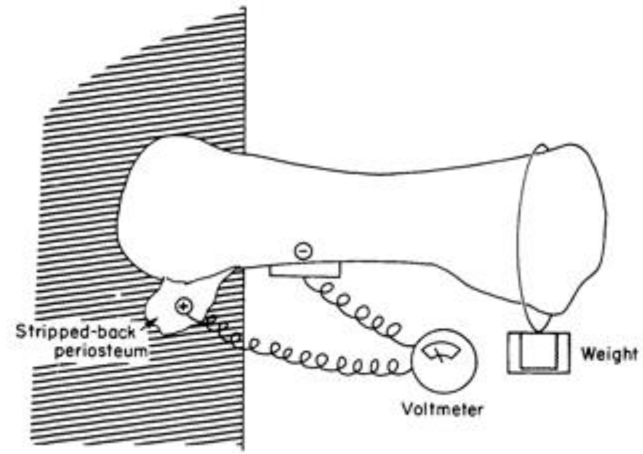
JOURNAL OF THE PHYSICAL SOCIETY OF JAPAN Vol. 12, No. 10, OCTOBER, 1957

On the Piezoelectric Effect of Bone

By Eiichi FUKADA
Kobayasi Institute of Physical Research, Kokubunji, Tokyo
and Iwao YASUDA
Department of Orthopaedic Surgery, Kyoto Prefectural Medical University, Kamikyo-ku, Kyoto

(Received August 15, 1956, Revised July 9, 1957)

FIG. 3. Drawing depicting bone fixed on one end with weight applied to the other end. Region under compression is electronegative.



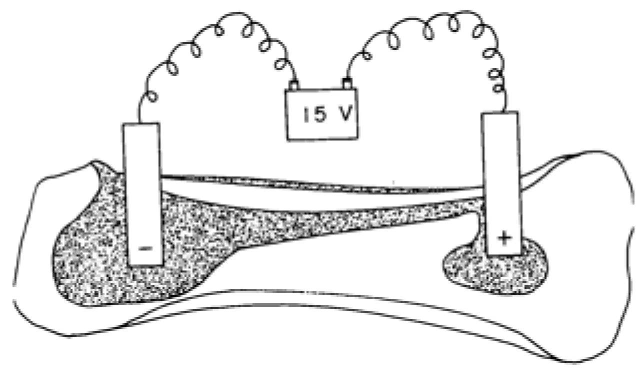
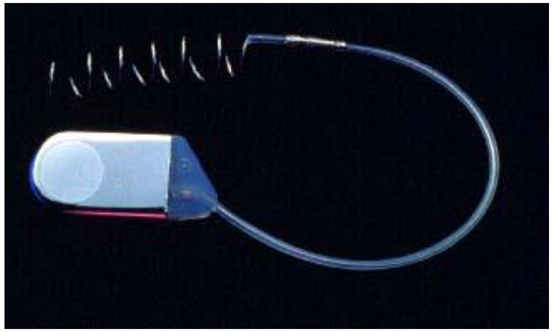


FIG. 4. Drawing depicting electrodes inserted into rabbit femur. The darkened areas surrounding the electrodes represent new bone formation.

Yasuda I. Fundamental aspects of fracture treatment. J Kyoto Med Soc. 4: 395 – 406, 1953.

3 Types of Electrical Stimulation

- Direct current (implanted)
  - Constant
  - Pulsed

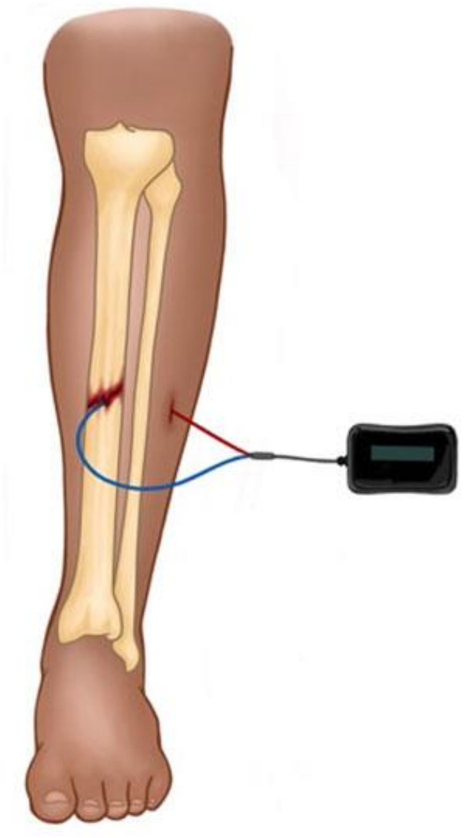


- Inductive coupling
  - Time varying magnetic fields to induce electrical currents

- Capacitive coupling
  - Time varying electrical fields to induce electrical currents

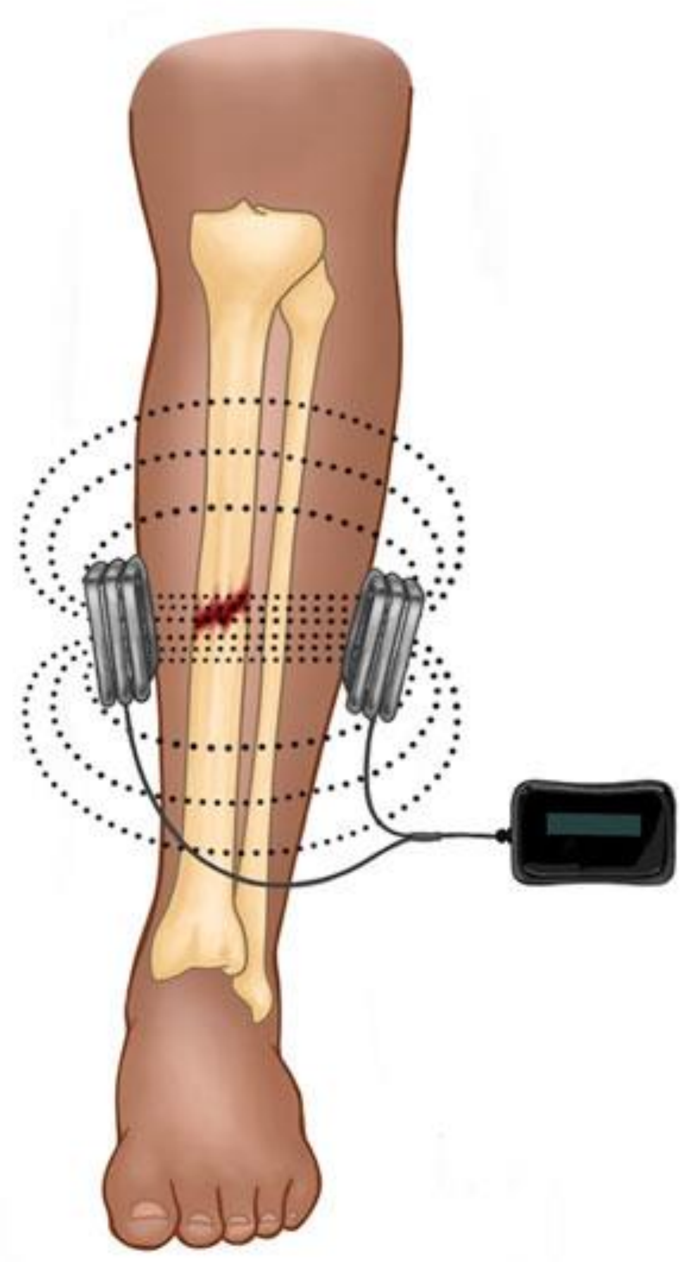
Direct Current Electrical Stimulation

- Cathode placed directly at nonunion site.
- Anode implanted in nearby soft tissue.



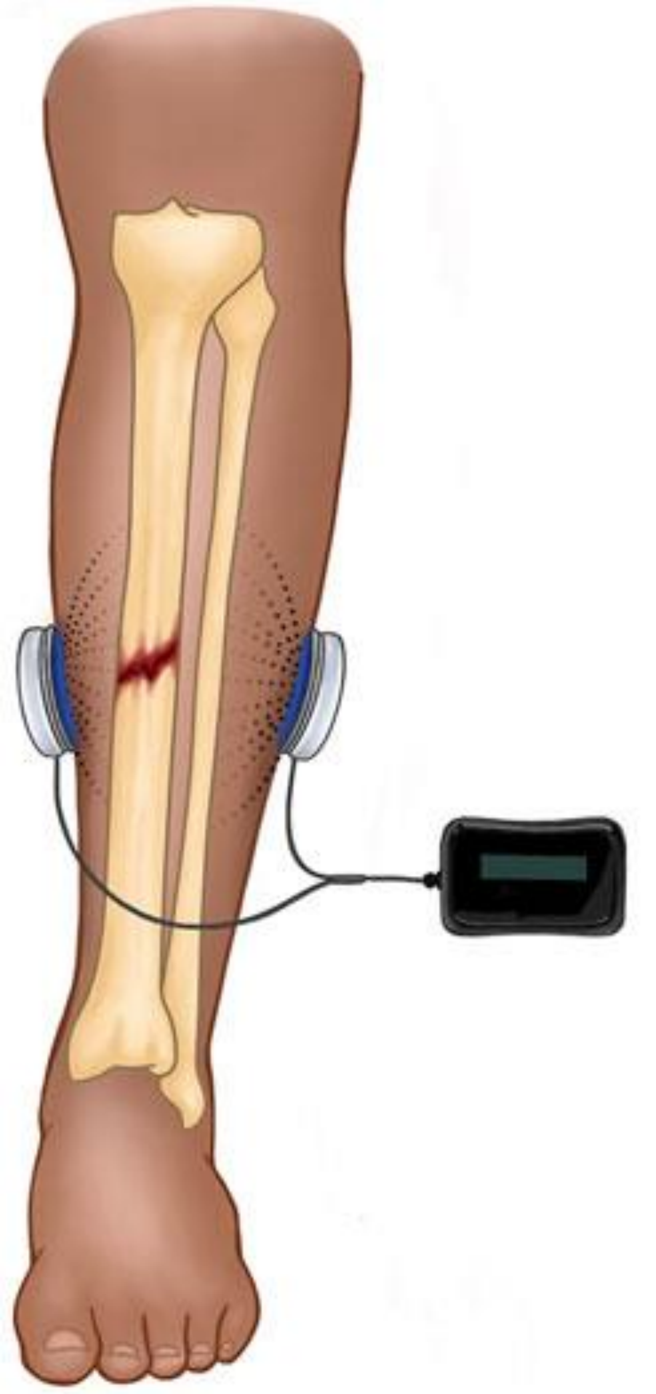
Inductive Coupling

- Solenoids are placed on opposite sides of the bone, parallel to the skin surface.
- Current is pulsed through the solenoids and generates a magnetic field between them.
- The magnetic field induces a perpendicular electric field in tissue.



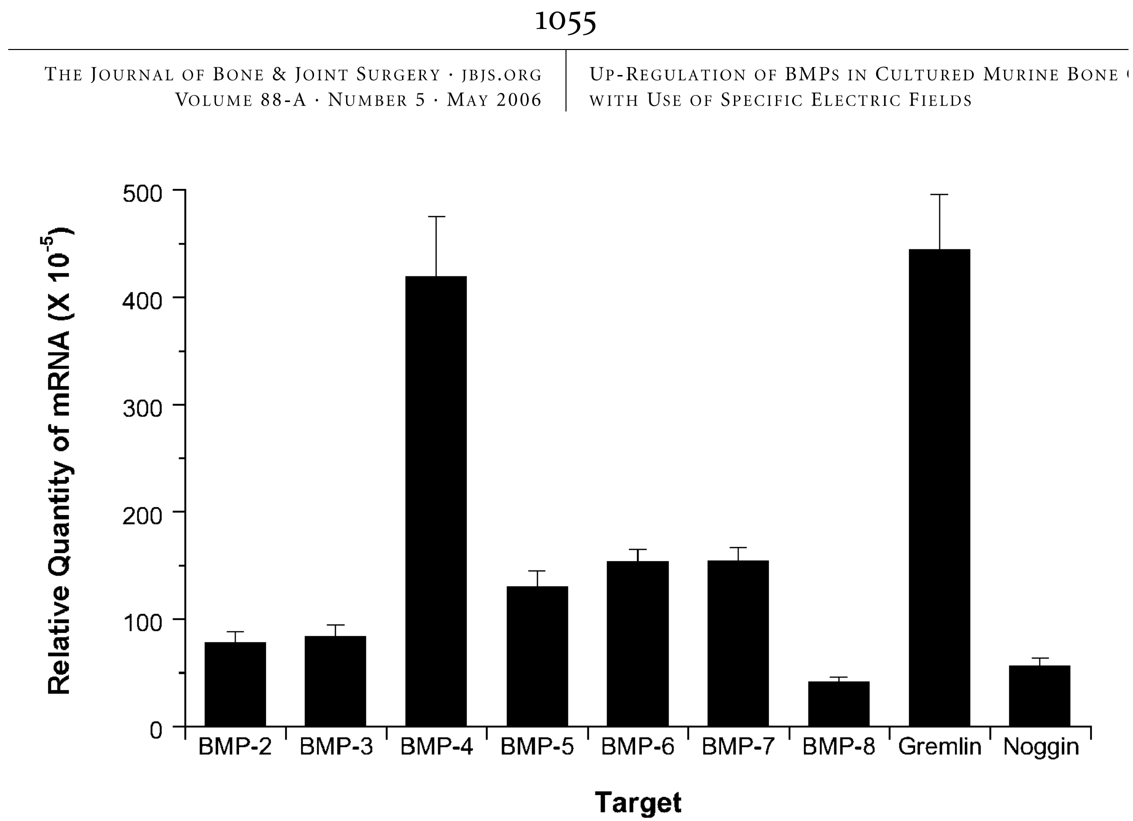
Capacitive Coupling

- Two electrodes are placed on the opposite sides of the bone, generating an electric field between them
- Stainless steel capacitor plates applied to the skin surface



Mechanism of Action

- Protein synthesis is increase
- Cellular markers associated with osteogenesis increased.



Wang et al, JBJS 2006

- As of 2018, there are 9 FDA-approved, commercially available electrical bone growth stimulators.
    - Spinal fusion
    - Fracture nonunion
- Also studied in fresh fractures, osteotomies, and treatment of osteoporosis

Direct Current Electrical Stimulation

- 178 nonunions in 175 patients, variety of bones
- Treated from 1970 to 1981
- Constant direct current
  - 4 implanted cathodes
  - Continuous treatment for 12 weeks

Brighton C et al. J Bone Joint Surg. 63A: 2 - 13, 1981.

Direct Current Electrical Stimulation

Brighton C et al. J Bone Joint Surg. 63A: 2 - 13, 1981.

Direct Current Electrical Stimulation

- 10/175 patients also had surgical fixation at time of cathode insertion
  - 8 plate fixation
  - 2 intramedullary nailing
- Some patients treated with multiple courses
  - 18 treated 2 times, 14 of which healed
  - 6 treated 3 times, 4 of which healed
  - 4 treated 4 times, 2 of which healed
  - 1 treated 5 times, persistent nonunion

Brighton C et al. J Bone Joint Surg. 63A: 2 - 13, 1981.

Direct Current Electrical Stimulation

- Overall success rate 83.7 %
- Prior osteomyelitis history 74.4 %

Brighton C et al. J Bone Joint Surg. 63A: 2 - 13, 1981.

Direct Current Electrical Stimulation

Tibia	75/90	83.3 %
Femur	24/31	77.4 %
Ulna	12/16	75 %
Clavicle	10/15	66.7 %
Humerus	8/13	61.5 %
Medial maleolus	11/11	100 %
Radius	4/7	57.1 %
Scaphoid	4/5	80 %
Fibula	1/1	100 %

Brighton C et al. J Bone Joint Surg. 63A: 2 - 13, 1981.

Inductive Coupling Electrical Stimulation

- 125 patients with 127 ununited fractures of tibial diaphysis
  - 28 delayed unions (4 – 9 months from fracture)
  - 99 nonunions (> 9 months from fracture)
- All treated with pulsed electromagnetic field

Bassett CAL, et al. J Bone Joint Surg. 63A: 511 - 523, 1981.

Inductive Coupling Electrical Stimulation

- All 125 tibias treated nonoperatively
  - 2 treated with fibulectomy to correct angular deformity
- All patients initially kept non-weight bearing in a flexed knee long leg cast
- Duration of treatment 2 – 22 months
  - Average 5.2 months
- Overall success rate 87 %
  - 82 % success rate in 49 patients with history of prior infection
  -

Bassett CAL, et al. J Bone Joint Surg. 63A: 511 - 523, 1981.

Inductive Coupling Electrical Stimulation

A DOUBLE-BLIND TRIAL OF PULSED ELECTROMAGNETIC FIELDS FOR DELAYED UNION OF TIBIAL FRACTURES

W. J. W. SHARRARD

From the Royal Hallamshire Hospital, Sheffield

- Randomized double-blind trial
- PEMF for 12 weeks vs. placebo
- 45 tibial delayed unions
    - 16 – 32 weeks after fracture
- Continued cast treatment

Inductive Coupling Electrical Stimulation

Radiologist's interpretation

	Electrical Stim*	Control
• Number of patients	20	25
• Union	5	1
• Progressive healing	5	1
• No progress	10	23

* p=0.002 in favor of e-stim

Sharrard et al. J Bone Joint Surg. 72B: 347, 1990.

Inductive Coupling Electrical Stimulation

Orthopaedists interpretation

	Electrical Stim*	Control
• Number of patients	20	25
• Union	9	3
• Nonunion	11	22

* p=0.02 in favor of e-stim

Sharrard et al. J Bone Joint Surg. 72B: 347, 1990.

Capacitive Coupling Electrical Stimulation

- 22 nonunions in 20 patients
  - Multiple sites
  - 17 recalcitrant (failed bone grafting or other type of electrical stimulation)
  - 20 were ≥ 12 months after initial injury

Brighton CA and Pollack SR. J Bone Joint Surg. 67A: 577 - 585, 1985.

Capacitive Coupling Electrical Stimulation

- 17 (77.3 %) achieved solid union after an average of 22.5 weeks of capacitive coupling treatment

Brighton CA and Pollack SR. J Bone Joint Surg. 67A: 577 - 585, 1985.

Capacitive Coupling Electrical Stimulation

- Prospective, randomized, double-blind trial
- 21 patients with nonunions
  - 15 tibia
  - 4 femur
  - 2 ulna

Scott and King. J Bone Joint Surg. 76A: 820, 1994.

Capacitive Coupling Electrical Stimulation

- Active units: 60 % unions
- Inactive units: 0 % union
- Statistically significant ($p = 0.004$)

Scott and King. J Bone Joint Surg. 76A: 820, 1994.

Gaps in Knowledge: Electrical Stimulation

- Some studies in animals have shown that pulsed electromagnetic fields accelerates fracture healing, other studies have failed to demonstrate any effect
- No clinical studies have shown that electrical stimulation accelerates the healing of fresh fractures.
- In reported clinical studies, device specifications are heterogenous and incomplete, rendering studies unrepeatable. The stimulation protocols also varied greatly.

Einhorn TA. AAOS Instructional Course Lectures. 45: 401 - 416, 1996.
Nicksic et al, Front. Bioeng. Biotechnol. 10:879187, 2022

Summary: Electrical Stimulation

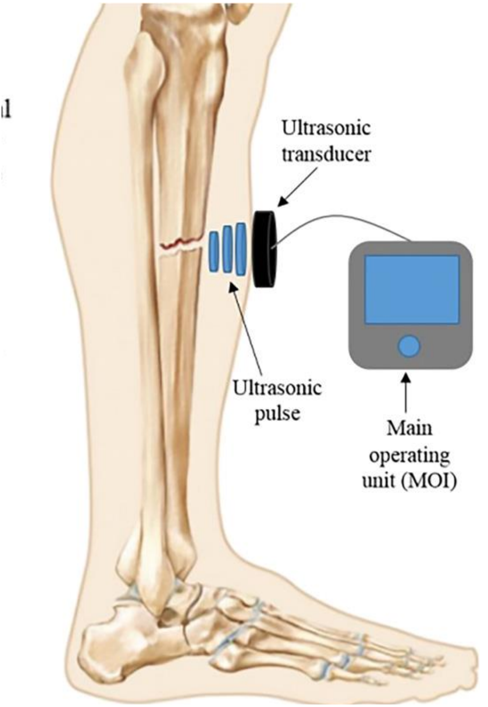
- *In vitro* and small-animal studies show benefits of e-stim
- Less successful in large-animal / human studies
  - Size of limb / thickness of surrounding tissues?
- Available research heterogeneous regarding stimulation strength, stimulation protocols and incomplete / uncertain reporting of device specs.

Einhorn TA. AAOS Instructional Course Lectures. 45: 401 - 416, 1996.

Ultrasound

Ultrasound

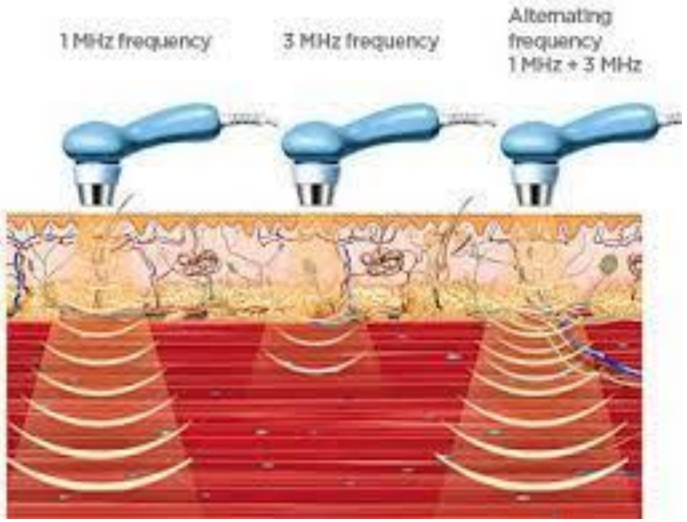
- Acoustic radiation at frequencies above the limit of human hearing.
- A form of energy that may be transmitted into the body as high frequency acoustical pressure waves
- Produces micromechanical stresses and strains in tissue



Haglin, JBJS Rev, 2017;5(8):e8

Ultrasound: Diagnostic vs Therapeutic

- Diagnostic human ultrasound use low intensity of 1 – 50 µW/cm^2



- Therapeutic ultrasound uses higher intensity energy of 1 - 50 mW/cm^2

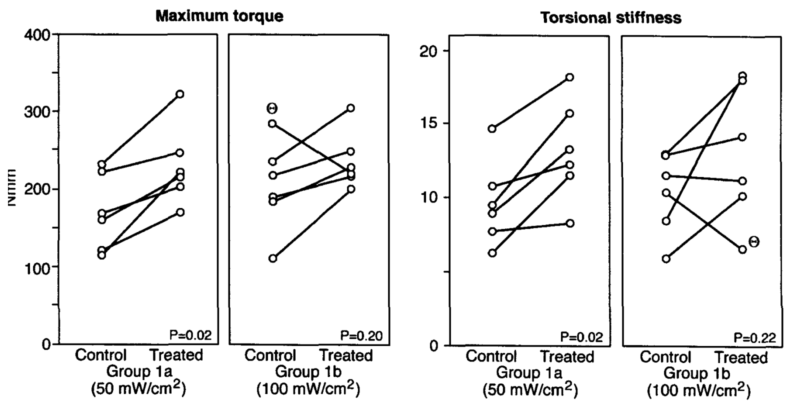
Animal data suggests that ultrasound stimulation increases the mechanical properties of the fracture callus by stimulating earlier synthesis of extracellular matrix proteins.

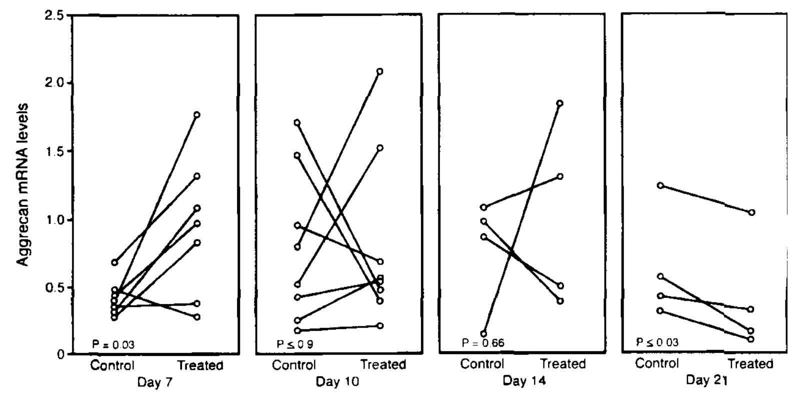
Journal of Orthopaedic Research
14:802-809 The Journal of Bone and Joint Surgery, Inc.

Exposure to Low-Intensity Ultrasound Increases Aggrecan Gene Expression in a Rat Femur Fracture Model

Kyu-Hyun Yang, *Javad Parvizi, †Shyu-Jye Wang, *David G. Lewallen, ‡Randall R. Kinnick, ‡James F. Greenleaf, and *Mark E. Bolander

*Department of Orthopedic Surgery, Yonsei University College of Medicine, Seoul, Korea, †Department of Orthopedics, Tri-Service General Hospital, Taipei, Taiwan, R.O.C., *Department of Orthopedics, and ‡Biodynamics Research Unit, Department of Physiology and Biophysics, Mayo Clinic/Foundation, Rochester, Minnesota, U.S.A.*





Ultrasound stimulates angiogenesis, increasing blood flow to the fracture site

J Ultrasound Med 22:145–153, 2003

Power Doppler Assessment of Vascular Changes During Fracture Treatment With Low-Intensity Ultrasound

Nandkumar M. Rawool, MD, Barry B. Goldberg, MD, Flemming Forsberg, PhD, Alan A. Winder, PhD, Eric Hume, MD

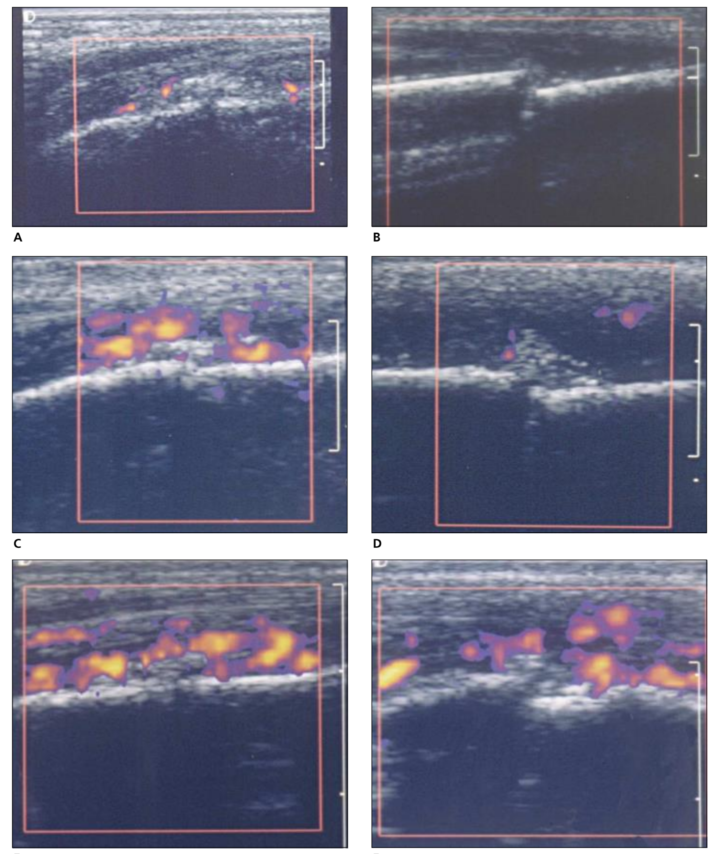


Figure 4. Power Doppler image of the area around the fracture site. POD 1 shows minimal blood flow in treated (**A**) and control (**B**) limbs. On POD 7, increased flow is shown around fracture sites in the treated limb (**C**) but not in the control limb (**D**). On POD 11, increased flow is shown in both limbs, but it is still greater in the treated limb (**E**) than in the control limb (**F**).

Acceleration of Tibial Fracture-Healing by Non-Invasive, Low-Intensity Pulsed Ultrasound*

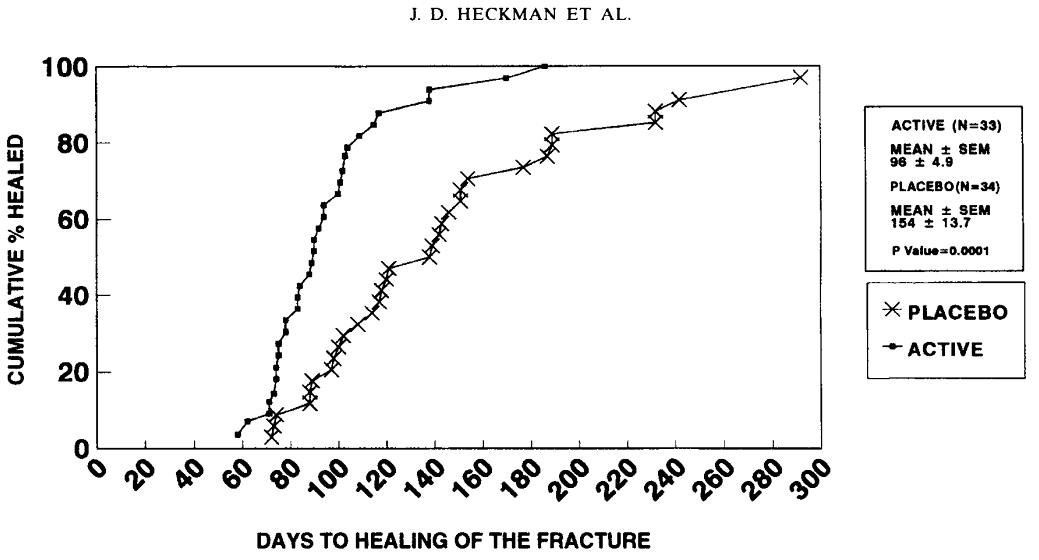
BY JAMES D. HECKMAN, M.D.†, JOHN P. RYABY‡, JOAN McCABE, R.N.§, JOHN J. FREY, PH.D.¶, AND RAY F. KILCOYNE, M.D.#, SAN ANTONIO, TEXAS

Investigation performed at The University of Texas Health Science Center at San Antonio, San Antonio

- Prospective, randomized, double-blind, placebo-controlled study
- 67 closed or grade-I open tibial fractures
  - 33 treated with active device
  - 34 treated with placebo device

Heckman JD et al. J Bone Joint Surg. 76A: 26 - 34, 1994.

- Statistically significant decrease in the time to clinical healing (p = 0.01)
  - Ultrasound 86 ± 5.8 days
  - Placebo 114 ± 10.4 days



Heckman JD et al. J Bone Joint Surg. 76A: 26 - 34, 1994.

thebmj

BMJ 2017;356:j656 doi: 10.1136/bmj.j656

Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials

Stefan Schandelmaier *methodologist*[1 2], Alka Kaushal *physician*[1 3], Lyubov Lytvyn *methodologist*[4], Diane Heels-Ansdell *biostatistician*[1], Reed A C Siemieniuk *methodologist*[1 5], Thomas Agoritsas *assistant professor*[1 6], Gordon H Guyatt *distinguished professor*[1 7], Per O Vandvik *associate professor*[8 9], Rachel Couban *medical librarian*[3], Brent Mollon *orthopedic surgeon*[10], Jason W Busse *associate professor*[1 3 11]

- 26 randomized controlled trials with a median sample size of 30 (range 8-501)
- LIPUS did not reduce
  - time to return to work (95% CI 7.7% earlier to 14.3% later)
  - # of subsequent operations (95% CI 0.55 to 1.16)
- Effects on pain, days to weight bearing, and radiographic healing varied substantially.
  - For all three outcomes, trials at low risk of bias failed to show a benefit with LIPUS, while trials at high risk of bias suggested a benefit (interaction P<0.001).
  - When only trials at low risk of bias trials were considered, LIPUS did not reduce days to weight bearing (4.8% later, 4.0% earlier to 14.4% later; high certainty), pain at four to six weeks (mean difference on 0-100 visual analogue scale: 0.93 lower, 2.51 lower to 0.64 higher; high certainty), and days to radiographic healing (1.7% earlier, 11.2% earlier to 8.8% later; moderate certainty).

Ultrasound

- Not all studies have shown that ultrasound has a beneficial influence on fracture healing
- Based on radiographic outcomes, the FDA and the UK National Institute for Health and Care Excellence (NICE) have approved LIPUS for fracture healing.

Summary

- Electrical stimulation and ultrasound provide noninvasive primary and adjunctive methods to achieve bone healing
- There is no question that these modalities induce changes in protein synthesis and augment the normal response to bone healing
- The clinical benefits of these modalities remains uncertain

European Journal of Trauma and Emergency Surgery
https://doi.org/10.1007/s00068-019-01127-z

REVIEW ARTICLE

Check for updates

Electrical stimulation-based bone fracture treatment, if it works so well why do not more surgeons use it?

Mit Balvantray Bhavsar[1] · Zhihua Han[1] · Thomas DeCoster[2] · Liudmila Leppik[1] · Karla Mychellyne Costa Oliveira[1] · John H Barker[1]

- 72 animal studies of which 77% reported positive outcomes
  - dog, tibia, large bone defects, and DC
- 69 clinical studies, 73% reported positive outcomes
  - tibia, delayed/non-unions, and PEMF
- 161 surgeons were surveyed: 73% aware of the positive outcomes reported; 32% used EStim in their patients.
  - Cost
  - Inconsistent results
  - Impractical, difficult to use

Two Examples

Follow-up: minimal callus

Tomogram @ 4 months

6.5 months

1 year

Conclusions

- Biophysical stimulation of bone affects gene expression and produces synthesis of proteins associated with osteogenesis, affects cellular systems and promotes angiogenesis.
- Several devices are available for specific clinical indications.
- The literature is deficient, so it is hard to draw conclusions regarding efficacy in humans, both for accelerating fracture healing and treating delayed / nonunions.

Conclusions

- Definitive research regarding the clinical benefits of these modalities may never be achievable
  - Many of the RCTs at risk of bias
  - Patient-reported outcomes not studies.
  - Little incentive for independent funding
  - Little incentive for industry


Thank You