Pulsed Signal Therapy (PST)

Principles, Results of Clinical and in Vitro Studies and Clinical Application

Prof. Dr. med. Michael Faensen

PEMF

- Pulsed electromagnetic fields utilize a D.C. constant time varying signal.
- The signal is driven at a specific intensity and frequency

❖ The impulse is constant for the duration of the action.

The United States of America

The Director of the United States Patent and Trademark Office

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to any statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extensions.

Director of the United States Patent and Trademark Office

United States Patent

Dr. R. Markoll

No.: 6,524,233 B2

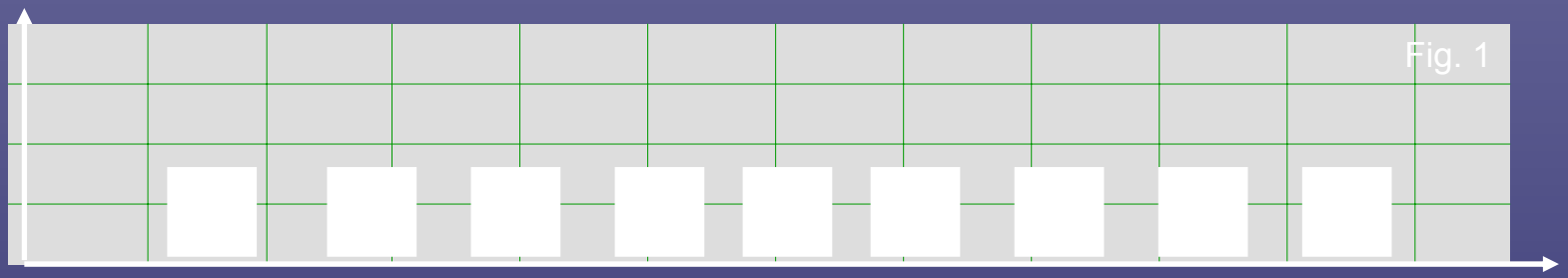
Date of Patent: Feb. 25, 2003

- PST is a result of further development of PEMF
- Differentially PST functions as a time varying, quasi rectangular wave form as the stimulatory function compared to PEMF (Fig 2).
- Intensity of the quasi rectangular wave form is between 0,5 and 1,5 Millitesla.
- Frequency between 10 and 20 Hertz

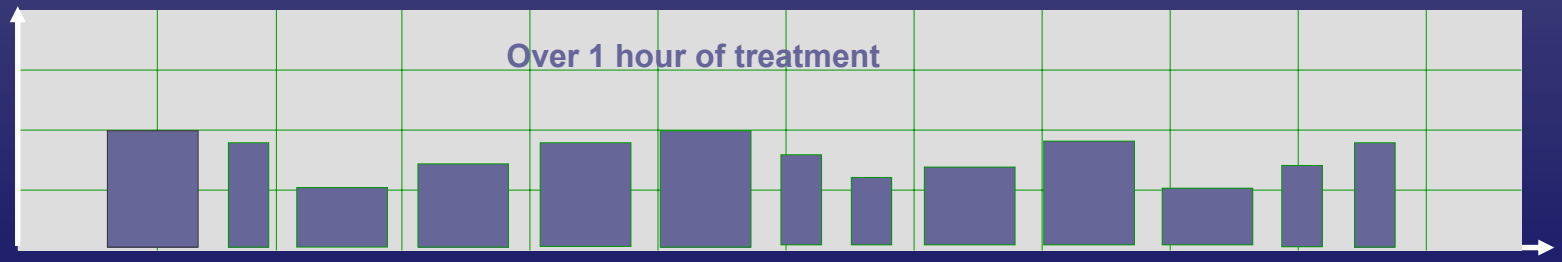
Comparison of Energy Characteristics

Characteristics of Energy Parameters of Apparatus	PEMF Application Pseudoarthritis	PST Musculoskeletal Disorders
Electromagnetic Character	Electrical Output	Pure Magnetic Field Output
Current Form	A.C. (Man Made)	D.C. Unidirectional (Biological)
Frequency	44-77 Hz	1-30 Hz
Waveform	Sinusoidal	Quasi retangular
Measured Field Output	2 G	12,5 G
Field Energized – Driven	Electro Magnetic Pulse	Pulsating Unidirectional D.C. Magnetic Field
Duty Cycle	< 50 %	> 50 %
Pulse Train	Continuous	Pulse Modulation
Frequency Spectrum	1 Dominant Frequency	2 Dominant Frequencies
Frequency Source	One fixed frequency source with 1 fixed fq. division ratio	6 Output Frequencies as part of a total therapy program. Free wheeling diode across the coil.
Implementation	Biasing Means	Inductance is optimized

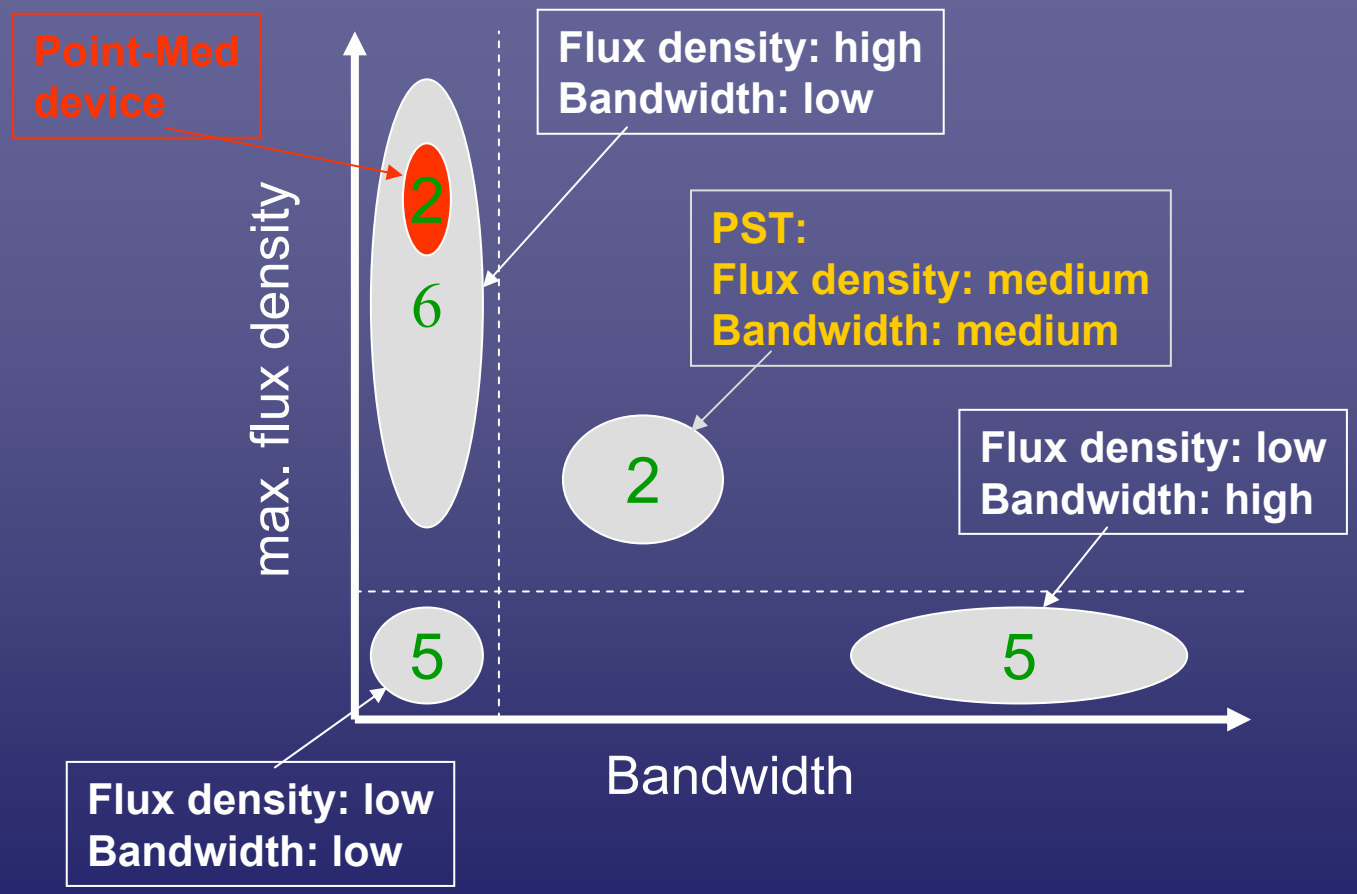
WAVEFORM COMPARISON



PEMF Pulsed Magnetic Field Devices

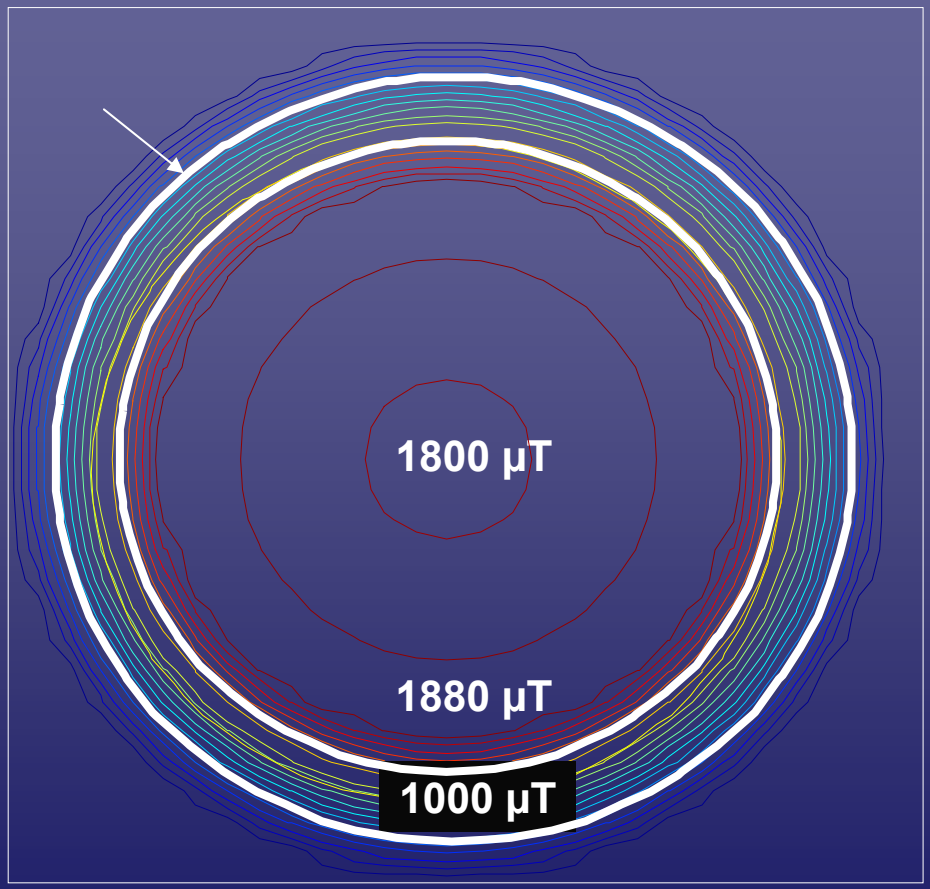


PST Pulsed Signal Therapy with alternating biological energy pulses as stimuli

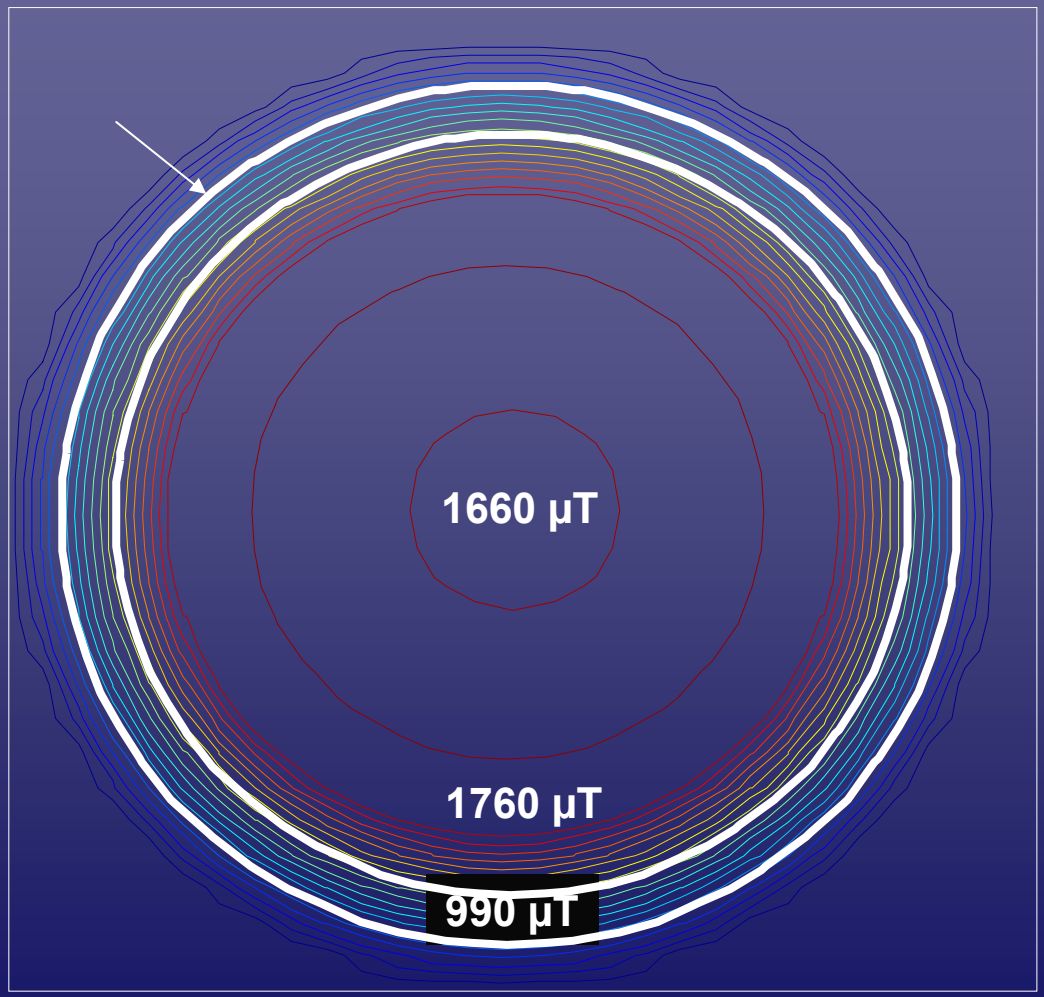


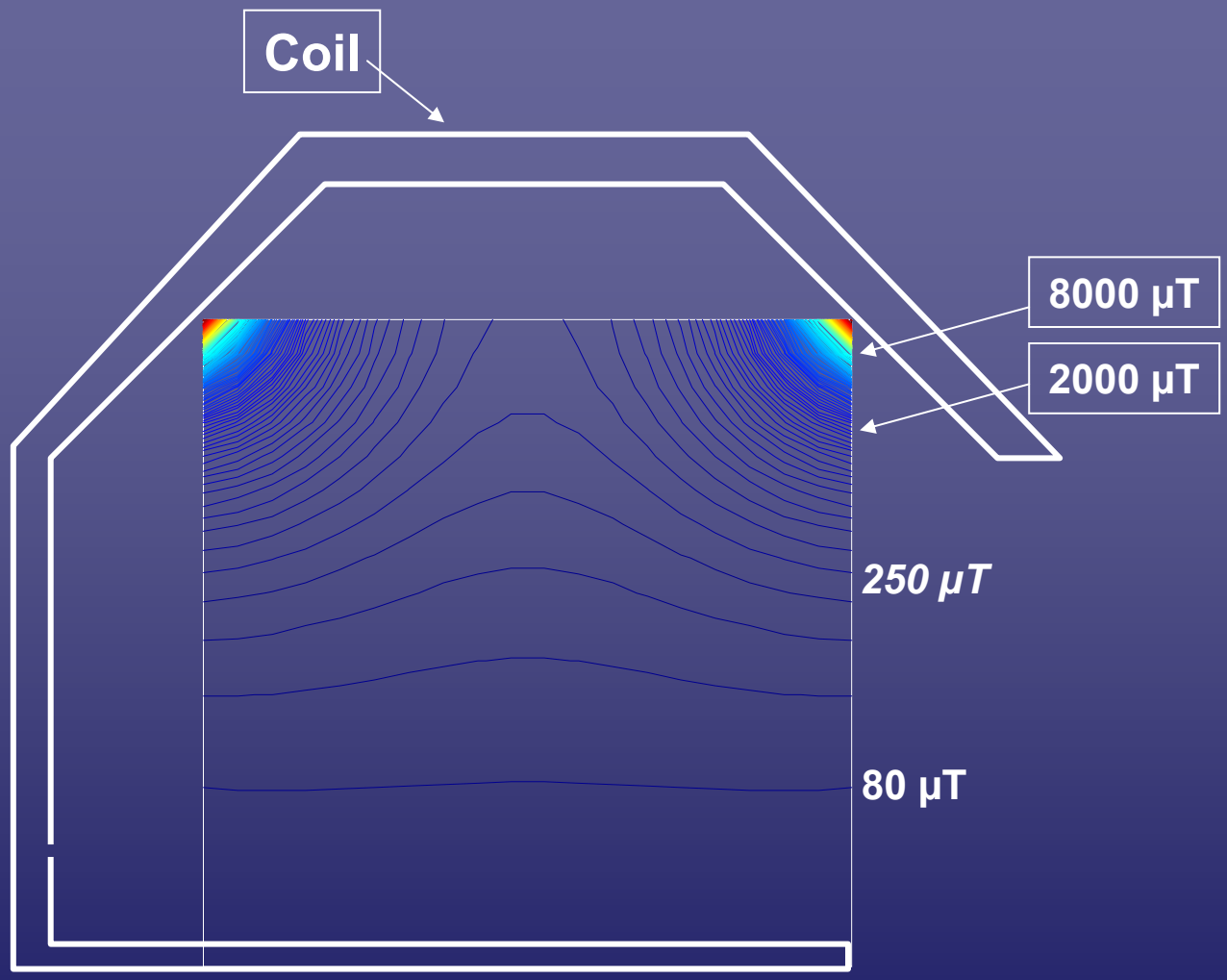
Comparison of 20 devices generating electro magnetic fields.

PST Knee Coil
Distribution of flux density

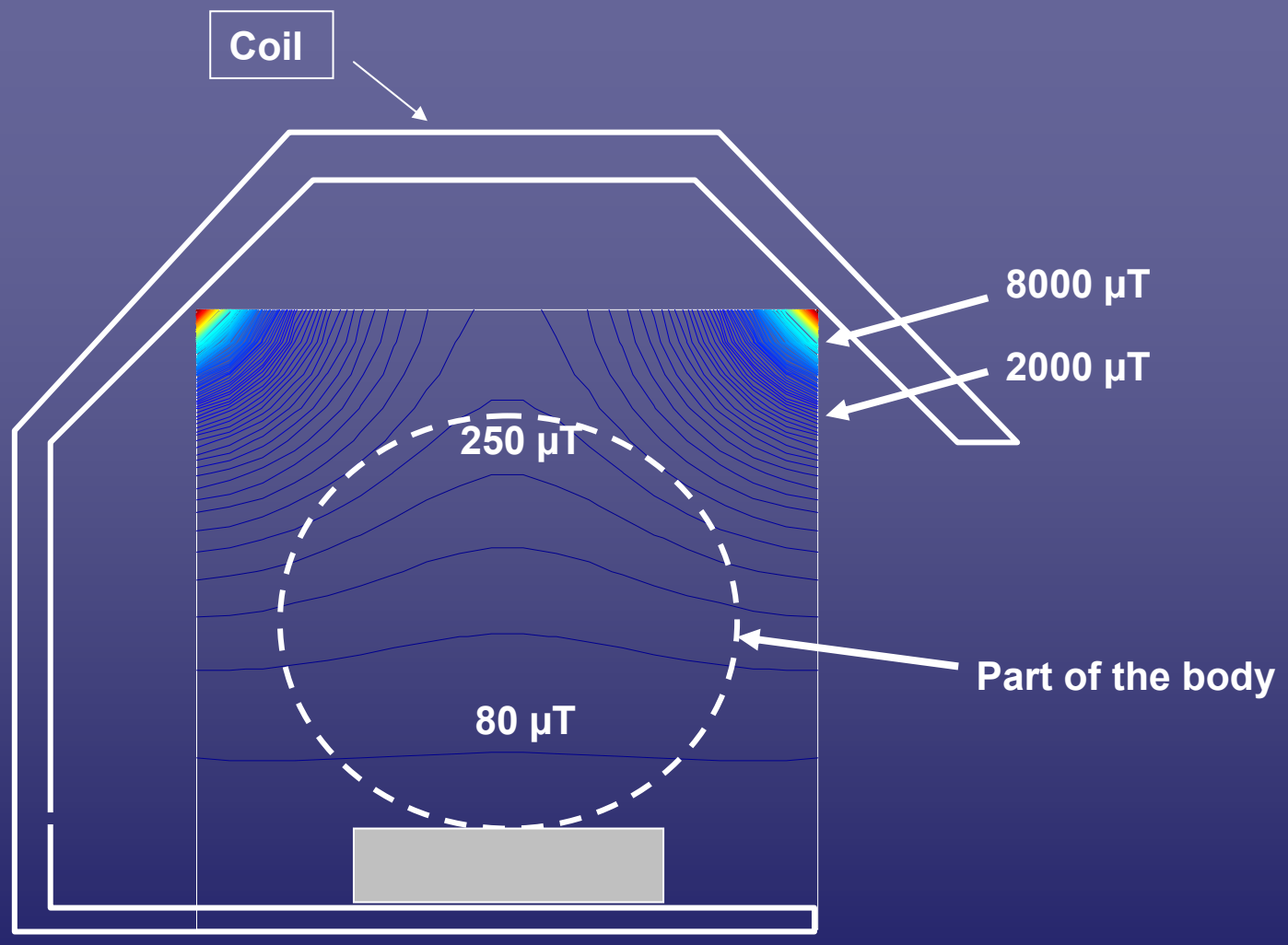


Trunk Coil:
Distribution of flux density

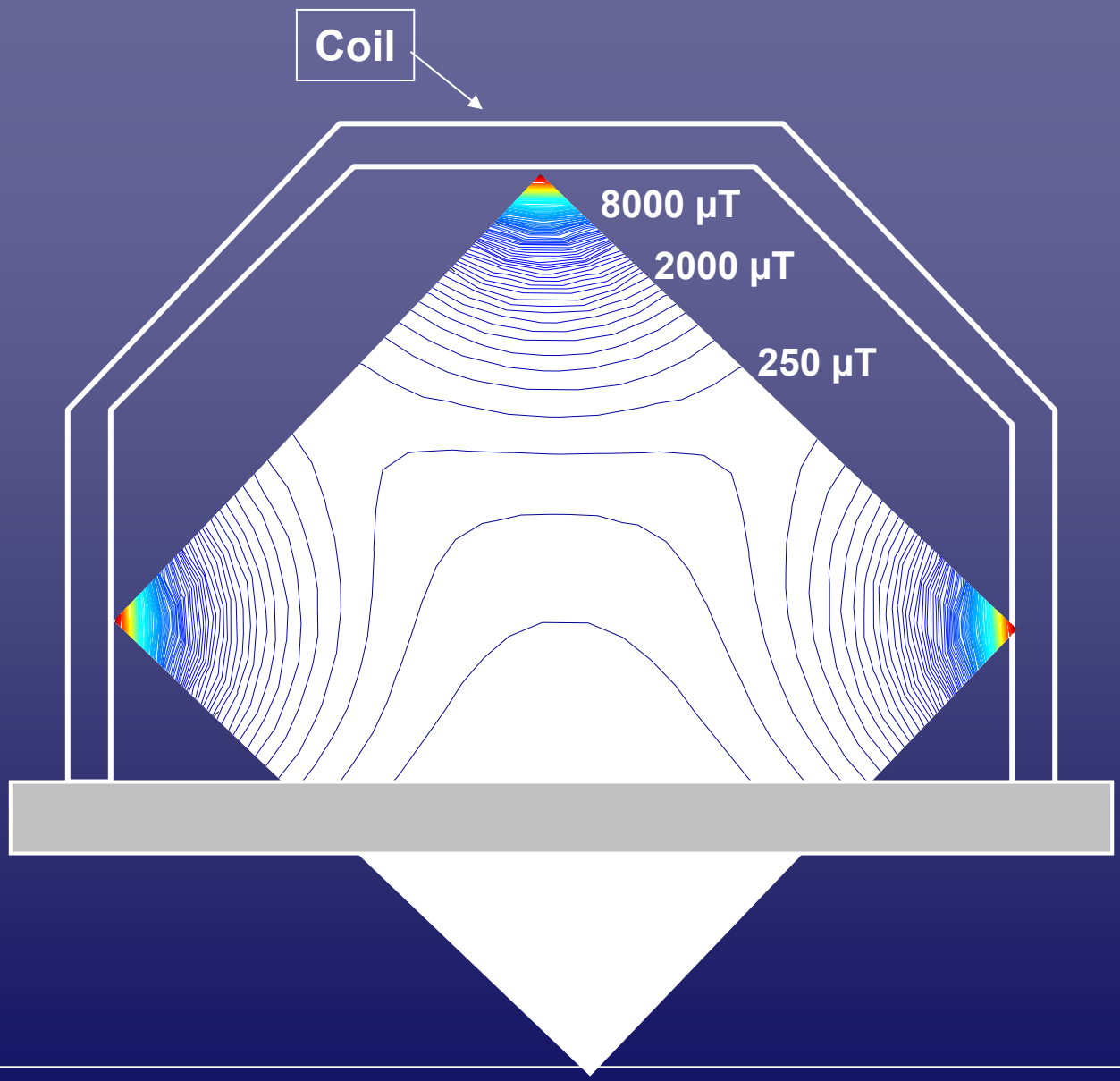




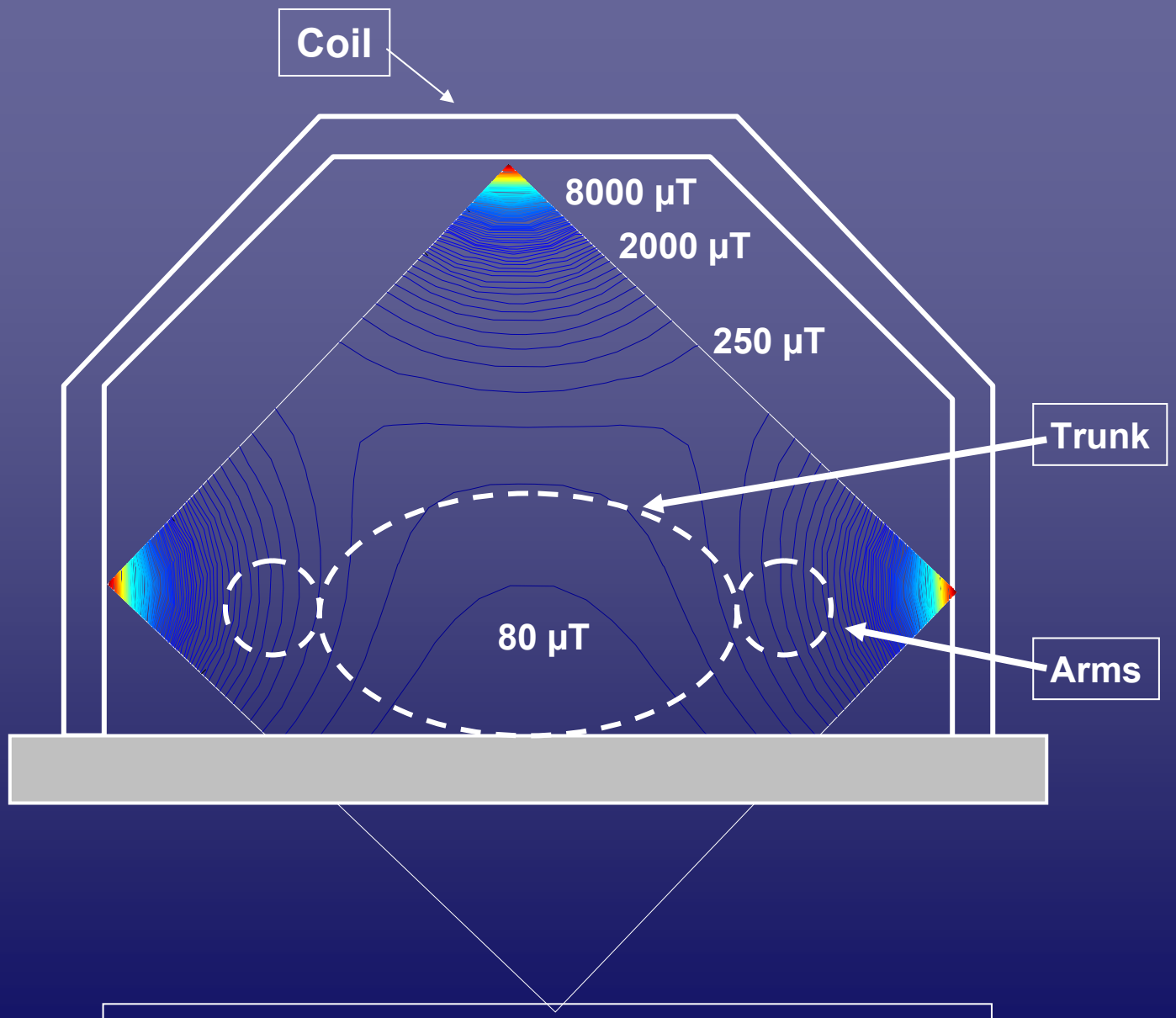
Distribution of flux density in the „Copy-cat“ device



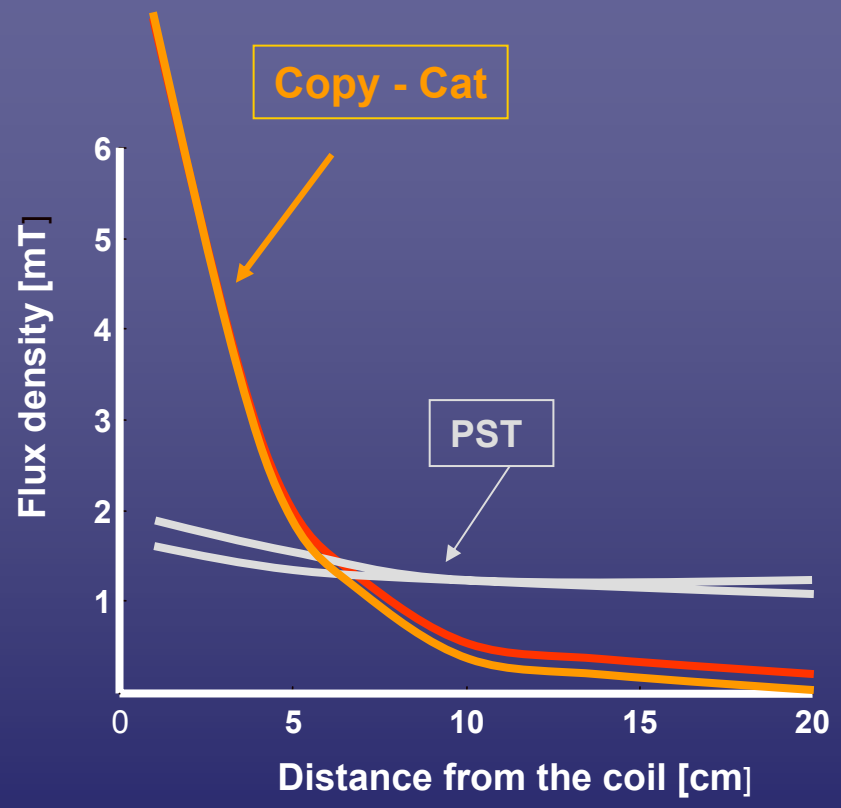
Postioning of a limb in the „copy cat“ coil



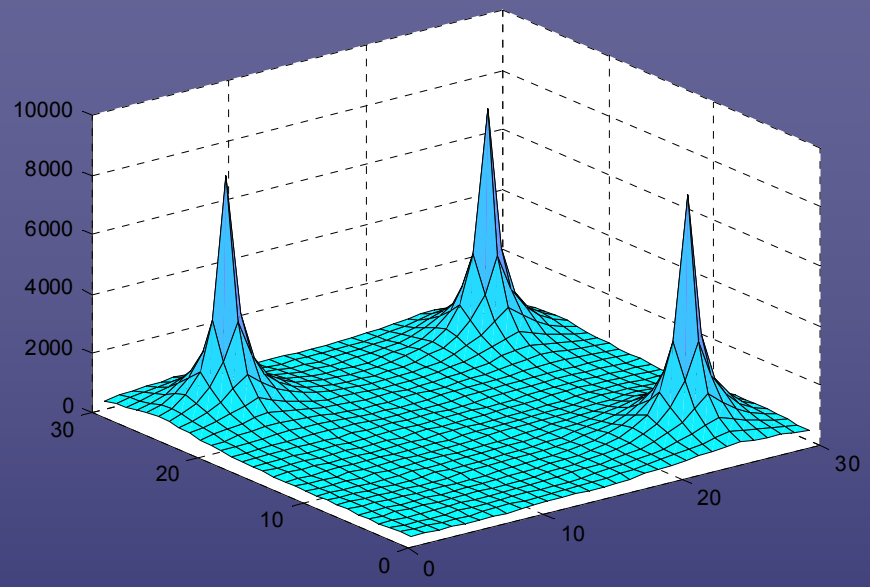
Distribution of flux density with the trunc in the coil

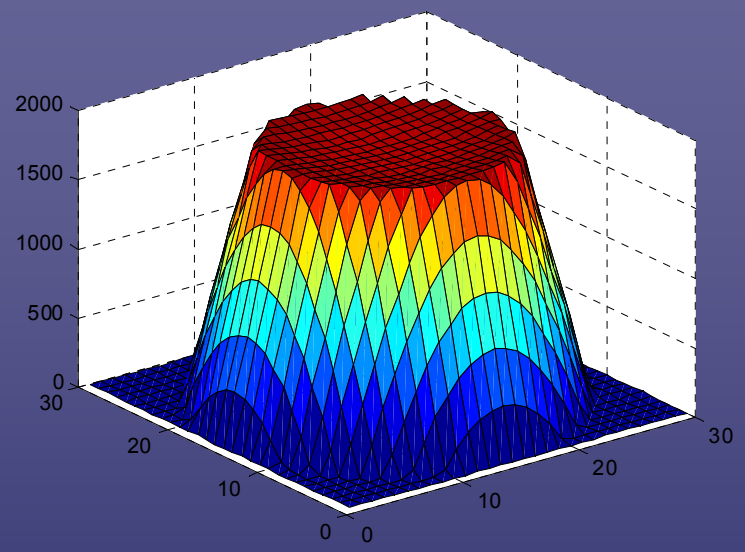


Postioning of the Trunk in the „Copy-cat“ Device



Flux density depending from the the distance from the coil

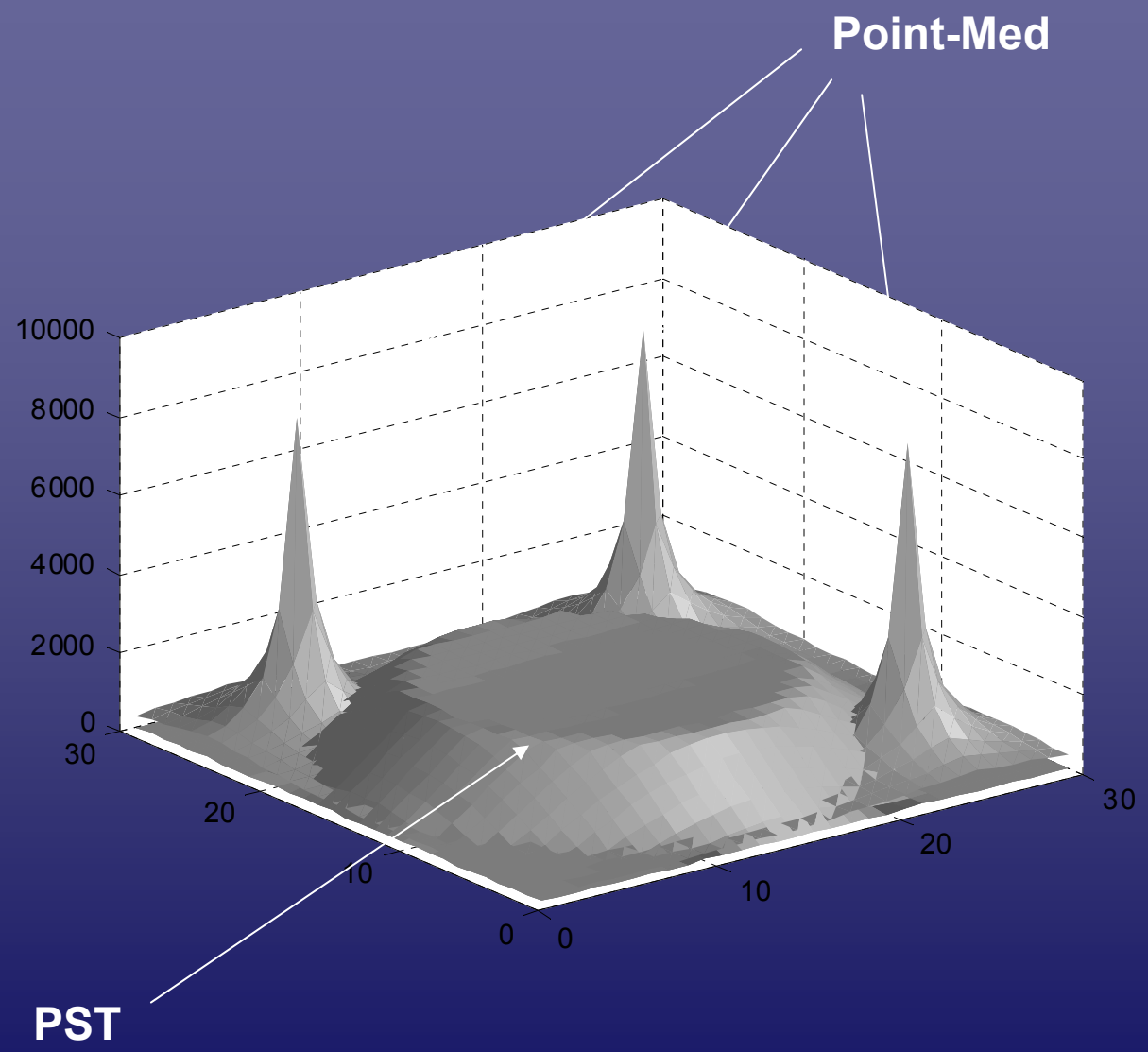




Copy cat

PST

Distribution of flux density inside the coils Applikators



Overlay of the pattern of distribution PST and Point Med

Postulated Mechanism of Action

- **Composition of connective tissues**
  Cartilage, ligaments, tendons, bone
- **Structure of connective tissues**
- **Electrophysiology**
- **Pathophysiology**

Regeneration of Cartilage

1

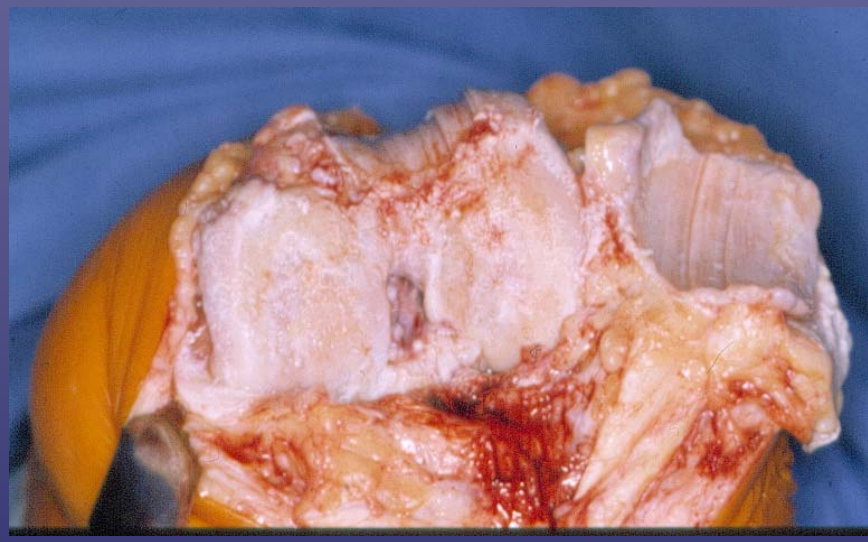


Fig. 1:

Pauwels F.: Biomechanical Principles of Varus/Valgus Intertrochanteric Oseotomy in the Treatment of Osteoarthrits of the Hip

J. Schatzker *(ed.)*The Intertrochanteric Osteotomy. Springer-Verlag 1984

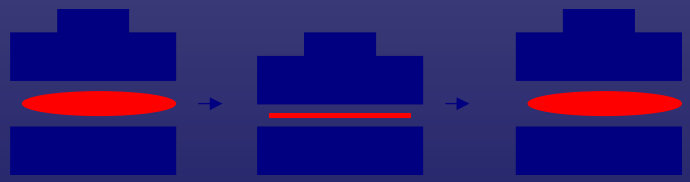
Comparison of Static / Dynamic Compression of the Proteoglycan-Synthesis

In vitro study: Bovine cartilage

1. **Static Compression**

⇓ PG Synthesis
($^{35}SO_4$)

2. **Dynamic Compression**



⇑ PG Synthesis
Frequency 1 Hz, 10 PSI

PST on Bovine Cartilage Discs Results

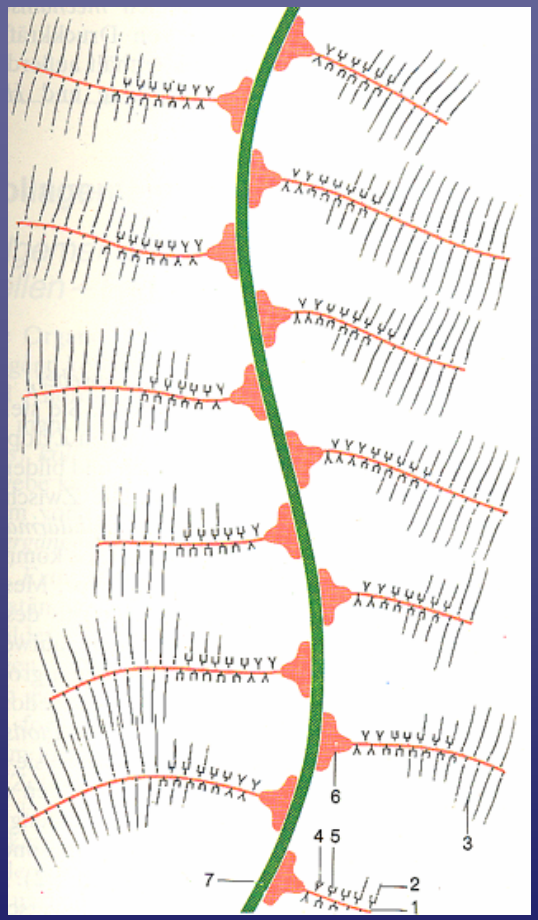
1. PST group: 413,0 cpm (SD=25,3)

2. Control group: 310,9 cpm (SD= 20,5)

Mean Proteoglycan Proteoglycan Synthesis (Sulfate=35)

- **No alteration of histology**
- **No increased ossification**

Proteoglykans



Complex biomolecules composed of a protein core to which GAG chains are attached

Structure and Function of Hyaline Cartilage

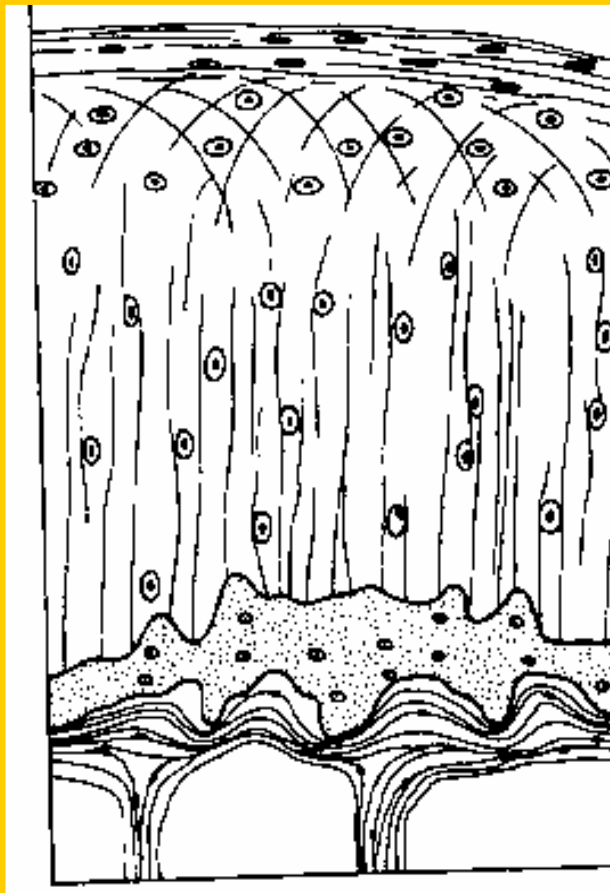
Superficial –Tangential (10-20%)

Middle (40 – 60%)

Deep (30%)

Tide mark

Calcified cartilage



MECHANISM OF ACTION OF PULSED SIGNAL THERAPHY

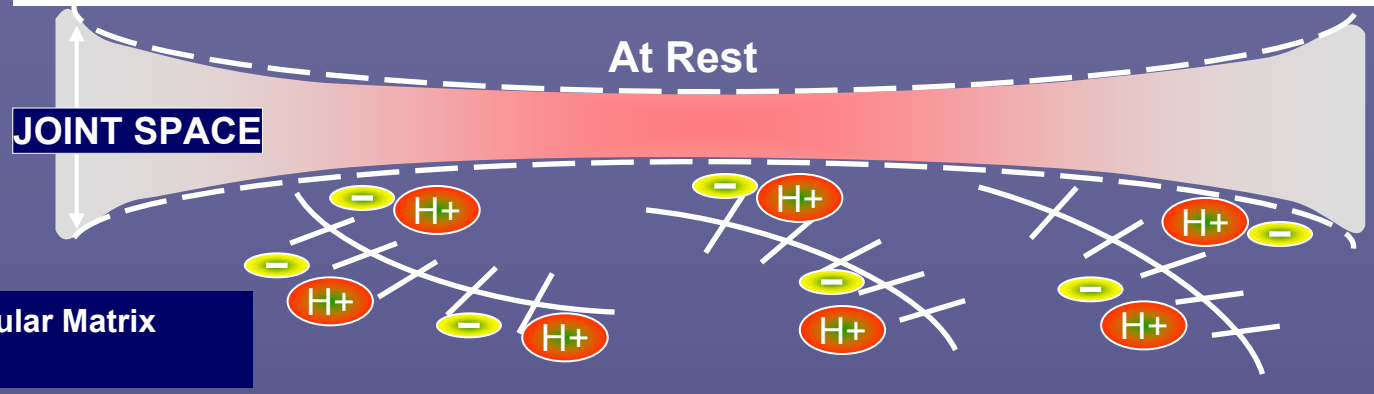


Fig. 1

Charge equilibrium between hydrogen protons and negative charge carriers in the extra cellular cartilage matrix
- no streaming potential -

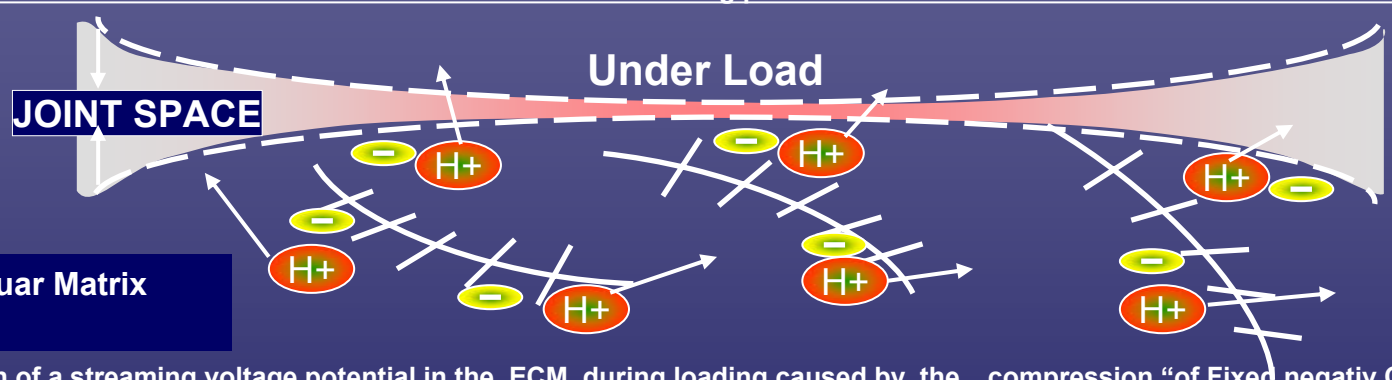


Fig. 2

Creation of a streaming voltage potential in the ECM during loading caused by the „compression "of Fixed negativ Charged fluid forced out of cartilage tissue with Forced Movement of hydrogen protons

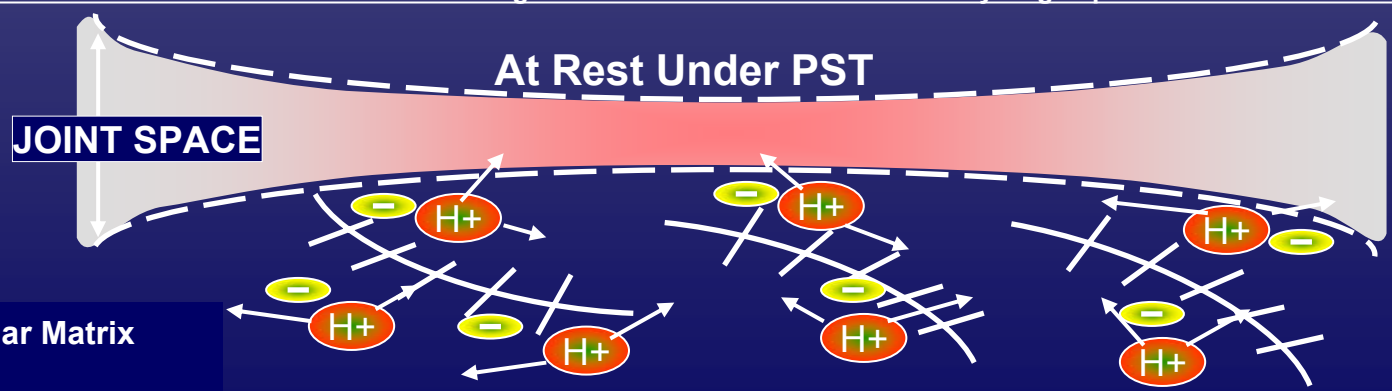
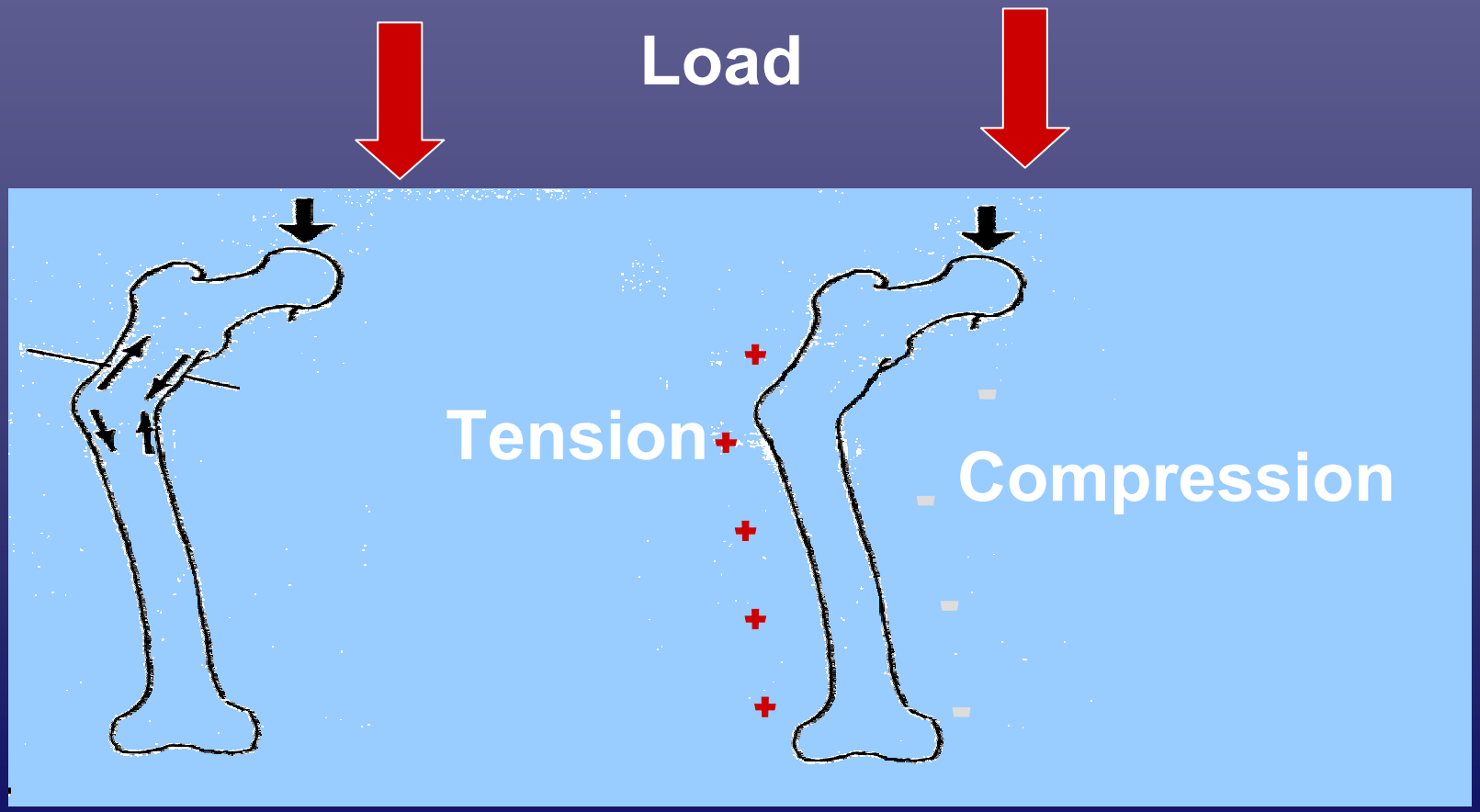


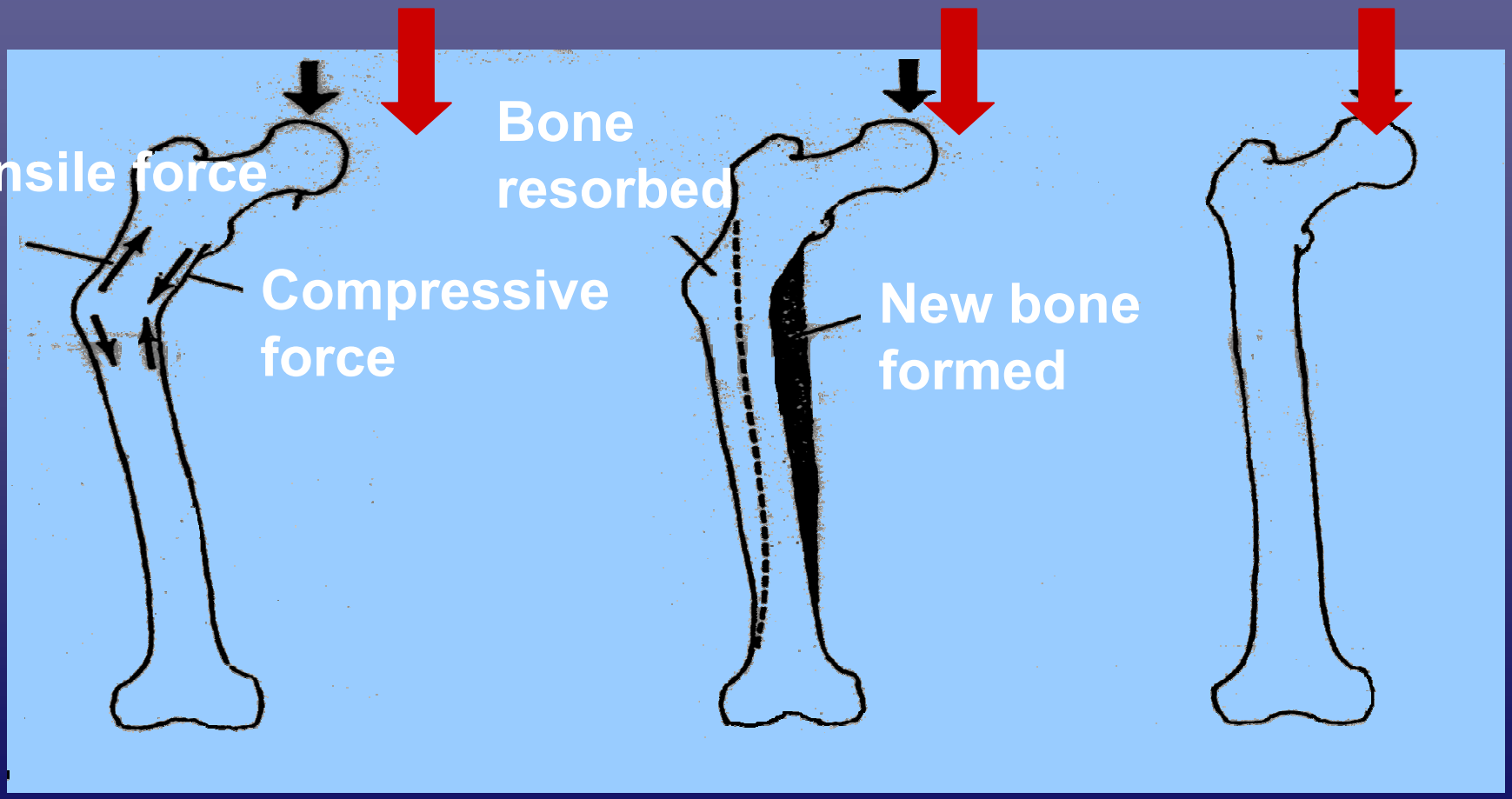
Fig. 3

Generation of Streaming Potentials flow in the Joint coused by forced movement of hydrogen protons in the ECM

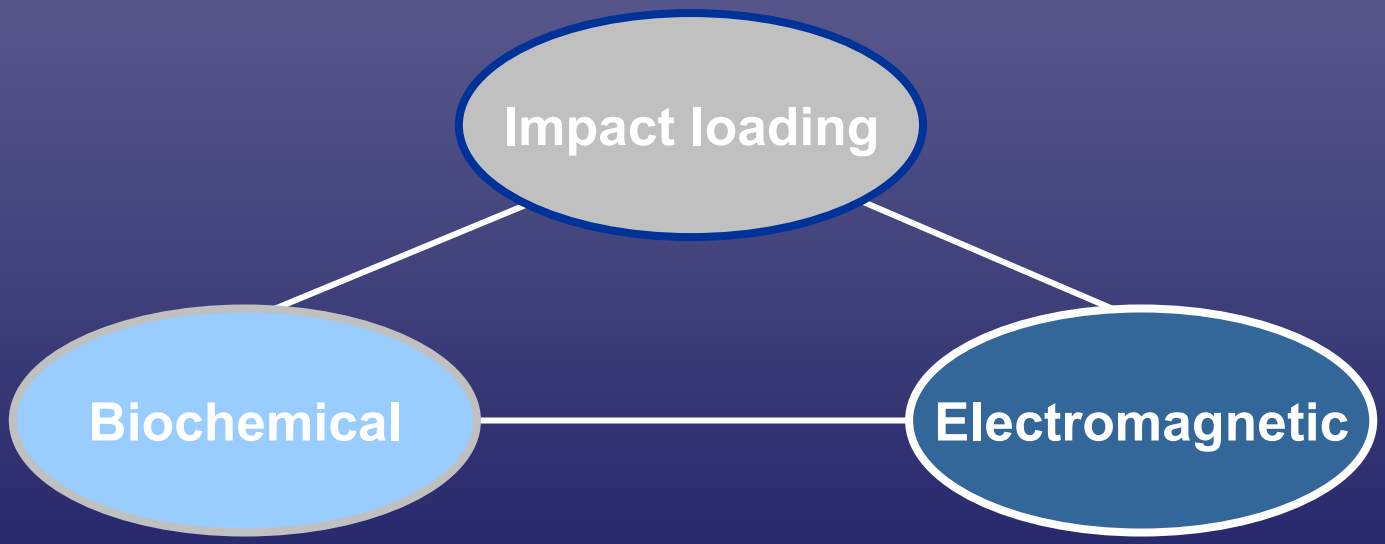
Stress-Generated Potentials in Bone



Bone Remodeling in Response to Stress



Relationship



Mechanism of Action of PST

- Reconstruction of the disturbed electrical field
- Recovery of the natural regenerative capability
- Reactivation of cartilage and other connective tissues

PST and Osteoarthritis
Possible Mechanism of Action

- Increased Proteoglycan Production
- Increased Collagen Production
- Repair of Cartilage Defects
- Repair of Subchondral Microfractures

Mechanism of action of PEMF in bone cells

- Induktive, capazitive und combined fields produce significant increases in bone-cell DNA.
- Ca^{2+} translocation through voltage-gated calcium channels
- Transduction of signals by means of itracellular release of Ca^{2+}

Brighton C.T., Wang G., Seldes R., Zhang G., Pollak S.R.:
Signal Transduction in Electrically Stimulated Bone Cells.
J. Bone Joint Surg 2001; 83-A: 1514 - 28

Pulsed Signal Therapy (PST) Enhances Proteoglycans Concentration in Human Chondrocyte Cultures

IL -1ß determins a significant decrease ($p < 0.05$) in PG levels, but when cells are cultured in the presence of IL-1β and submitted to PST Stimulation significant restoration ($p < 0.05$) of PG production is observed.

•R Markoll, F Nerucci, A Fioravanti, C Tofi, K Righeschi, R Marcolongo

Institute of Rheumatology, University of Siena, Italy

*Biomagnetic Therapy Systems

Action of PST on 3-dimensional chondrocyte culture

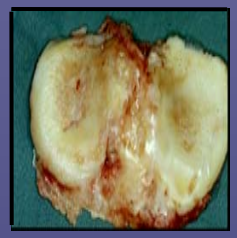
an in vitro study

Ina Krüger, engineer of biotechnology
Jürgen Zimmermann, Michael Sittinger

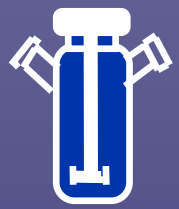
University medical center Charité
Faculty of the Humboldt-University Berlin
Laboratory for Tissue Engineering

Tucholskystr. 2,
10117 Berlin
in **cooperation with Prof. Faensen**,
Department Traumatology
Wenckebach Clinic, Berlin

Experimental approach

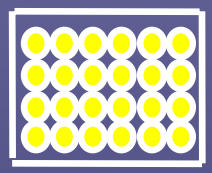


arthritic
articular cartilage
& meniscus

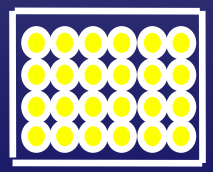


chondrocytes
isolation

cell proliferation
(monolayer)



forming of pools
and
pellet the cells



analysis:

- survey of the pellet grade
- histological staining
- vitality (MTT)
- hydroxyprolin (HPLC)
- rtPCR

Three-dimensional cartilage model

De- and Redifferentiation of Chondrocytes

Tissue *in vivo*	Monolayer *in vitro*	3D-culture *in vitro*
II	I+III	II
slowly **matrix synthesis**	no matrix synthesis	slowly **matrix synthesis**
reduced Proliferation capacity	enhanced **Proliferation** capacity	reduced Proliferation capacity
collagen type II	collagen type I & III	collagen type II

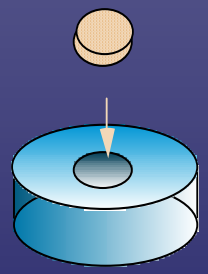
Benefits of 3D-cartilage models

Increasing complexity

monolayer

tissue model

animal model



Increasing defined parameters

Method
Pellet grade

- measurement of cell pellets by microscopy and image analysis

- **Pixel score P** describe the pellet area

→ the higher the number of pixels → the greater the pellet diameter

- **Average Luminance aL** describes the pellet density (color intensity)

→ the smaller the luminance value → indicates density of the pellet

- **Grade G** joins Pixels and average Luminance

→ the higher the grade → the bigger the pellet

$$G = P / aL$$

Method:

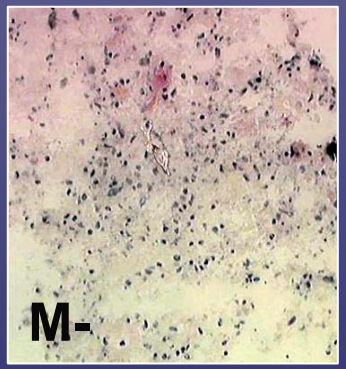
Quantification of hydroxyprolin by HPLC

- hydroxyprolin is an important amino acid of collagen,
  collagen marker
- fractionizing of isolated amino acids by HPLC
- quantification of hydroxyprolin by fluorescence detection

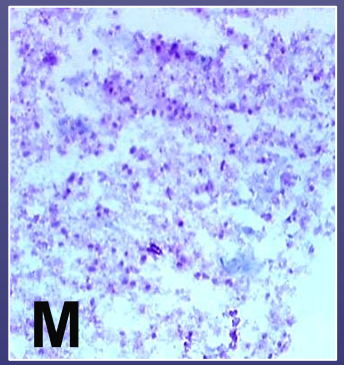
Results:

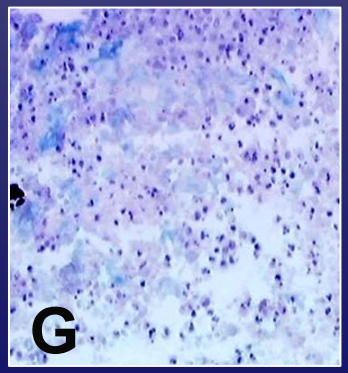
Histology

Cell distribution

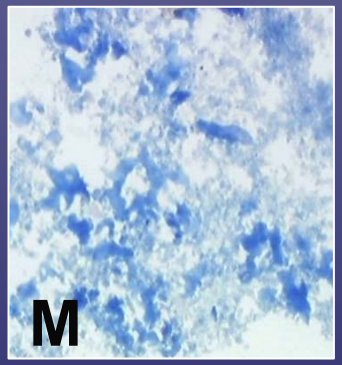


proteoglycan





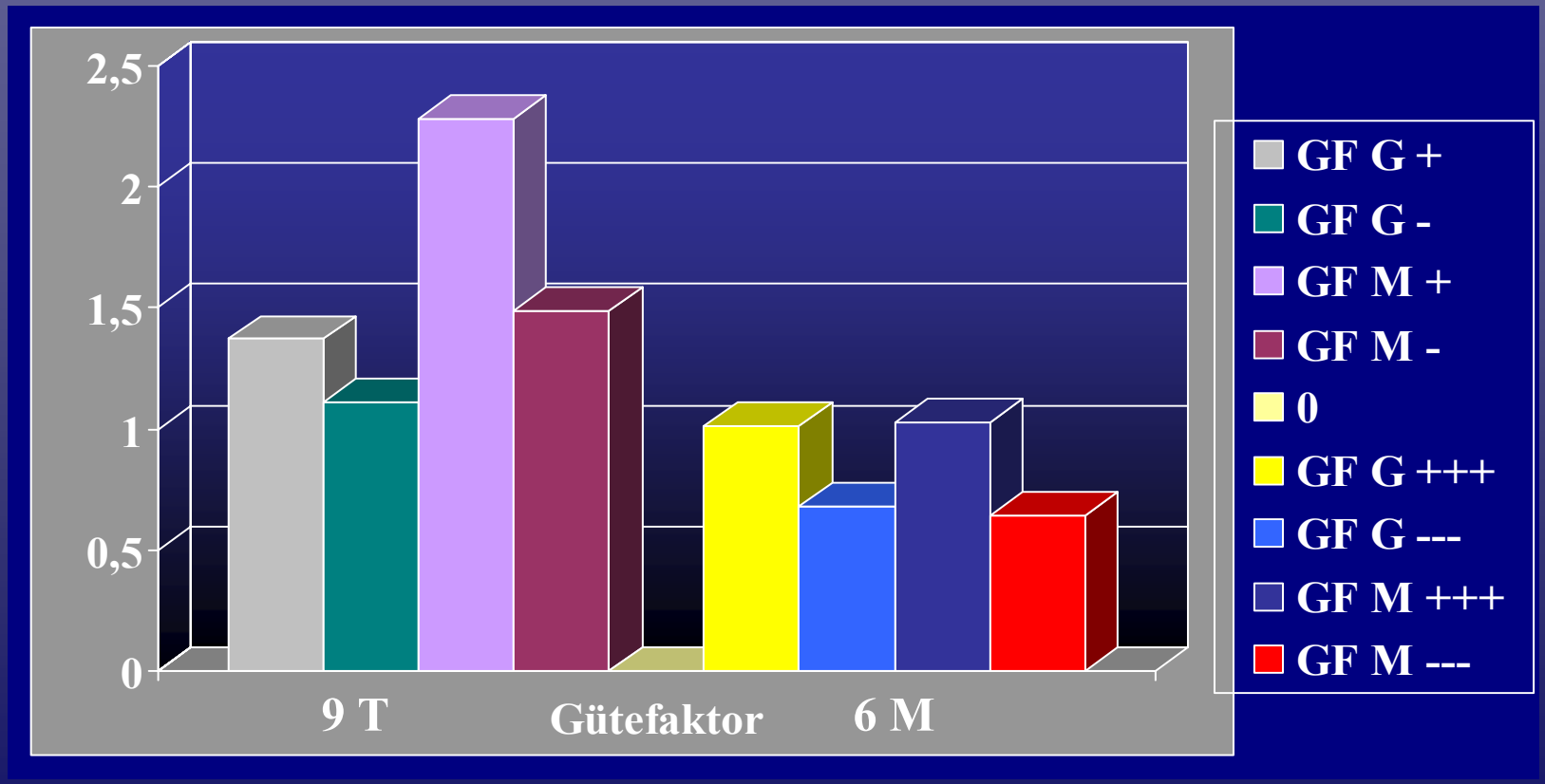
collagen



Krüger L et al

Wirkung der PST auf die Chondrocytenkultur

Gütefaktor = Pixelzahl / Luminanz

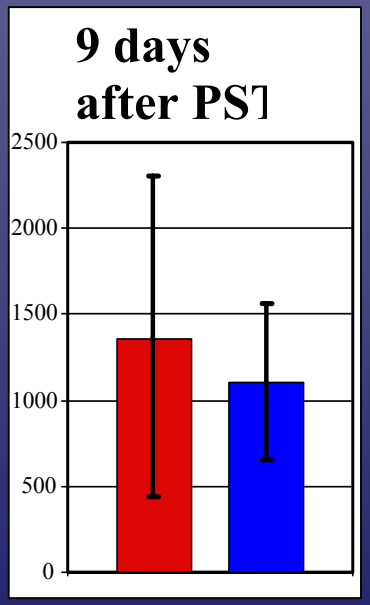


Krüger I, Sittinger M.

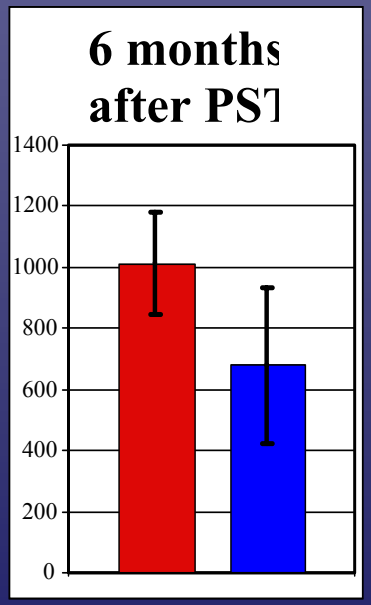
Results:

Pellet grade

articular chondrocytes

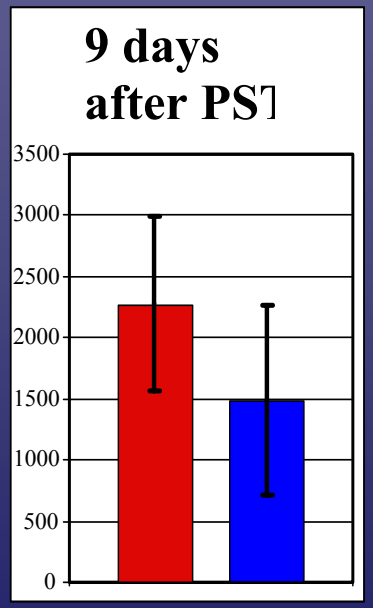


n = 8 res. 9
p-value = 0,5

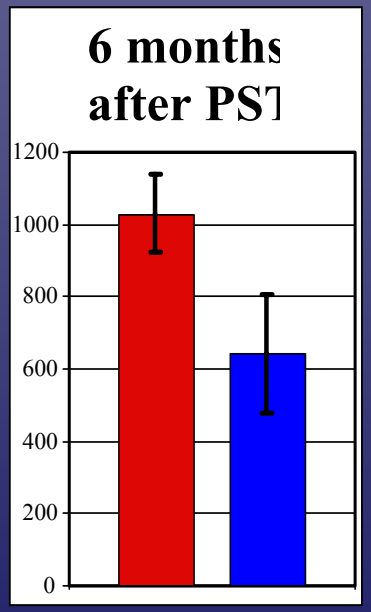


n = 8 res. 9
p-value = 0,009

meniscal chondrocytes



n = 6 res. 14
p-value = 0,06



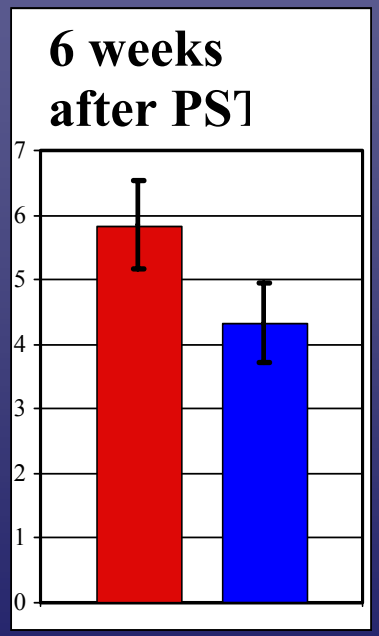
n = 6 res. 14
p-value < 0,0001

PST | control

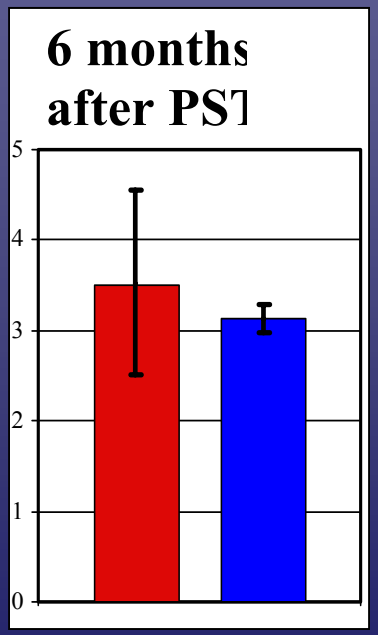
Results:
Quantification by hydroxyprolin-HPLC

articular chondrocytes

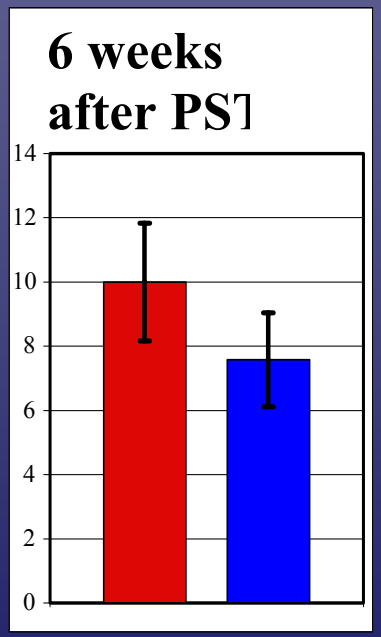
meniscal chondrocytes



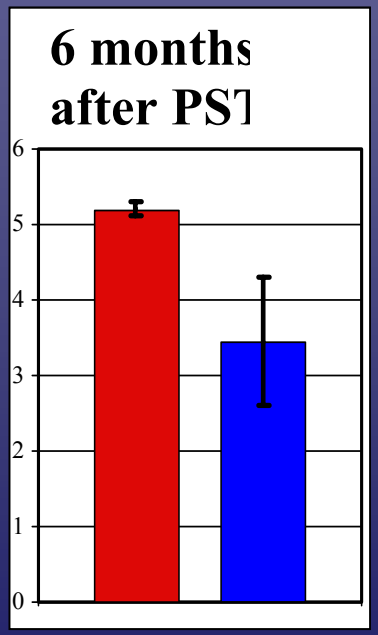
n = 4
p-value = 0,03



n = 2
p-value = 0,59



n = 3
p-value = 0,21



n = 2 res. 3
p-value = 0,01

PST | control

Summary:

- 6 month after PST: articular and meniscal chondocyte pellets are larger than the corresponding control pellets
- histological characteristics: Proteoglycans and collagens were stained
- verification of pellet vitality by MTT-test
- higher concentration of hydroxyprolin (collagen marker) in pellets after PST compared to the control group

  (after 6 weeks in articular chondrocytes; after 6 months in meniscal chondrocytes)

The Effect of PST on the Composition of the Joint Fluid in Knees with OA

Fundamentals:

- **Matrix Metalloproteinases (MMP) are Regulating the Turnover and the Catabolic Metabolismus of Cartilage, The Degradation of all Matrix Components is possible.**

- **There are 5 Essential MMPs: Collagenase, Gelatinase, Stromelysin, Matrilysin, and Membrane –Type MMP‘s .**

Laboratory: Prof. Dr. Dr. Schuppan, Medizinische Klinik II, Univ. Erlangen

- Regulation of the MMP- Activity:
  - Gene - Transkription: Primary Regulation
  - Proenzyme Activation
  - Activity of Tissue Inhibitors of
  - Metalloproteinases (TIMPs)

- The negative feedback is regulating the equilibrium between MMP‘s and TIMP‘s.

The Effect of PST on the Composition of the Joint Fluid in Knees with OA

Methods:

- In the Joint Fluid of Pat. with 2° OA of the Knee the Level of MMP, TIMP1 and Tenascin was Determined Before and Six Weeks after the Treatment with PST.
- The Ratio of the Measurements was Established.
- Simutanously the Pain Score was Assessed.

The Effect of PST on the Composition of the Joint Fluid in Pat. with 2° OA of the Knee

Results:

Parameter with statistically significant Results:

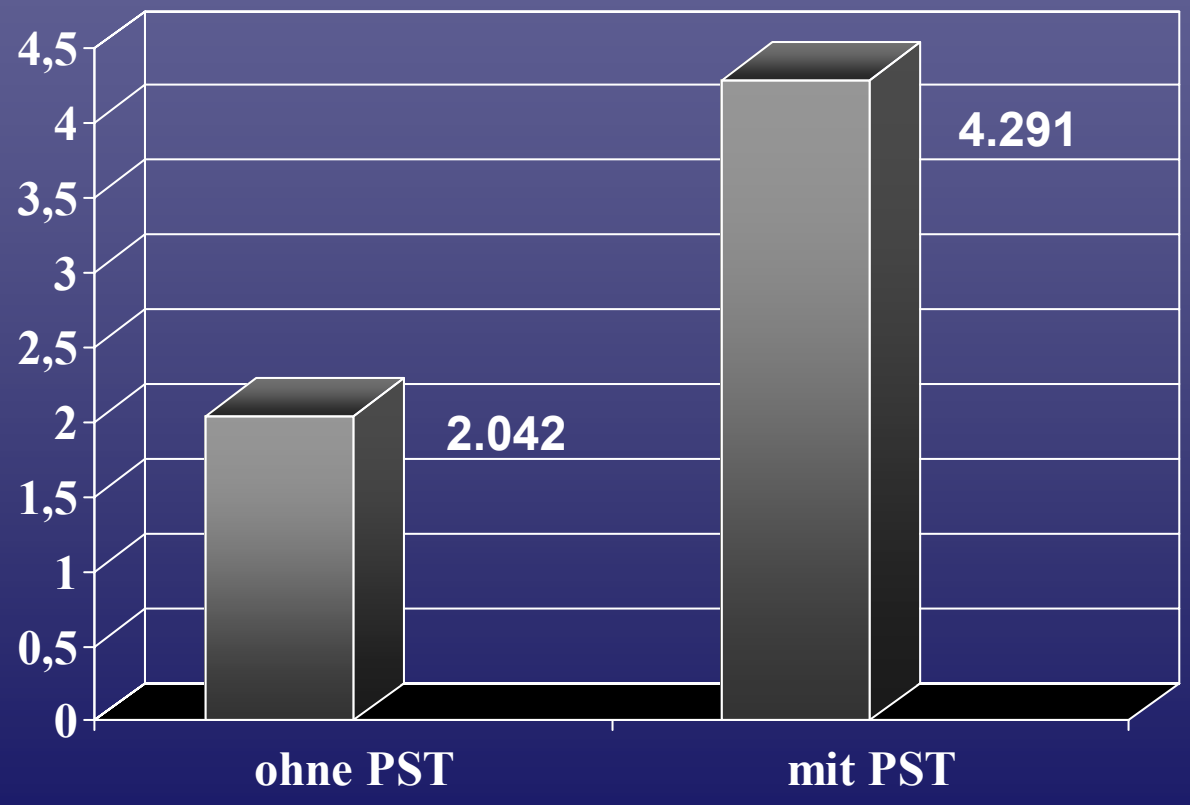
1) Biochemically:

- **MMP1**
- **Tenascin**
- **MMP 9 / TIMP 1**
- **MMP 9 / Kollagen IV**

2) Clinically:

Pain Intensity **(VAS)**

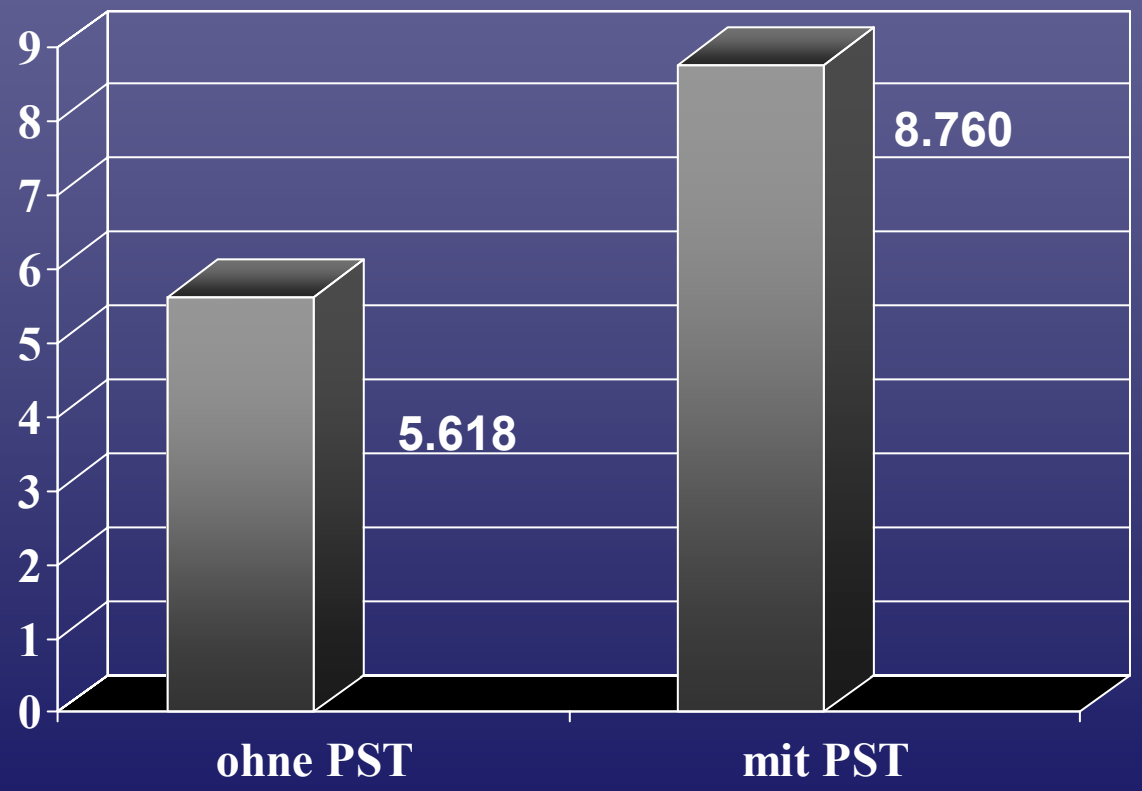
Paired T-Test
MMP1 / Protein



MMP1 Initiates the Anabolic Metabolism

t-value = 2.4602 alpha = 0.022210

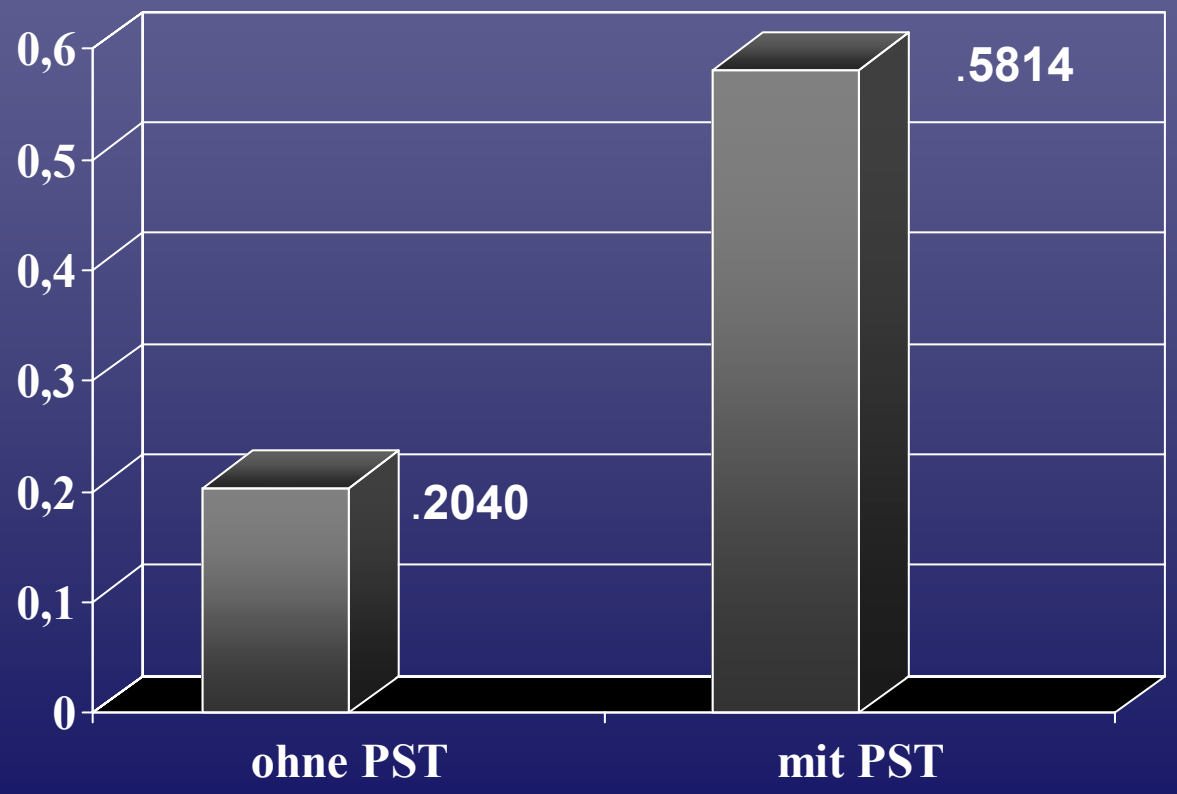
Paired T-Test
Tenascin / Protein



Tenascin is essential for the Matrix Synthesis.

t-value = 2.6537	alpha = 0.014508	Statistically significant

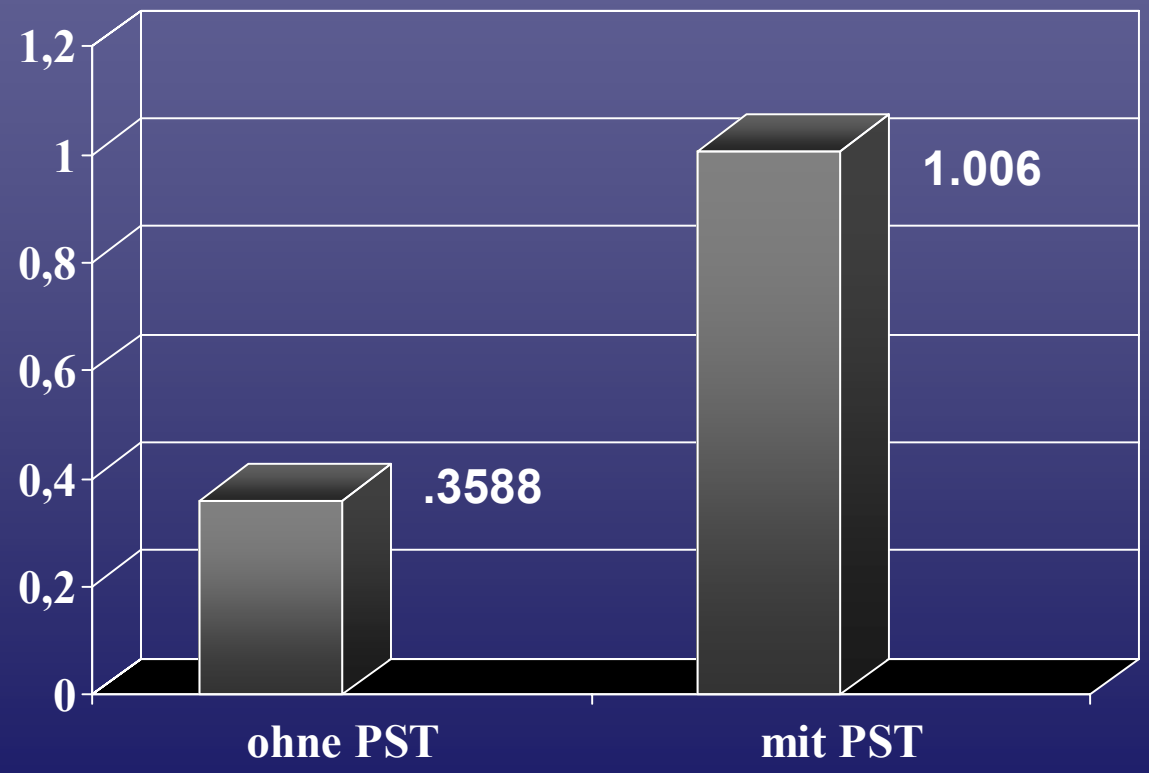
Paired T-Test MMP9/TIMP1



MMP9 participates in the Enchondral Ossifiation.

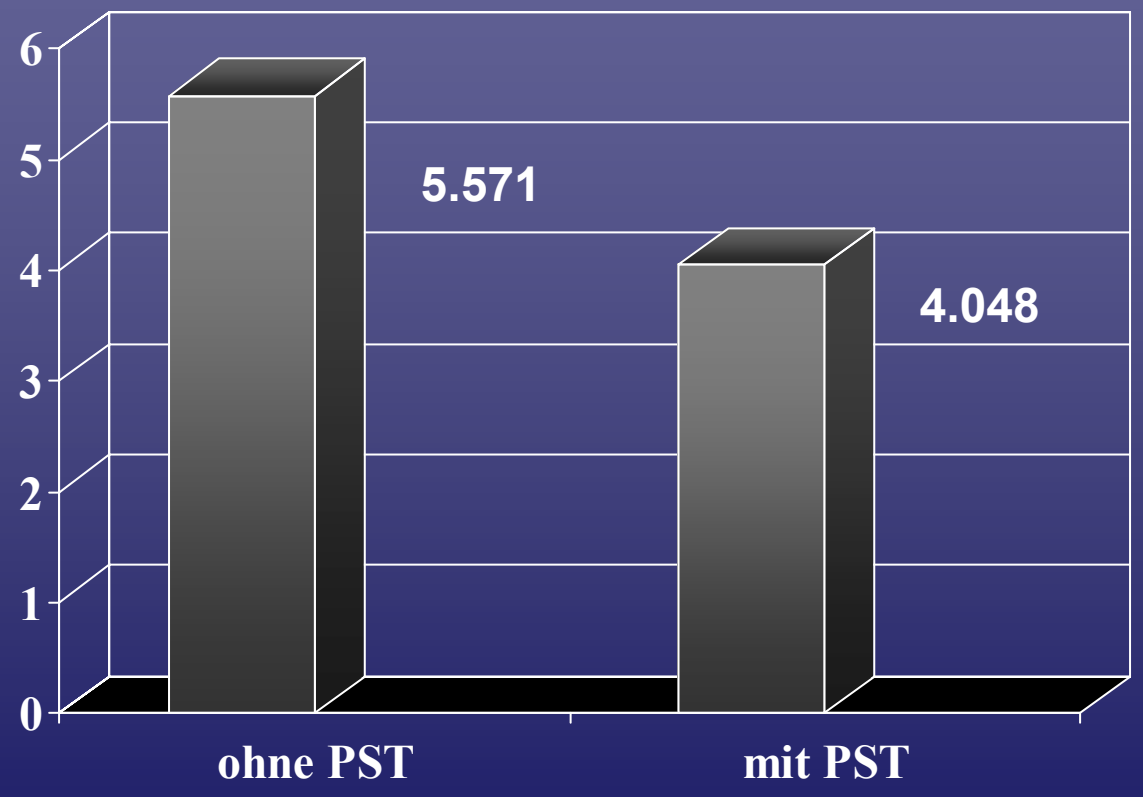
t-value = 2.2913	alpha = 0.033543	Statistically significant

Paired T-Test
MMP9/CollagenIV



t-value = 2.1905	alpha = 0.041160	Statistically significant

Paired T-Test
Pain: Stair climbing



t-value = 4.3627	alpha = 0.000301	Statistisch signifikant

The Effect of PST on the Composition of Synovial Fluid in Pat. with 2° OA of the Knee

Summery:

- **The Results Reveal that PST has an Influence on Cartilage Synthesis.**
- **The Clinical Results Exceed the Placebo Effect.**
- **This corresponds to the *in-vitro* Results.**

PST - Indications

- OA: primary
  secondary
- Osteochondritis dissecans
- Degenerative disorders of ligaments, tendons, intervertebral discs,
- **Overuse**
- **Posttraumatic disorders**

- **RSD, Osteoporosis, acute injuries**

Professionals in Germany

- DSV Deutscher Ski Verband
  (German Skiing Association)
- 1. FC Kaiserslautern
  (Footballclub)
- Professional Tennis Players

- And many others

Prospective, Randomized, Double-blind, Placebo Controlled Clinical Studies

- Trock DH, Bollet AJ, Dyer Jr RH, Fielding LP, Miner WK, Markoll R: **A Double Blind Trial of the Clinical Effects of Pulsed Electromagnetic Fields in Osteoarthritis.** J Rheumatol 1993;20:456-60

- Trock DH, Bollet AJ, Markoll R: **The Effect of Pulsed Electromagnetic Fields in the Treatment of Osteoarthritis of the Knee and Cervical Spine. Report of Randomized, Double Blind, Placebo Controlled Trials.** J Rheumatol 1994;21:1903-11

- Menkes C-J, Perrot S: **Etude de Verification de L`Efficacité Antalgique des Champs Electroniques Pulses (PST) dans la Gonarthrose.** Arthritis Rheumatology 1998;9:357

Materials and Methods

18 treatments were given for 30-min each for 3 to 5 times per week.

<u>Evaluation:</u> Baseline, Midway, End of Treatment, One Month Post EOT.

D H Trock et al 1994

Trock DH, Bollet AJ, Markoll R:

The Effect of Pulsed Electromagnetic Fields in the Treatment of Osteoarthritis of the Knee and Cervical Spine. Report of Prospective, Randomized, Double Blind, Placebo Controlled Trials.

J Rheumatol 1994;21:1903-11

Knee OA	Treated n = 42	Placebo n = 44
Sex	29 F / 13 M	31 F / 13 M
Age	69,24 ± 11.48	65.82 ± 11.66
Weight	178,02 ± 46.03	171.82 ± 39.96
Symptoms (yr)	9.08 ± 8.85	7.36 ± 7.15
Rad. Grade	2.86 ± 0.87	2.57 ± 1.13
NSAID	18	16
Other drugs	28	37

Results: Knee OA

		Midway	EOT	1 Month Post
Pain	Treat	<0.0001	<0.0001	0.001
	Plac	0.0006	0.02	0.07
ADL	Treat	0.0008	<0.0001	0.0003
	Plac	0.03	0.005	<0.01
P motion	Treat	0.07	0.0003	<0.0001
	Plac	0.2	0.009	0.2
Tenderness	Treat	0.0008	<0.0001	0.0003
	Plac	0.02	0.02	0.2

D H Trock et al 1994

OA Cervical Spine T (n= 42) P (n = 44)

Sex	12 M / 30 F	12 M / 26 F
Age	61.24 ± 13.4	67.38 ± 8.02
Weight	161.2 ± 39.0	161.8 ± 31.8
Symptoms (yr)	7.43 ± 6.66	8,07 ± 8,01
NSAID	21	7
Other drugs	26	31

Trock D H et al

Results: OA of the Cervical Spine

		Midway	EOT.	1 Month Post
Pain	Treat	<0.0001	<0.0001	0.0001
	Plac	0.03	0.0002	0.009
ADL	Treat	0.0006	0.0009	0.003
	Plac	0.008	0.002	0.04
Pain Motion	Treat	0.005	<0.0001	<0.0001
	Plac	0.3	0.02	0.6
Tenderness	Treat	0.0001	<0.0001	< 0.0001
	Plac	0.005	0.002	0.1

Trock DH et al

Double Blind Study – Hôpital Cochin Paris Service de Rhumatologie

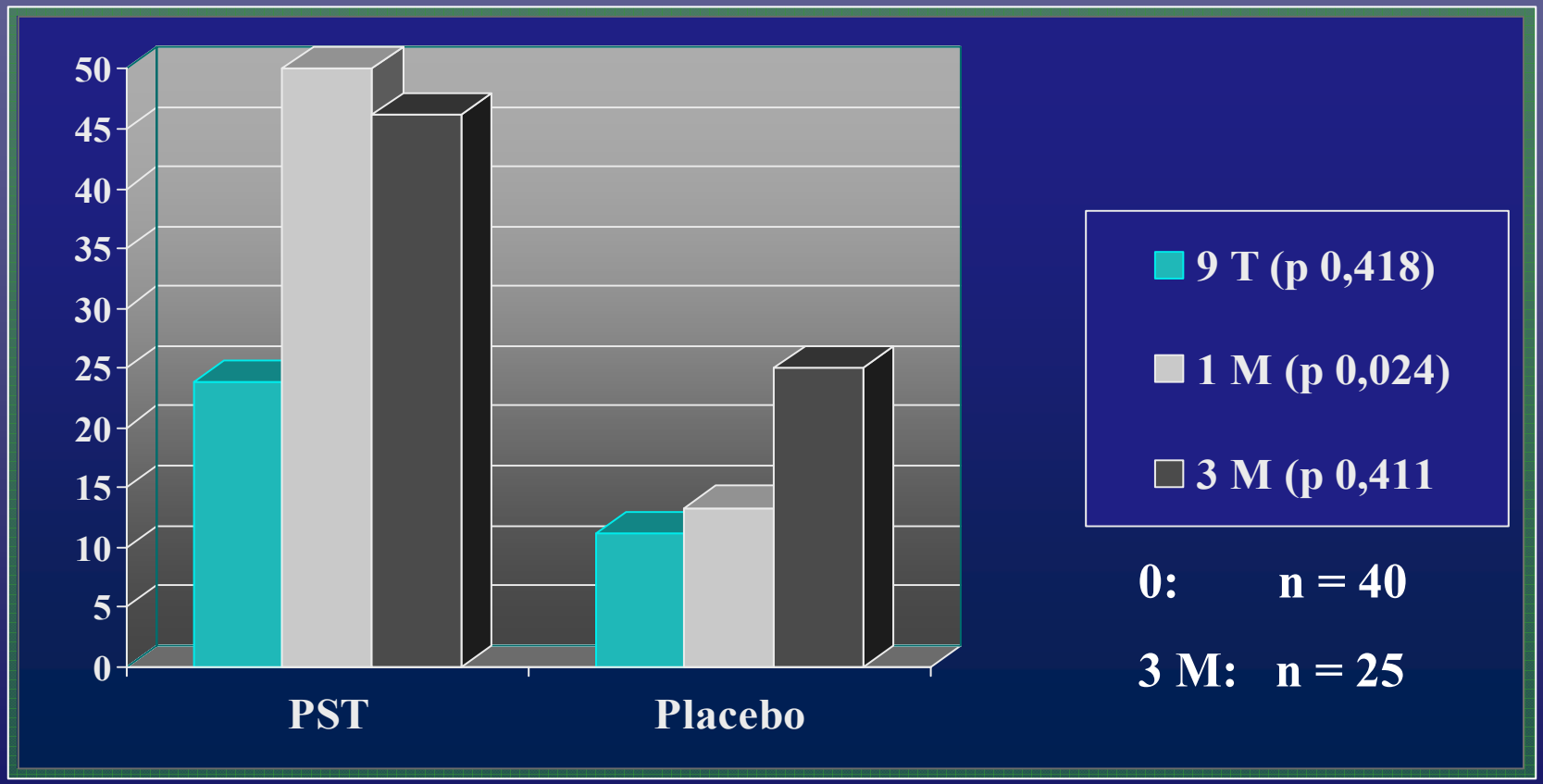
Perrot S, Marty M, Kahan A, Menkès C-J:

Efficacy of Pulsed Electromagnetic Therapy in Painful Knee Osteoarthritis

Arthritis Rheumatology 1998; 41 Suppl: S 357

Double – Blind PST Efficacy Study:

Responders: 30% Improvement VAS and Lequesne Scores

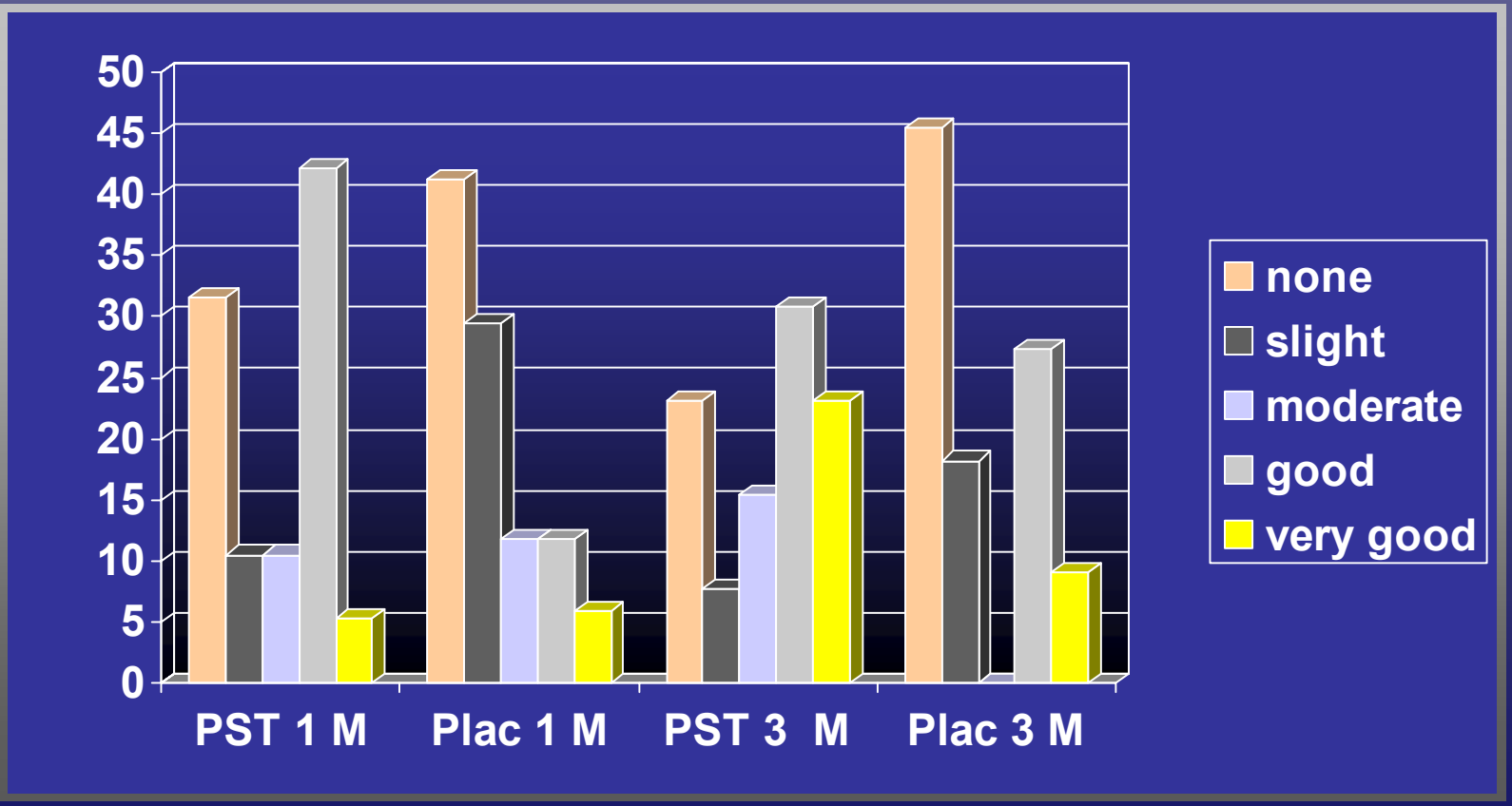


Marty M et al.

Double Blind Study:

Efficacy of PST in Painful Knee Osteoarthritis

Patient Assessment of Overall Improvement (p = 0,41)



Marty M et al.

Clinical Studies: Prospektive, Controlled:

- Leuci C, Sias N, Cossu M: Impiego della terapia a Segnale Pulsante (PST) nell`artrosi della mano. The use of Pulsed Signal Therapy (PST) in the treatment of arthritis of the hand. La Riabilitazione 2000; 33: 109-114
- Cossu M, Portale N: La PST (Terapia a Segnale Pulsante): proposta di condroprotezione con metodiche fisiche. (PST (Pulsed Signal Therapy): a proposal for a chondro-protection with physical methods). La Riabilitazione 1998;31:51-9
- V Gumppenberg, Martin H, Faensen M, Breul R: Kann die Pulsierende Signal Therapie (PST) bei arthrosebedingten Beschwerden sinnvoll eingesetzt werden ? Deutscher Orthopädenkongress 1999
- Faensen M, Breul R: Prospektive multizentrische Studie zur Behandlung von Gonarthrosen (Kellgren II und III) mit der Pulsierenden – Signal - Therapie. Orthopädische Praxis 2001; 37: 701- 709

Pulsed – Signal -Therapy in the Treatment of OA of the Knee

Cossu M, Sias N, De Vito G

La Riabilitazione 2001; 34:

Clinic Niguarda Ca`Granda, Milano

Prospective Study:

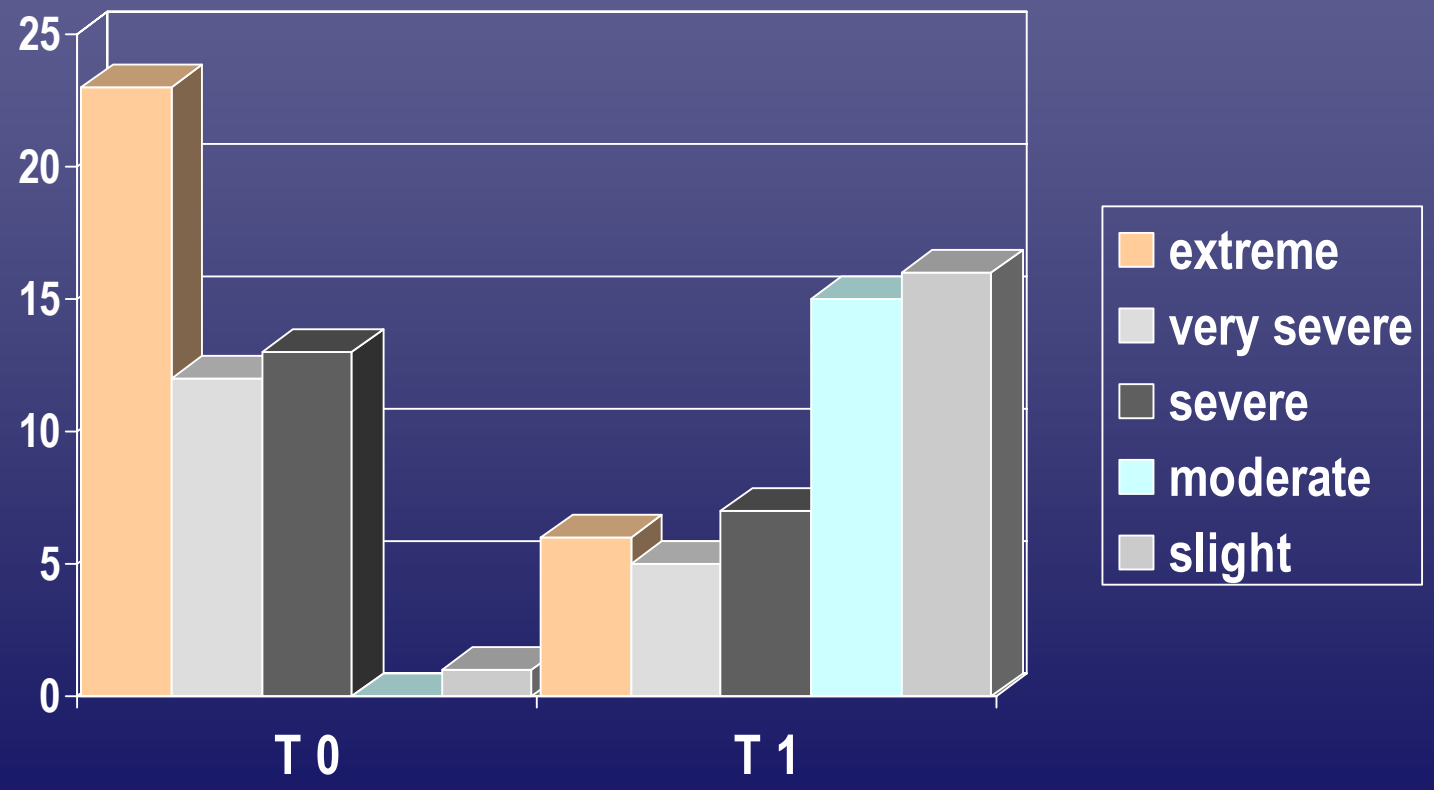
n = 49 (f 39, m 10, age 50 – 89 J Ø 69 J

Follow-up > 6 months

VAS and Lequesne`s algofunctional Index

Results:

Lequesne`s Algofunctional Index



Cossu M, Sias N, De Vitop G

Results:

Pain (VAS)

	moderate	severe	very severe	extreme	Total
No Effect.	1	4	8	1	14
Improvement	0	4	9	4	17
Signif. Impr	0	7	9	2	18
Total	1	15	26	7	49

Cossu M, Sias N, De Vitop G

Pulsed – Signal - Therapy in the Treatment of OA of the Knee

Summary:

Results of 6 - Months Follow - Up

VAS Significant Improvement: 71.4%

Lequesne Algofunctional Index: 87.0%

Cossu M,Sias N, De Vito G

Prospective Multicenter Study of the Treatment of Osteoarthritis of the Knee with Pulsed Signal Therapy (PST)

49 Treatment Centers:

- Patients: 303 (f = 206, m = 97)
- End of Treat. 298 (f = 204, m = 94)
- 6 Wk Follow - up 266 (f = 172, m = 94)
- 6 Mo Follow - up 221 (f = 148, m = 73)

Faensen M, Breul R

PST – Multi Center Study – OA of the Knee

49 Treatment Centers

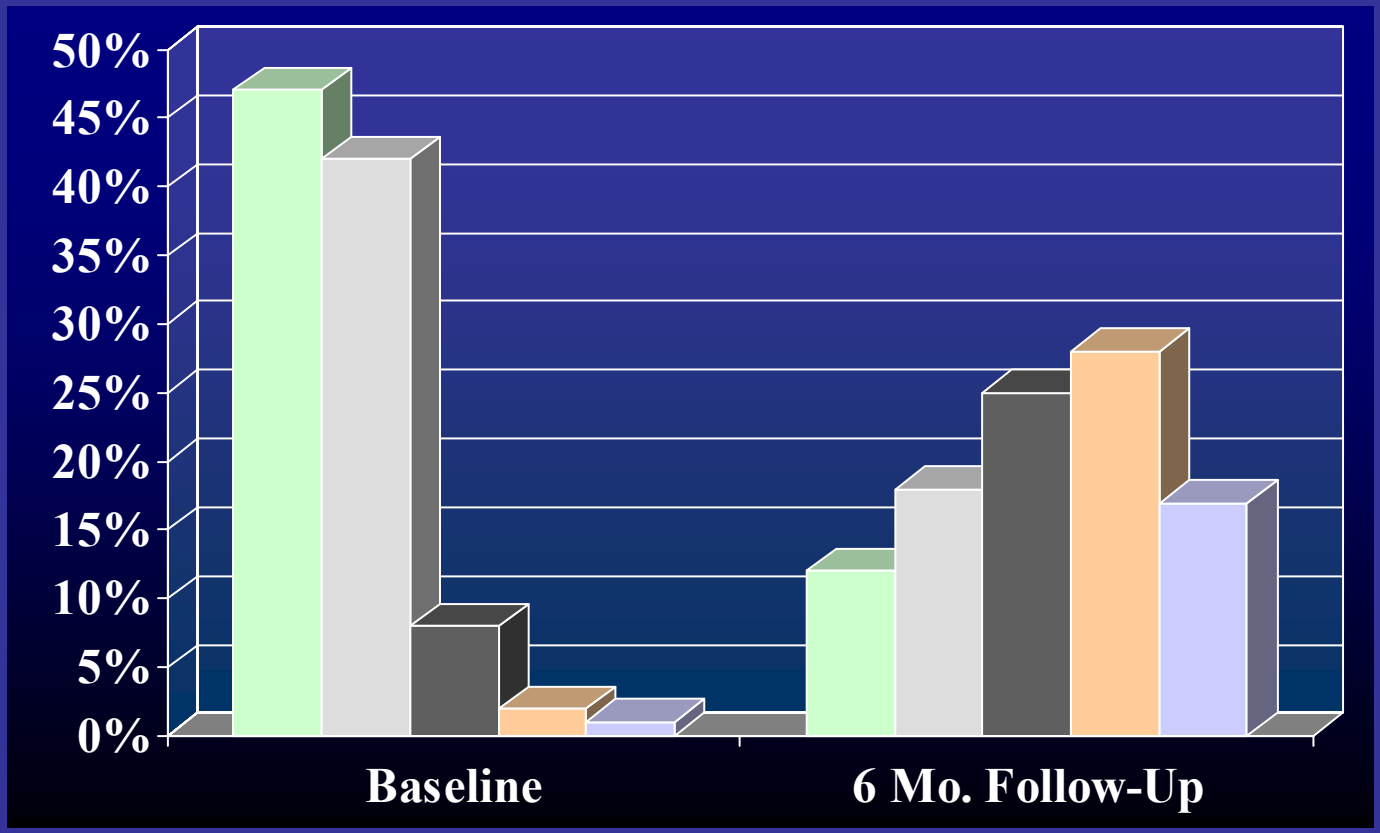
Patient Selection:

- OA of the Knee 2° und 3° Kellgren
- Lequesne`s - Index $\geq$ 10
- Symptoms of at least 1 Yr Duration
- At least 4 cm VAS Assessment for Severity of Pain
- At least 30 Yr of Age
- No Rheumatoid Arthritis

Faensen M, Breul, R

PST Multi – Center – Study: Knee OA

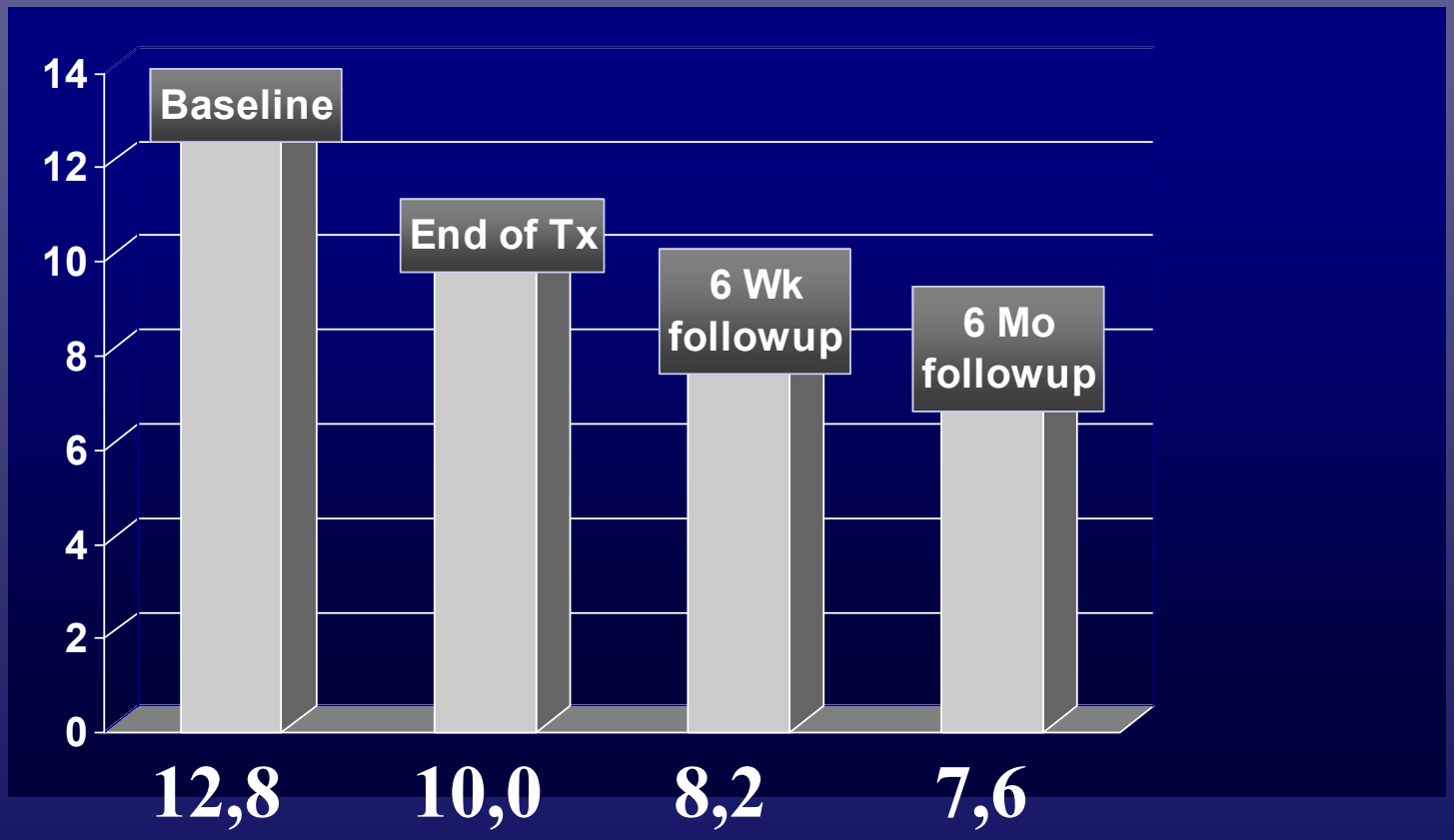
Lequesne´s Algofunctional Index



Faensen M, Breul R

PST – Prospektive Multi – Center - Study OA of the Knee

Lequesne´s algofunctional index



Faensen M, Breul R

PST – Multi – Center – Study Osteoarthrosis of the Knee

Summary:

- Significant improvement (> 60%) in over 70% of Patients.
- Improvement Followed and Maintained > 6 Mo. Ergo, No Placebo Effects.
- Extremely Significant P Value 0,0001 – Lequesne Scores.

Faensen M , Breul R.

Benson K, Hartz A J:

A Comparison of Observational Studies and Randomized Contolled Trials

Conclusions:

We found little evidence that estimates of treatment effects in observational studies … are either consistently larger than, or qualitatively different from, those obtained in randomized, controlled trials.

N Engl J Med 2000; 342: 1878-86

PST
Conclusions:

- The Mechanism of Action is an accepted biophysical concept.
- In vitro Studies are supporting this Theory
- Clinical studies are confirming the Efficacy without Side Effects