Shockwave Biology

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Agenda

1. What is a shockwave

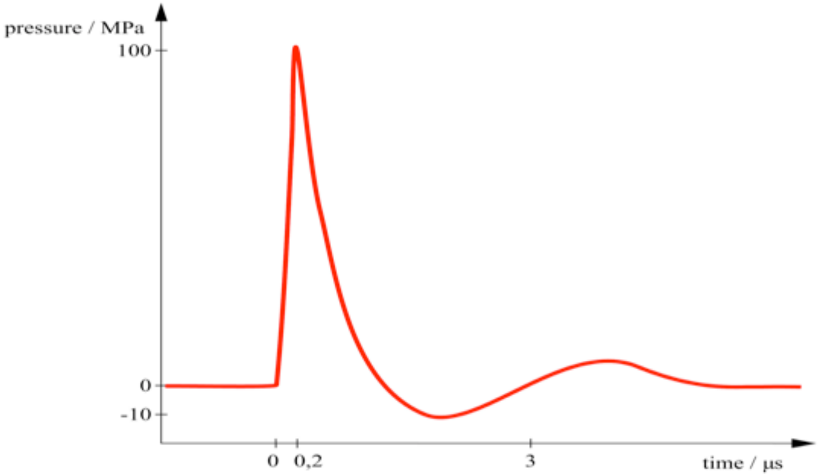
2. Shockwave effects on
   - Vascular Endothelium
   - Stem cells
   - Nerve cells
   - Immune cells

3. Clinical indications

SHOCKWAVES

A Typical Shockwave:

Shockwaves are very short pressure pulses/ acoustic waves, with
Fast rise time: 10-100 ns
High over-pressure: 150MPa for lithotripsy; 5-20MPa for Li-ESWT
Negative pressure phase

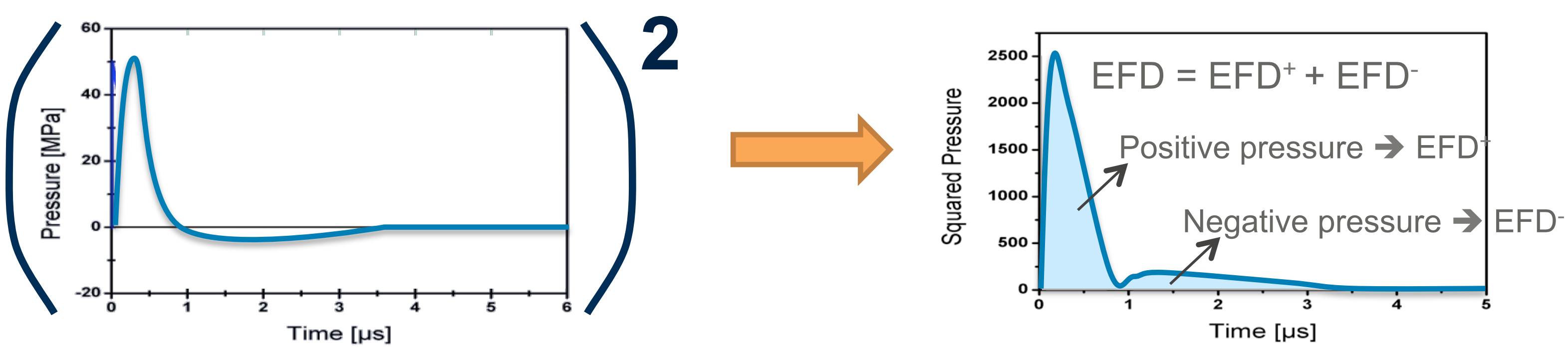


ISMST冲击波物理学基础 https://www.shockwavetherapy.org/about-eswt/physical-principles-of-eswt/

Energy Flux Density

Energy Flux Density (EFD) is the energy related to the pressure pulse **passing through a point** at coordinate (x, y, z).

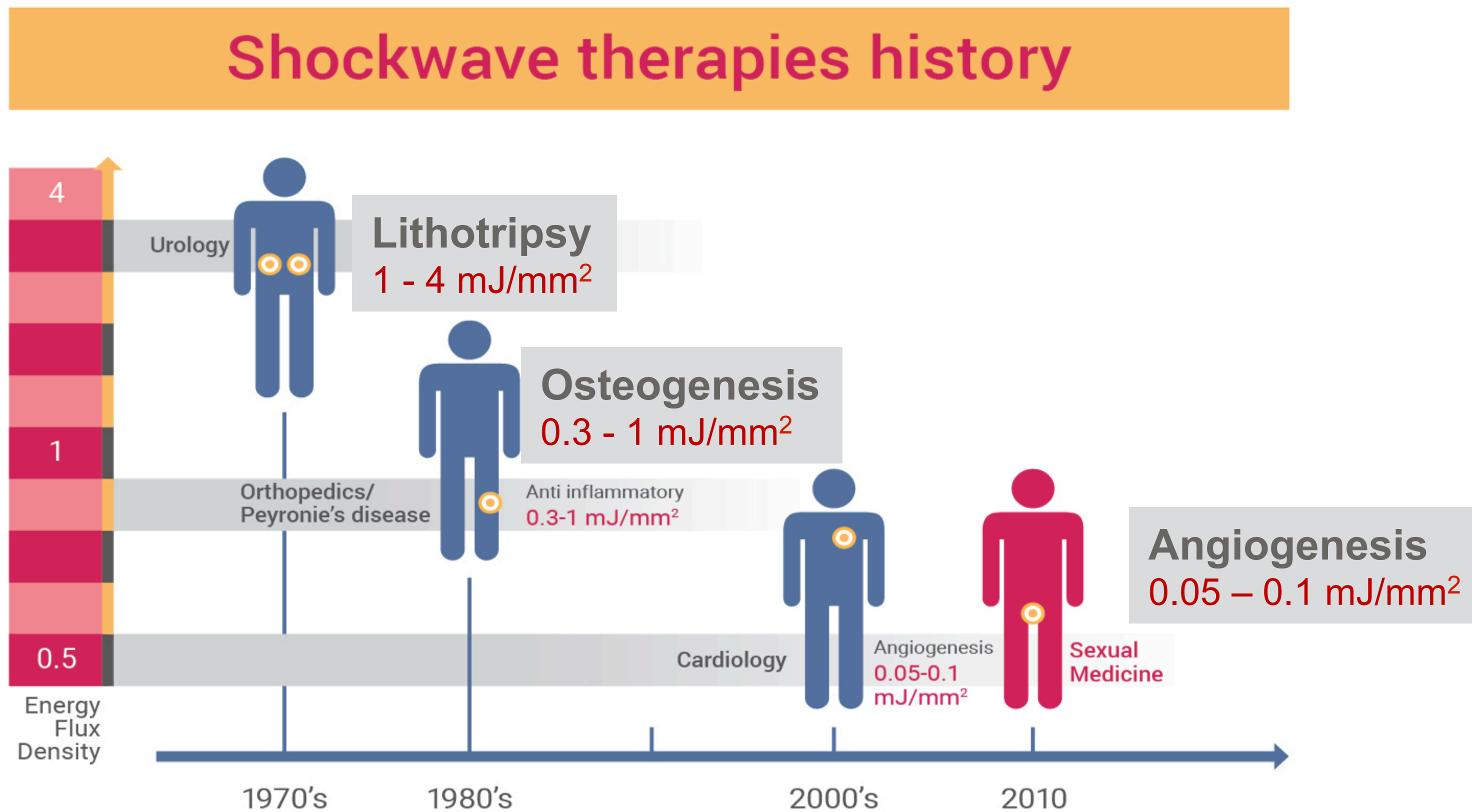
The measured pressure pulse p(t) is squared and integrated over time. The area under the squared pressure curve corresponds to Energy Flux Density:



$$EFD = \frac{1}{Z}\int_t p^2(t)dt \qquad Z = \rho \cdot c$$

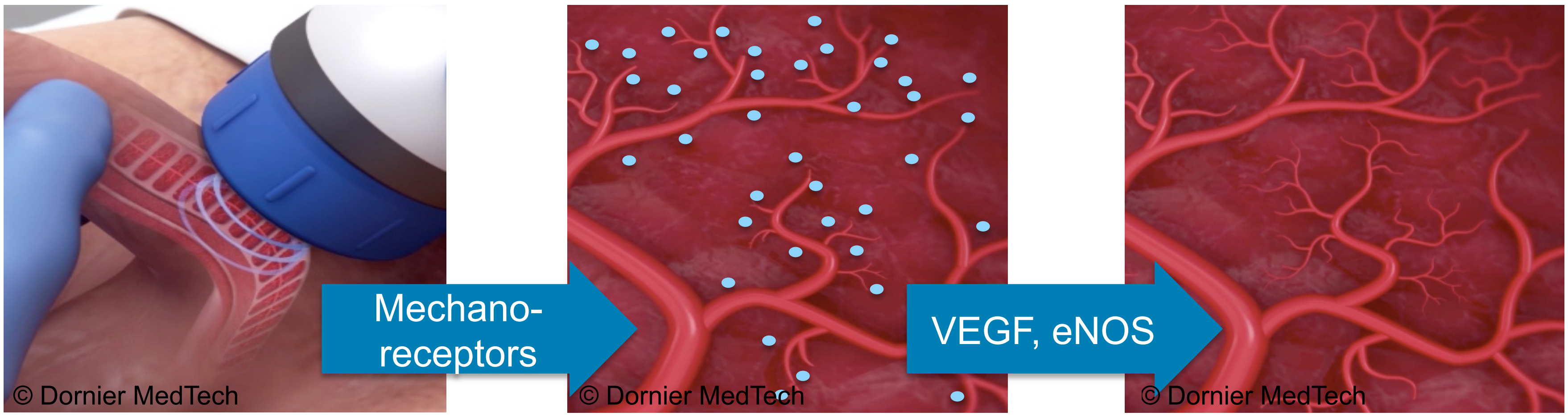
c Speed of sound

ρ Density of the medium


Shockwave therapies history
4
1
0.5
Energy Flux Density
Urology
Lithotripsy
1 - 4 mJ/mm²
Osteogenesis
0.3 - 1 mJ/mm²
Orthopedics/ Peyronie's disease
Anti inflammatory
0.3-1 mJ/mm²
Cardiology
Angiogenesis
0.05-0.1 mJ/mm²
Sexual Medicine
Angiogenesis
0.05 – 0.1 mJ/mm²
1970's
1980's
2000's
2010

Low-intensity Shockwaves for Tissue Healing

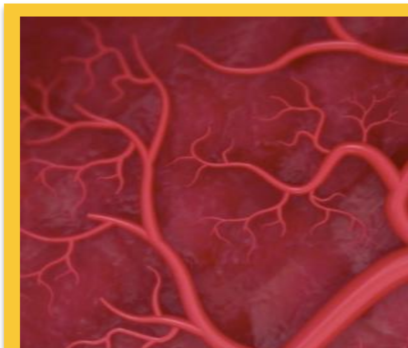
Mechanism: cell activation and growth factor release



Shockwave energy | Growth factors | Angiogenesis

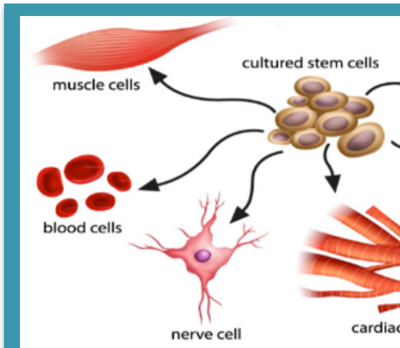
Hatanaka et al. Am J Physiol Cell Physiol. 2016 Sep 1;311(3):C378-85.

ESWT activates multiple cell types



1

Vascular Healing & Angiogenesis



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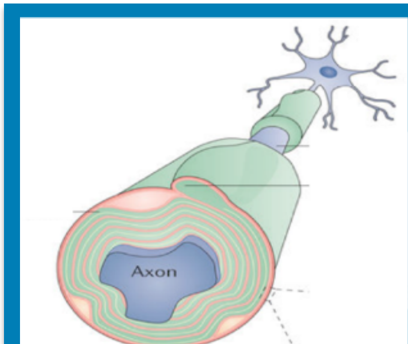
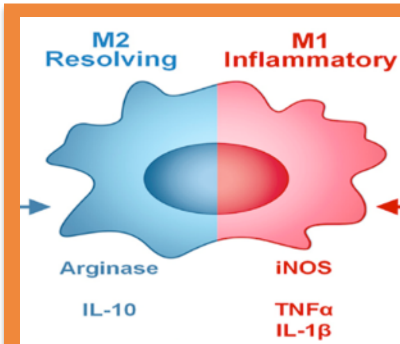
Stem cell Recruitment & Activation



3

Nerve cell Activation & Repair



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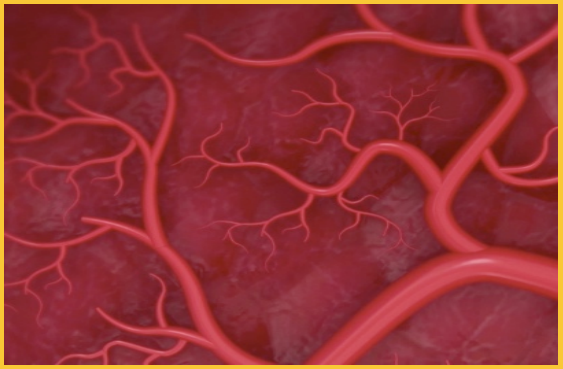
Immune Regulation

Dornier MedTech

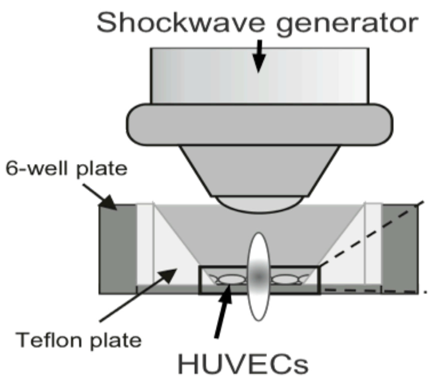


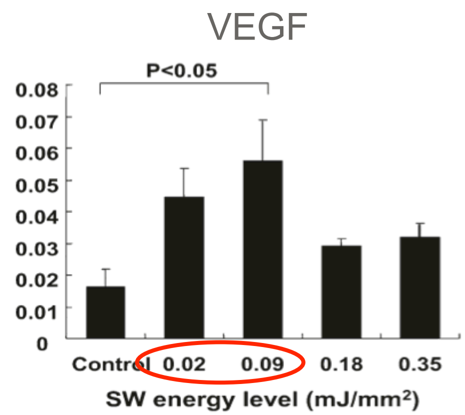
1. Vascular Healing & Angiogenesis

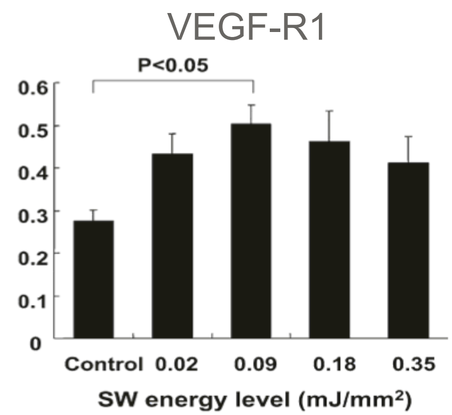
Shockwaves heal and regenerate endothelium

Shockwaves stimulate VEGF production

Very low energies (0.02 mJ/mm²) can activate angiogenesis



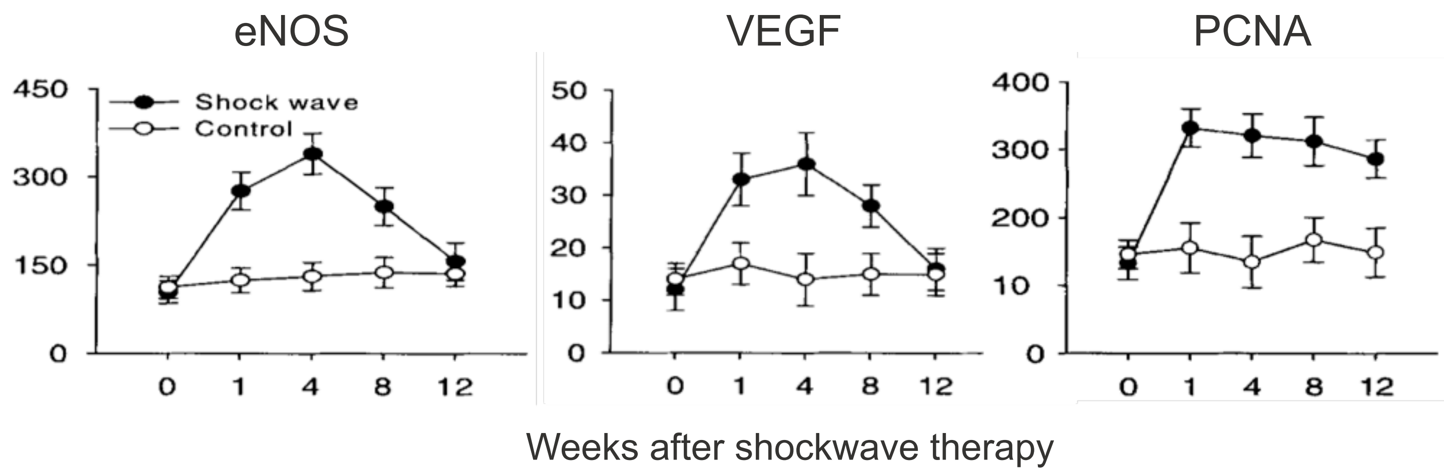




500 SWs at different ED were applied to HUVEC cells. VEGF and Flt-1 mRNA were analyzed 24h after treatment.

Nishida et al. Circulation. 2004;110:3055-3061.

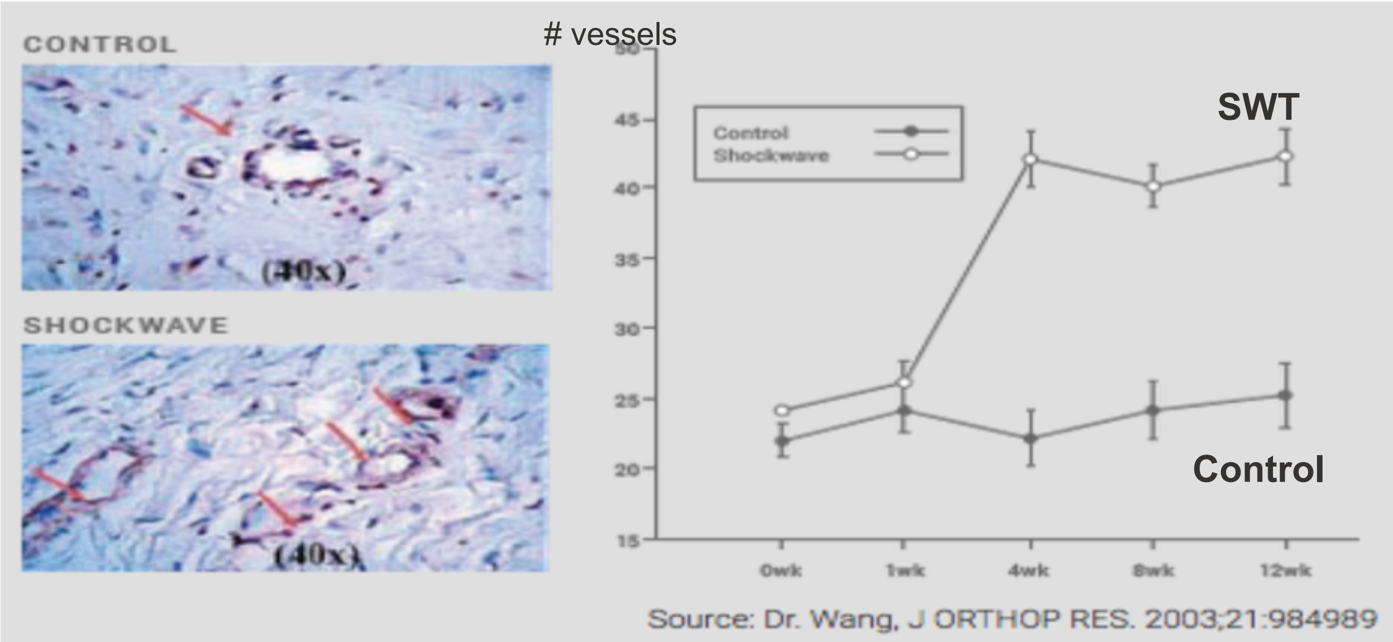
Shockwaves stimulate VEGF production *in vivo*



500SW @ 0.12mJ/mm^2 delivered to right Achilles tendon near insertion site at d0 (fluoroscopic verification; NZ white rabbit). Tendons were dissected and examined at different time points.

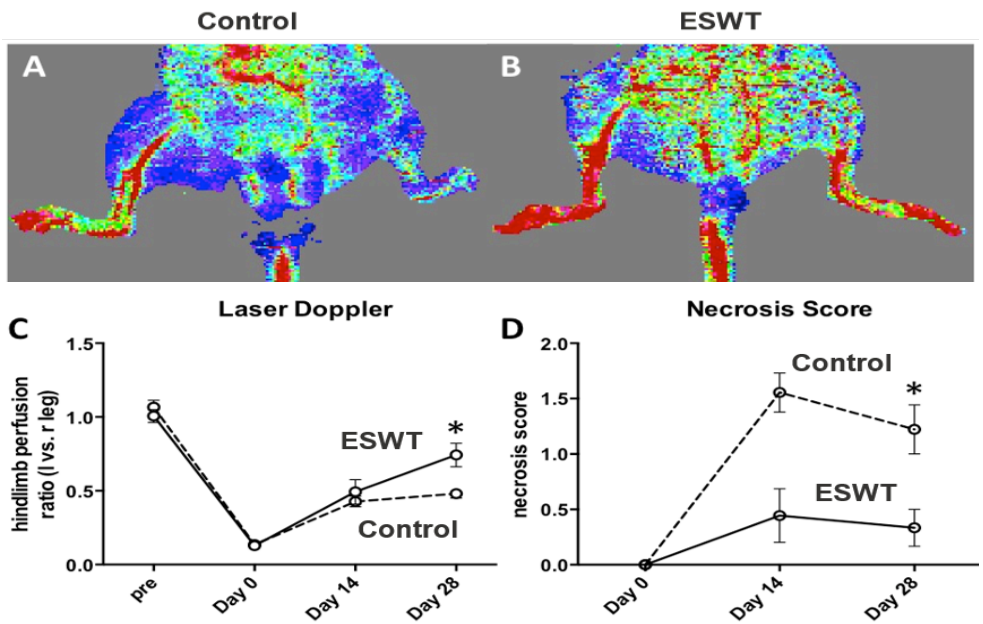
Wang et al. J Orthop Research 2003 (21): 984-89.

SWT: Tendon neovascularization

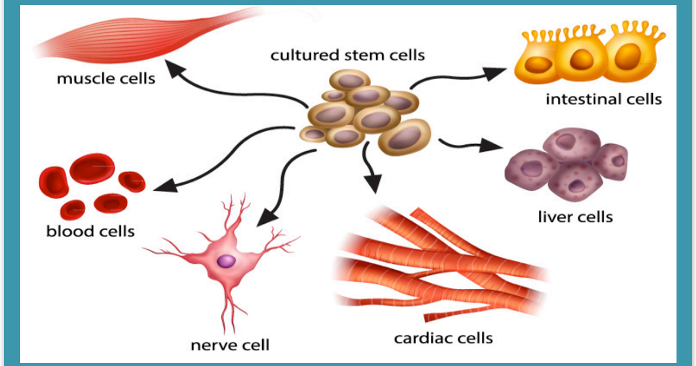


500SW @ 0.12mJ/mm^2 delivered to right Achilles tendon near insertion site at d0 (fluoroscopic verification; NZ white rabbit). Tendons were dissected and examined at different time points.

SWT: Functional angiogenesis



A section of the left femoral artery was ligated and excised (C57/BL6 mice). 300SW @ 0.1mJ/mm² delivered to injury site immediately after surgery. Blood flow was measured by laser Doppler. Necrosis score was assigned at 14d and 28d. 0 – no necrosis; 1 – skin necrosis; 2 – below ankle amputation; 3 – above ankle amputation.

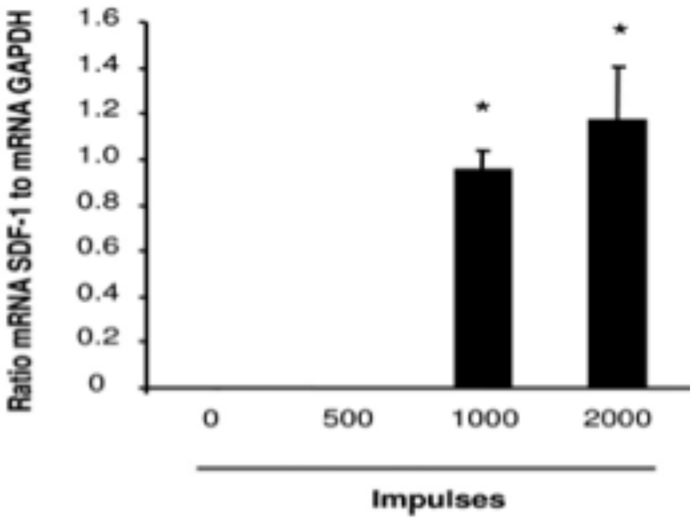


2. Stem cell recruitment and activation

Shockwaves recruit and activate stem cells

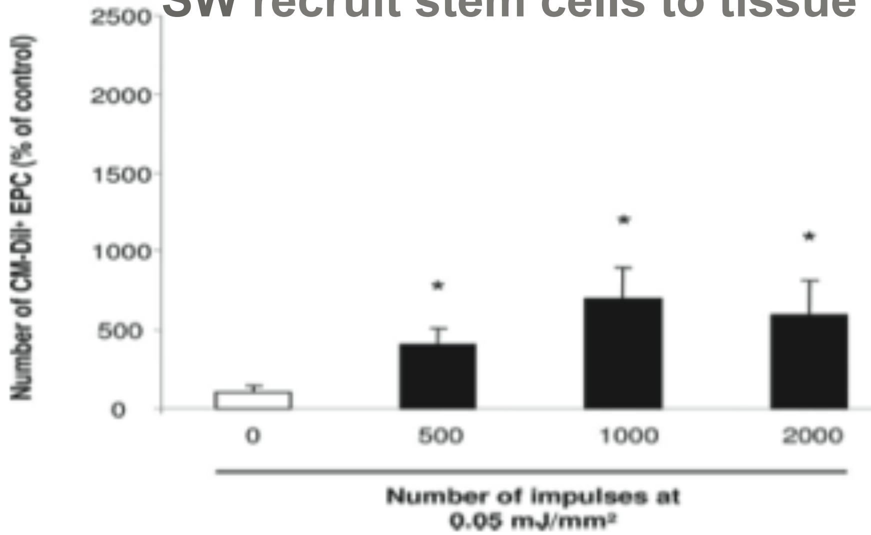
Shockwaves recruit stem cells

SW → stem cell chemo-attractant



Healthy nude rats were treated with SW @ 0.05 mJ/mm^2 (Dornier Biotripter, focused on adductor muscle). 24hr after SWT, the muscle was harvested and SDF-1 expression was quantified by rtPCR.

SW recruit stem cells to tissue

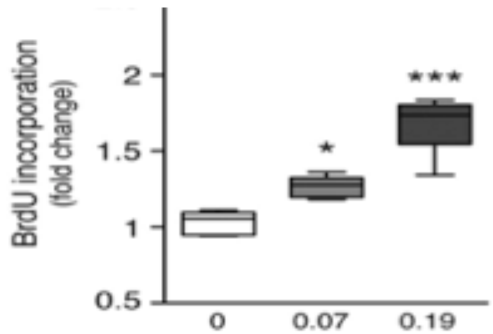


Healthy nude rats were treated with SW @ 0.05 mJ/mm^2 (Dornier Biotripter, focused on adductor muscle). 24hr after SWT, 10^6 human endothelial progenitor cells were injected i.v. Muscle harvest and histology was performed 24hr after.

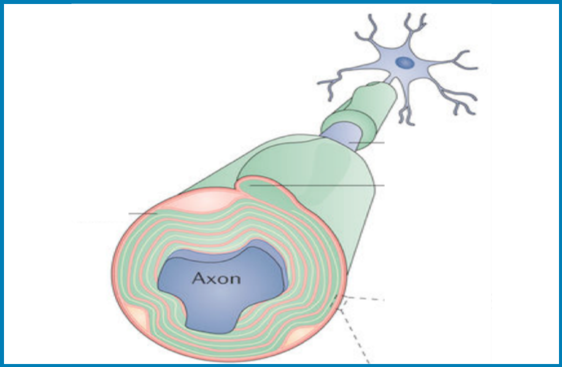
Aicher et al. Circulation. 2006 Dec 19;114(25):2823-30.

Shockwaves stimulate stem cell proliferation

SW increase stem cell proliferation



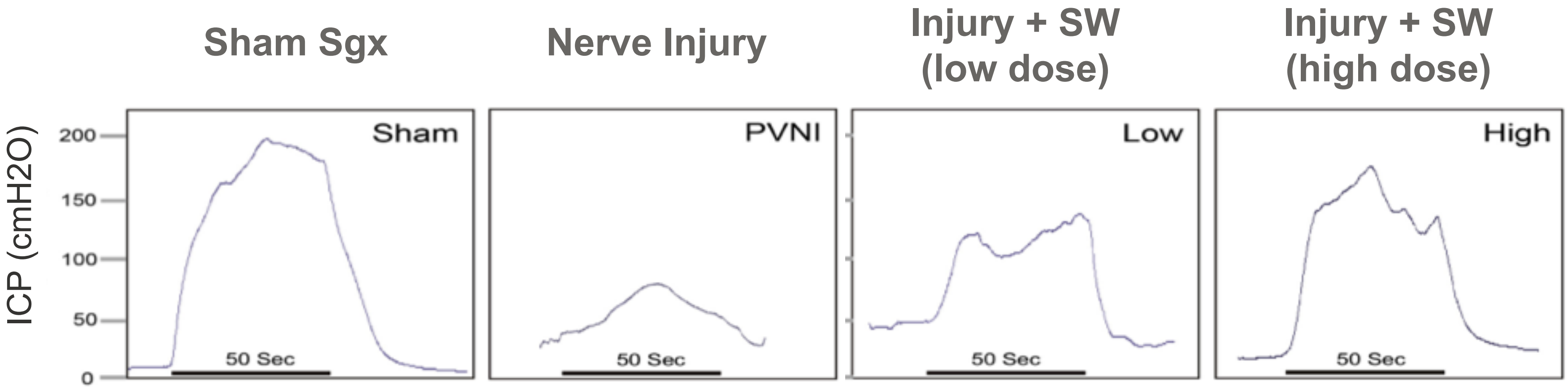
C3H10T1/2 mouse mesenchymal stem cells, 100 SW at each energy level



3. Nerve cell Activation & Repair

Shockwaves stimulate nerve repair

SW restores Erectile Function after Nerve Injury

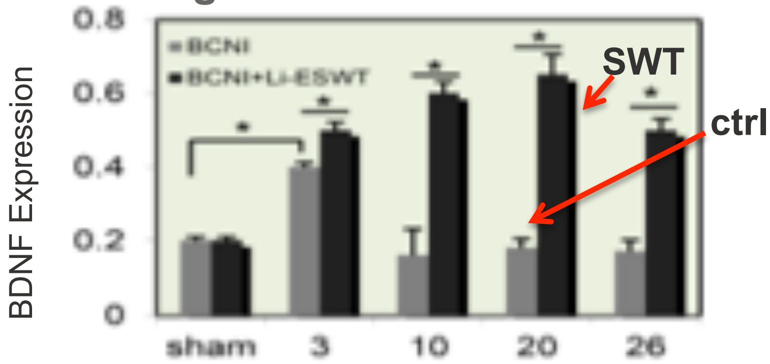


Sprague Dawley rats underwent bilateral cavernosal nerve crush injury and suture ligation of the internal pudendal bundle, then treated with 300 SW @ 0.06 mJ/mm^2 (low dose), or 1000 SW @ 0.06 mJ/mm^2 (high dose), from 48hr after surgery. Intracavernous pressure (ICP) test was used to evaluate erectile function 5 weeks after injury.

Li et al. J Sex Med. 2016 Jan;13(1):22-32.

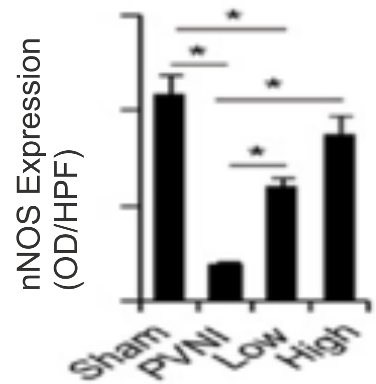
SW → Nerve Growth signals

SW increases neuronal growth factor release



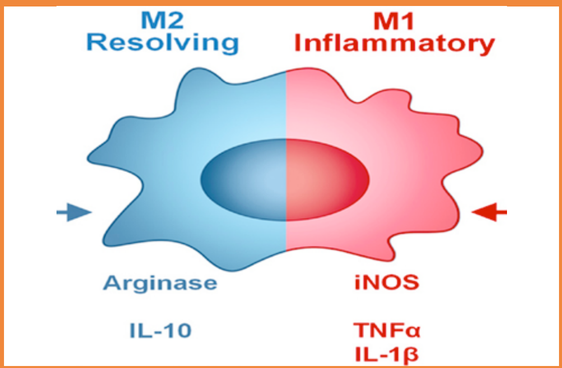
Sprague Dawley rats underwent bilateral cavernosal nerve crush injury, then treated with 500 SW @ 0.06 mJ/mm^2, twice/week, from 48hr after surgery. Penile BDNF expression was quantified by rtPCR, 3, 10, 20 or 26 days after surgery.

SW maintains number of nNOS+ nerves



Sprague Dawley rats underwent bilateral cavernosal nerve crush injury and suture ligation of the internal pudendal bundle, then treated with 300 SW @ 0.06 mJ/mm^2 (low dose), or 1000 SW @ 0.06 mJ/mm^2 (high dose), from 48hr after surgery. nNOS expression was quantified by IF (Image-Plus 5.1).

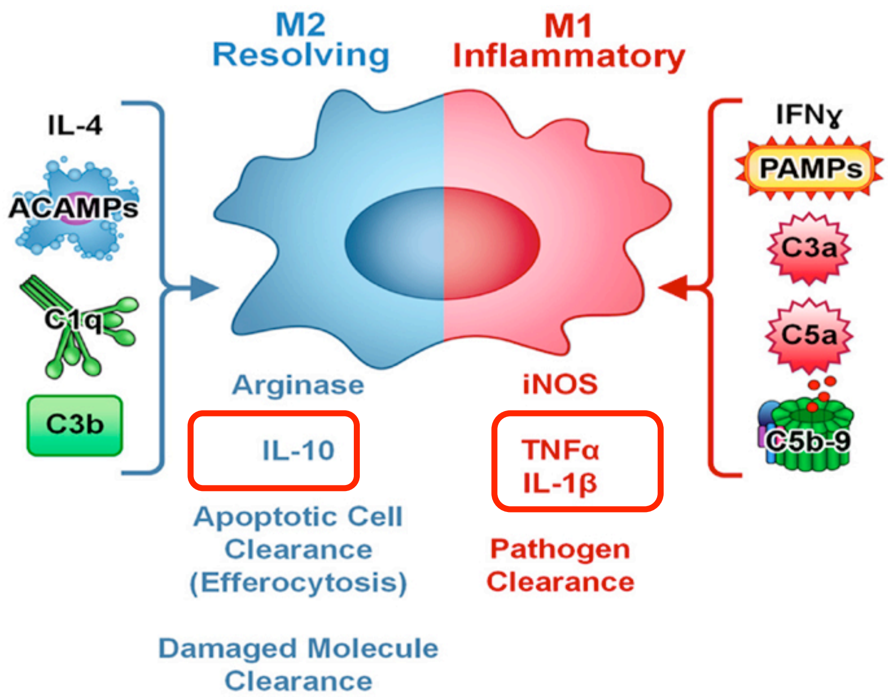
Wang et al. Int J Mol Sci. 2017 Feb 16;18(2). pii: E433
Li et al. J Sex Med. 2016 Jan;13(1):22-32.



4. Immune Regulation

Shockwaves reduce inflammation

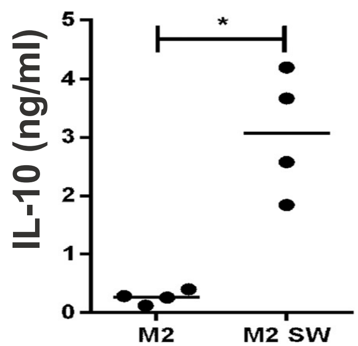
"Wound-healing" vs "Inflammatory" Macrophages



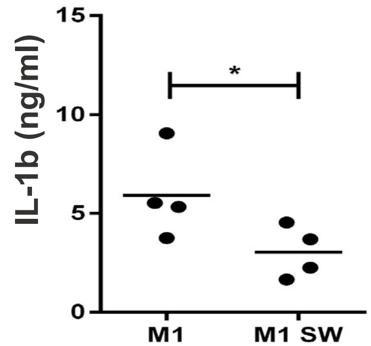
Front Immunol. 2014 Aug 21;5:402.

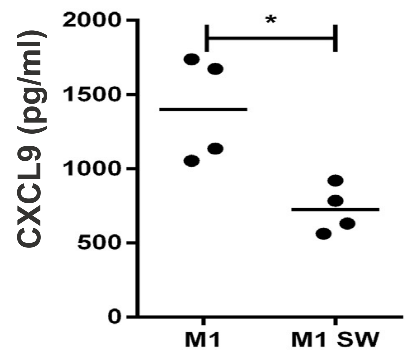
SW enhances "wound-healing" phenotype

SW increases anti-inflammatory signals from M2 macrophages



SW decreases pro-inflammatory signals from M1 macrophages



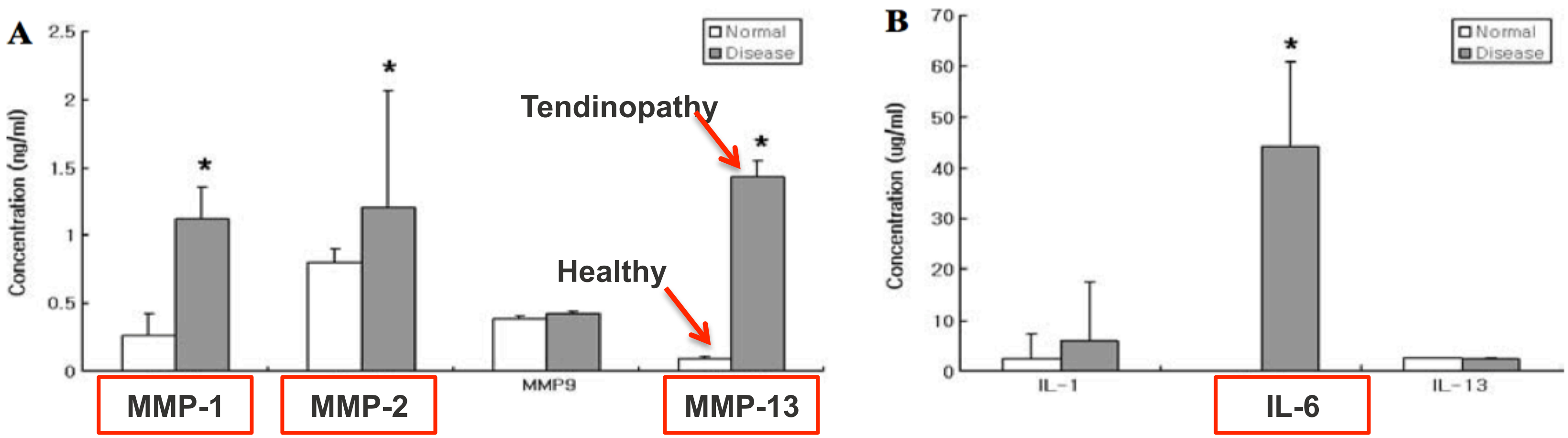


In vitro macrophages were polarized into the M1 (LPS+IFN-g) or M2 (IL-4) phenotype, and exposed to 400 SW @ 0.03 mJ/mm^2. Cytokines released into the supernatant were quantified by ELISA.

Sukubo et al. Int J Surg. 2015 Dec;24(Pt B):124-30.

Increased inflammatory signals in Tendinopathy

Increased MMP-1, MMP-2, MMP-13 and IL-6 in diseased Achilles tendons

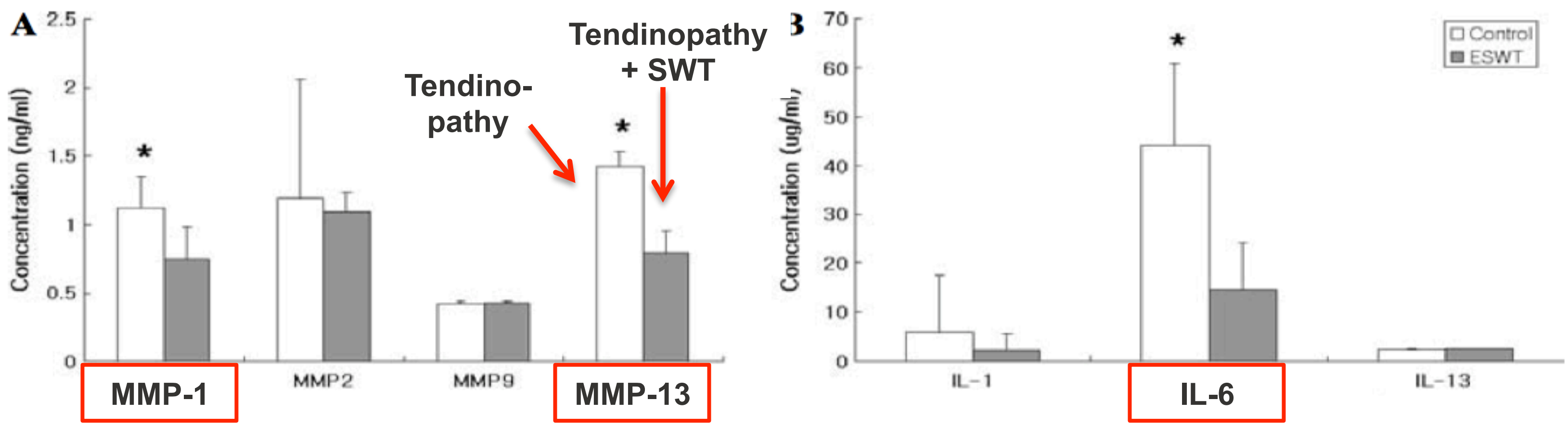


Human diseased Achilles tendon and normal flexor hallucis longus tendon were surgically obtained. Tenocytes were cultured for 10-14 days, then trypsinized and re-plated (no SW exposure). Media was collected 72h after, and cytokines were quantified by ELISA.

Han et al. Foot Ankle Int. 2009 Feb;30(2):93-8.

SW reduce inflammatory signals

Decreased MMP-1, MMP-13 and IL-6 after shockwave therapy



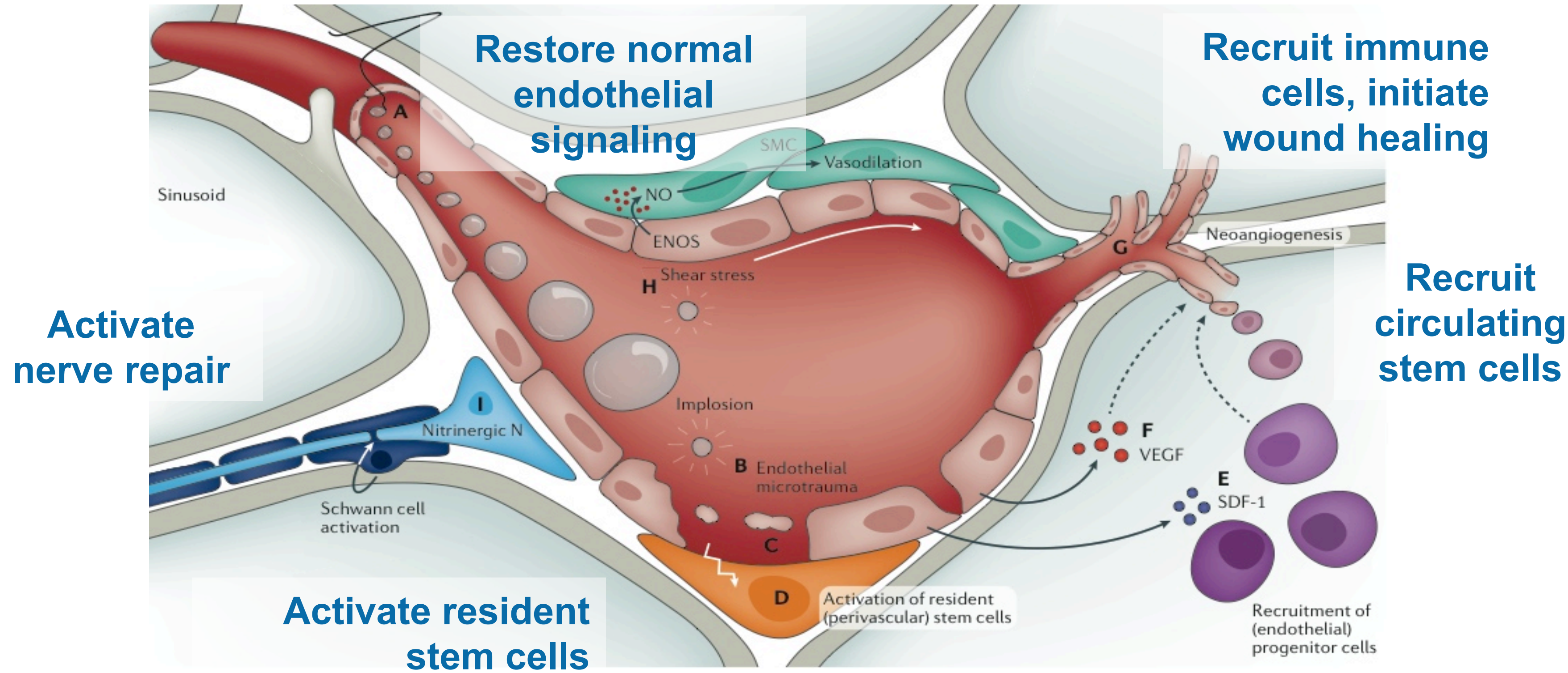
Human diseased Achilles tendon was surgically obtained. Tenocytes were cultured for 10-14 days, then exposed to SW @ 0.17 mJ/mm^2. Media was collected 72h after SW exposure, and cytokines were quantified by ELISA.

Han et al. Foot Ankle Int. 2009 Feb;30(2):93-8.

Multiple Cellular Responses to Shockwaves

Mediator	Signaling	Clinical effect	References
Erk 1/2, Akt, nitric oxide synthase	• Vasodilation • **Angiogenesis** • **Anti-atherogenesis** • **Immune-suppression**	• Increased vascularity • Wound healing • Immune regulation	Ha et al. Int J Cardiol. 2013 Oct 9;168(4):4168-77
VEGF, VEGF-R	• Angiogenesis	• Increased vascularity	Nishida et al. Circulation. 2004;110:3055-3061.
Extracellular ATP, Erk 1/2, MAPK	• Cell division • **Stem cell activation**	• Wound healing	Weihs et al. J Biol Chem. 2014 Sep 26;289(39):27090-104
Extracellular RNA + LL37 anti-microbial peptide	• TLR3 signaling?	• Wound healing	Holfeld et al. 1) J Cell Mol Med. 2017 Apr; 21(4): 791–801. 2) Inflammation. 2014 Feb;37(1):65-70
PERK, eIF2a, ATF4	• ER stress pathway • **Cell growth/ survival**	• Nerve healing	Wang et al. Int J Mol Sci. 2017 Feb 16;18(2). pii: E433
Stem cell derived factor-1 (SDF-1)	• Stem cell recruitment	• Increased vascularity • Wound healing	Aicher et al. Circulation. 2006 Dec 19;114(25):2823-30

Summary: Tissue Response to Shockwaves

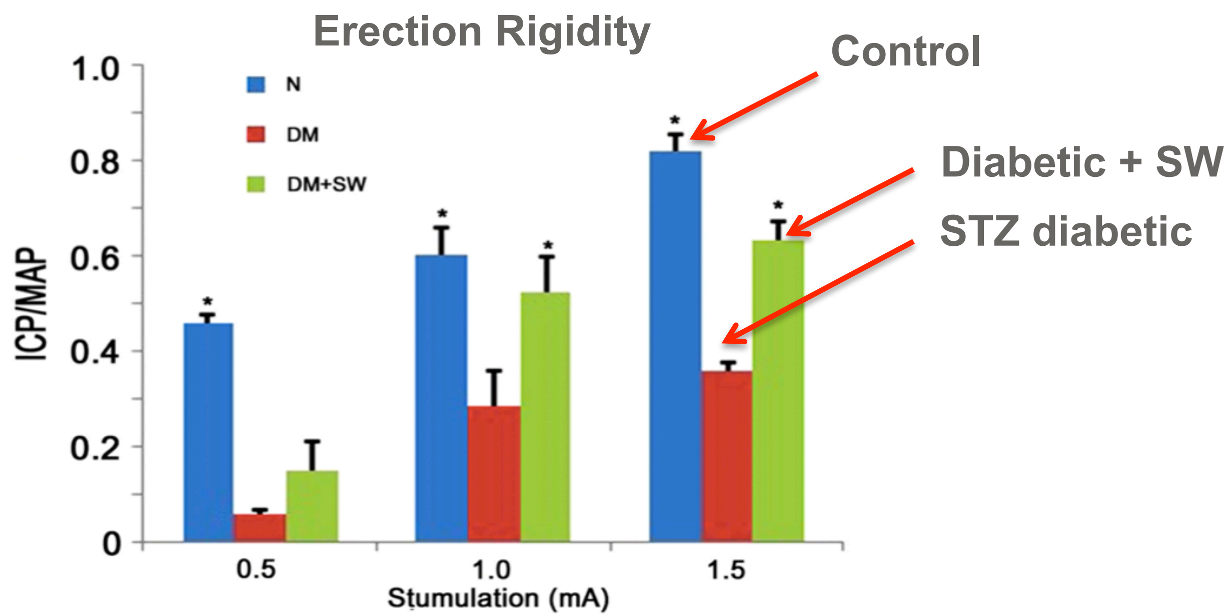


Fode et al. Nat Rev Urol. 2017 Jul 25.

Dornier MedTech

ESWT for Erectile Dysfunction

SWT improves ED in STZ Diabetic Rat model

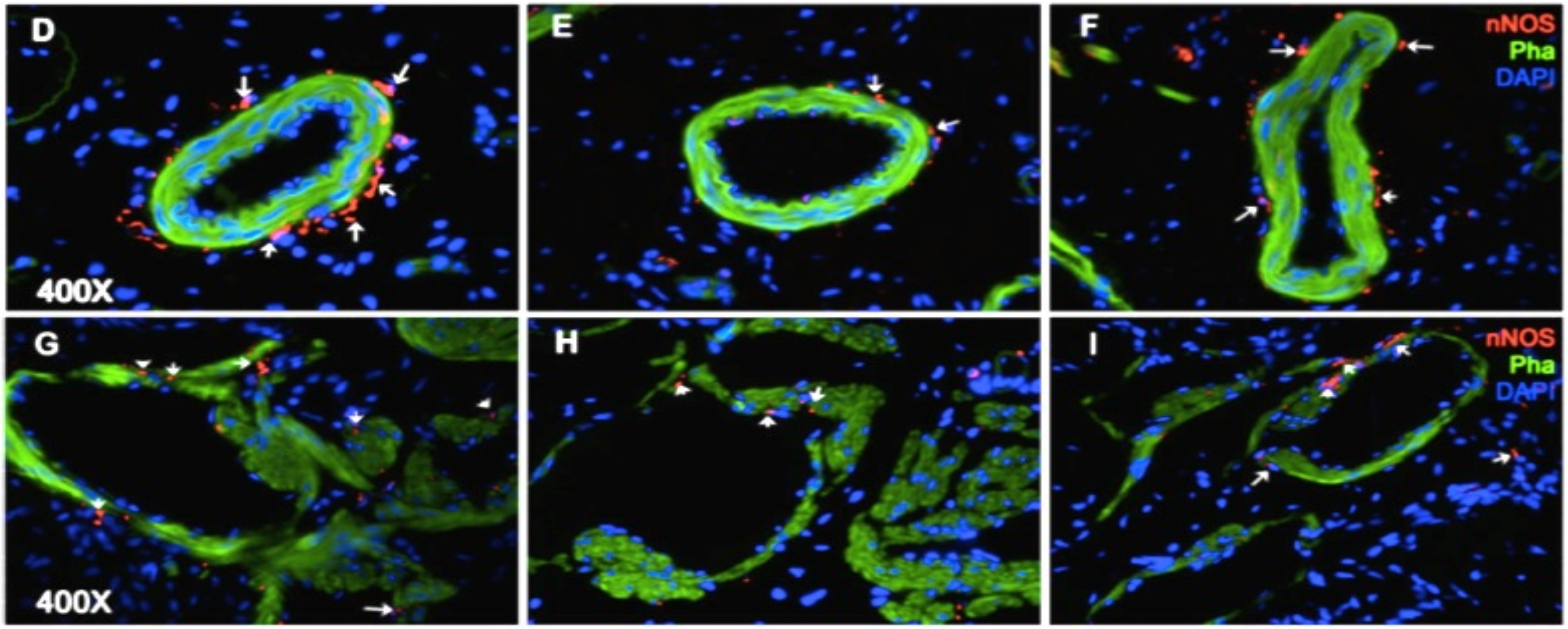


8wo Sprague Dawley rats were injected with i.p. streptozocin (STZ) 60mg/kg. Rats with fasting blood glucose >200mg/dl, were treated 4wk after with 300 SW @ 0.1 mJ/mm^2, 3x/week for 2 wk. Erectile function was tested 2wk after final SWT session, and the penis harvested for histology.

SWT increases number of nNOS+ nerves

nNOS
Pha
DAPI

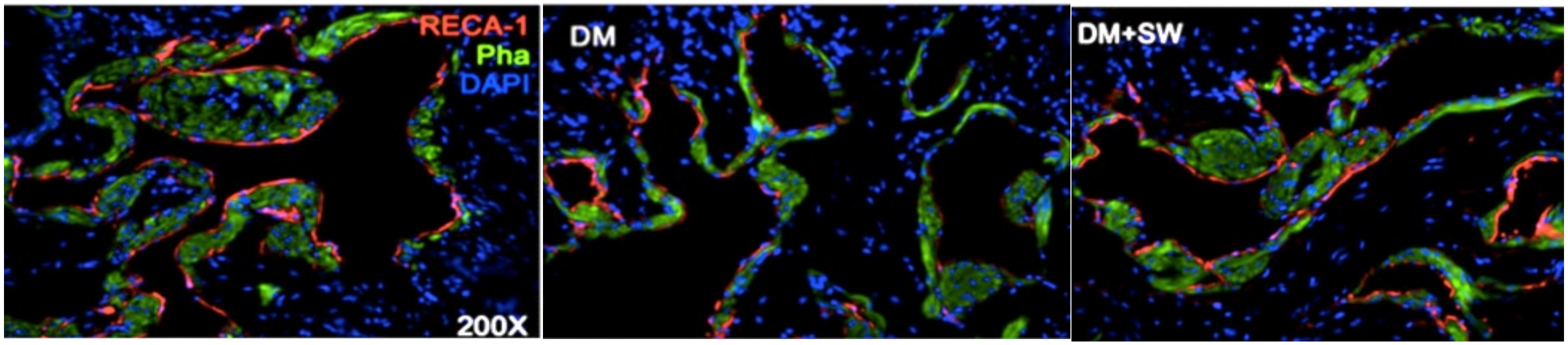
Control **STZ diabetic** **Diabetic + SW**



Qiu et al. J Sex Med. 2013 Mar;10(3):738–746.

SWT increases number of endothelial cells

Control | STZ diabetic | Diabetic + SW

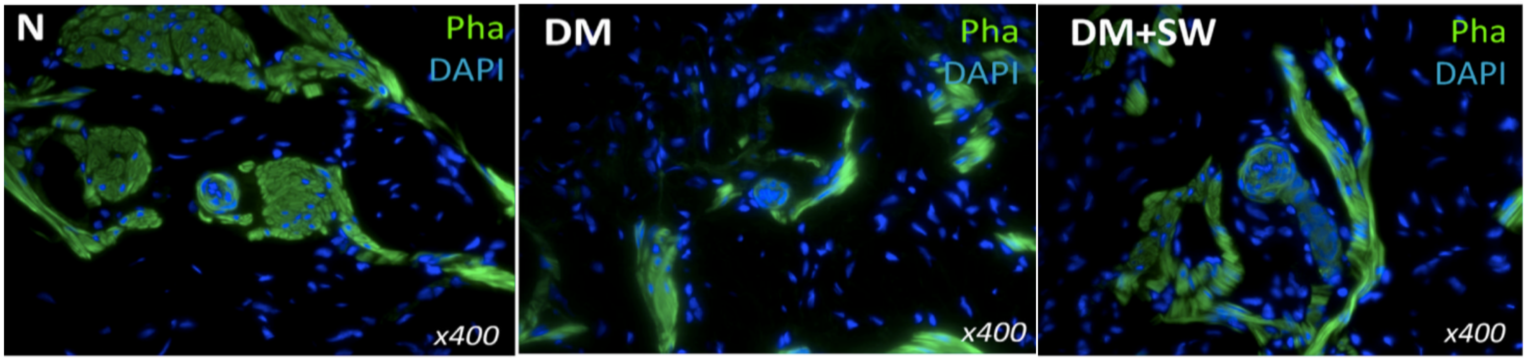


RECA-1 (rat endothelial cell antigen)
Pha
DAPI

Qiu et al. J Sex Med. 2013 Mar;10(3):738–746.

SWT increases number of smooth muscle cells

Control | STZ diabetic | Diabetic + SW

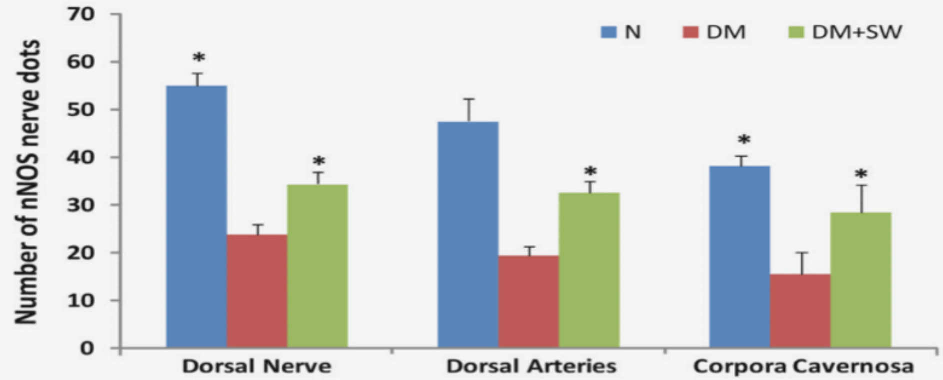


Pha
DAPI

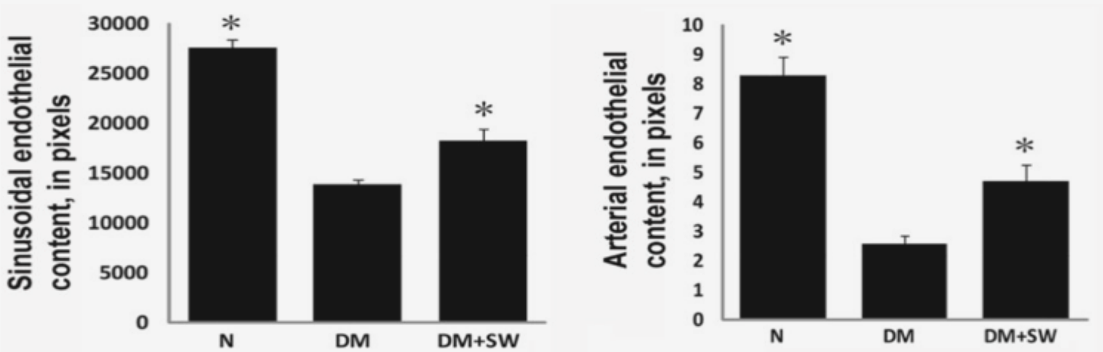
Dornier MedTech

Qiu et al. J Sex Med. 2013 Mar;10(3):738–746.

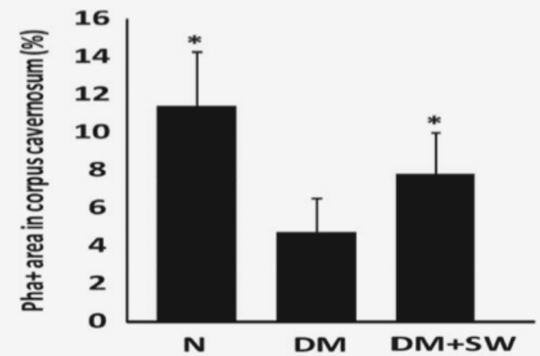
Nerves (nNOS)



Endothelial cells (RECA-1)



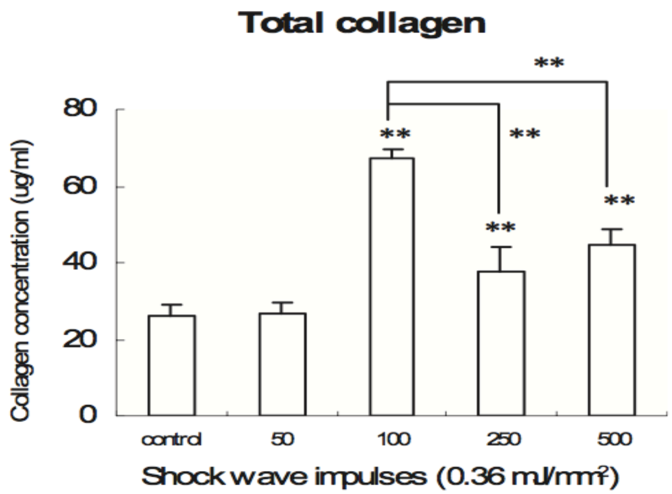
Smooth mm (Pha)

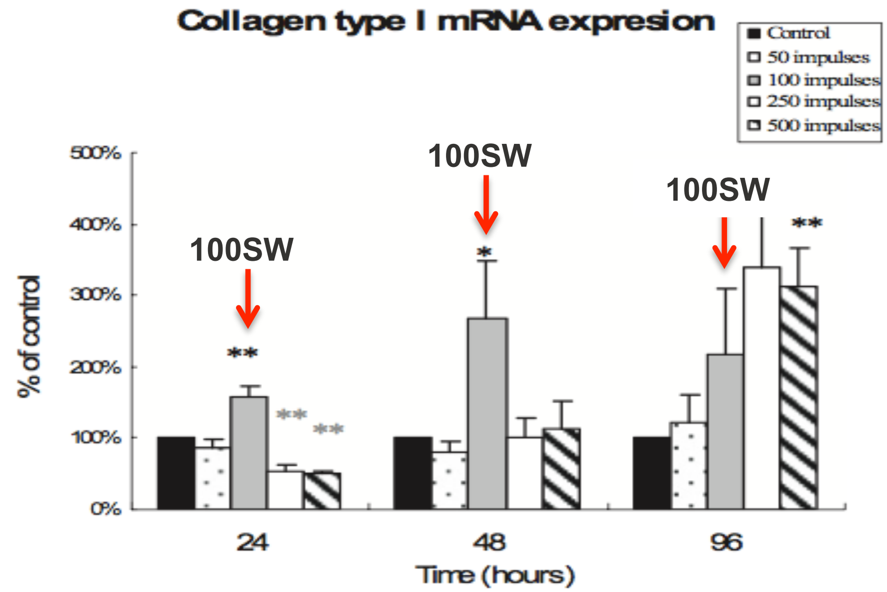


Qiu et al. J Sex Med. 2013 Mar;10(3):738–746.

ESWT for Tendinopathy

Shockwaves promote collagen synthesis

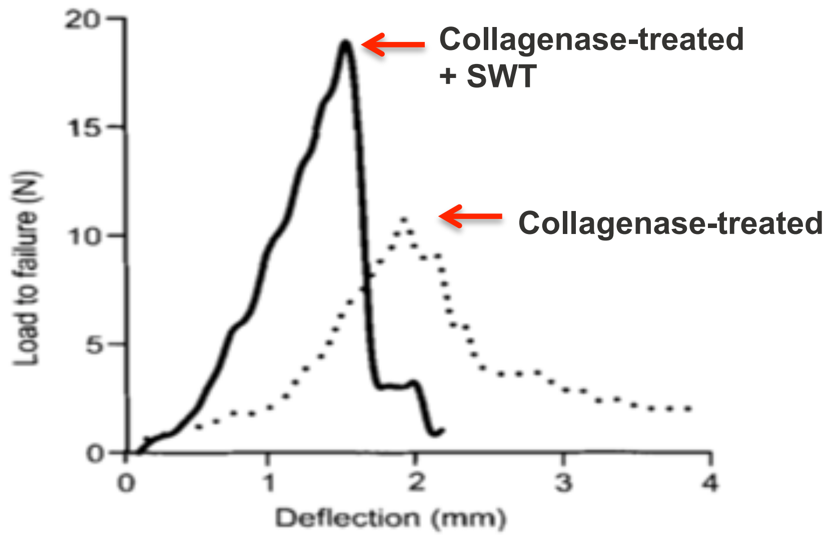




Tenocytes were cultured from rat Achilles tendon. SW @ 0.36 mJ/mm^2 were delivered. Gene expression was analyzed by rtPCR, and total collagen produced in 7-days was quantified by the Sircol dye reagent.

Chao et al. Ultrasound Med Biol. 2008 May;34(5):841-52.

Shockwaves restore tendon strength after injury

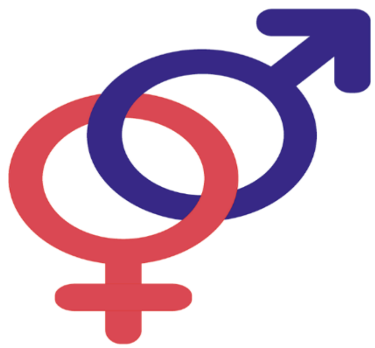


Sprague-Dawley rats were injected with 250U collagenase near the osteotendinous junction of the left Achilles tendon. 200SW @ 0.16 mJ/mm^2 were delivered at d3. Tendons were excised and assessed 12wk after SWT (loading rate 20mm/min).

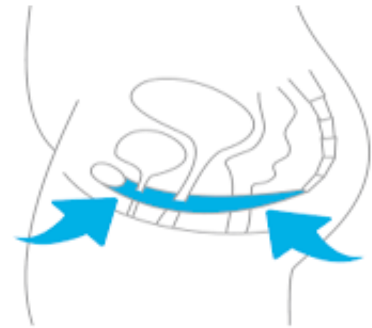
Applications of Shockwaves

Myoskeletal System
- Myofascial pain
- Tendinopathies
- Bone Pathologies
- Osteochrondritis

Sexual Medicine
- Erectile Dysfunction
- Peyronie’s Disease (Pain)



Others
- Chronic Pelvic Pain
- Chronic Wounds
- Neuropathies



ISMST Consensus: 38+8 Indications for SWT

1. Approved standard indications

1.1. Chronic Tendinopathies
1.1.1. Calcifying tendinopathy of the shoulder
1.1.2. Lateral epicondylopathy of the elbow (tennis elbow)
1.1.3. Greater trochanter pain syndrome
1.1.4. Patellar tendinopathy
1.1.5. Achilles tendinopathy
1.1.6. Plantar fasciitis, with or without heel spur
1.2. Bone Pathologies
1.2.1. Delayed bone healing
1.2.2. Bone Non-Union (pseudarthroses)
1.2.3. Stress fracture
1.2.4. Avascular bone necrosis without articular derangement
1.2.5. Osteochondritis Dissecans (OCD) without articular derangement
1.3. Skin Pathologies
1.3.1. Delayed or non-healing wounds
1.3.2. Skin ulcers
1.3.3. Non-circumferential burn wounds

2. Common empirically-tested clinical uses

2.1. Tendinopathies
2.1.1. Rotator cuff tendinopathy without calcification
2.1.2. Medial epicondylopathy of the elbow
2.1.3. Adductor tendinopathy syndrome
2.1.4. Pes-Anserinus tendinopathy syndrome
2.1.5. Peroneal tendinopathy
2.1.6. Foot and ankle tendinopathies
2.2. Bone Pathologies
2.2.1. Bone marrow edema
2.2.2. Osgood Schlatter disease: Apophysitis of the anterior tibial tubercle
2.2.3. Tibial stress syndrome (shin splint)
2.3. Muscle Pathologies
2.3.1. Myofascial Syndrome
2.3.2. Muscle sprain without discontinuity
2.4. Skin Pathologies
2.4.1. Cellulite

3. Exceptional indications – expert indications

3.1. Musculoskeletal pathologies
3.1.1. Osteoarthritis
3.1.2. Dupuytren disease
3.1.3. Plantar fibromatosis (Ledderhose disease)
3.1.4. De Quervain disease
3.1.5. Trigger finger
3.2. Neurological pathologies
3.2.1. Spasticity
3.2.2. Polyneuropathy
3.2.3. Carpal Tunnel Syndrome
3.3. Urologic pathologies
3.3.1. Pelvic chronic pain syndrome (abacterial prostatitis)
3.3.2. Erectile dysfunction
3.3.3. Peyronie disease
3.4. Others
3.4.1. Lymphedema

4. Experimental Indications

4.1. Heart Muscle Ischemia
4.2. Peripheral nerve lesions
4.3. Pathologies of the spinal cord and brain
4.4. Skin calcinosis
4.5. Periodontal disease
4.6. Jawbone pathologies
4.7. Complex Regional Pain Syndrome (CRPS)
4.8. Osteoporosis

ISMST

https://www.shockwavetherapy.org/about-eswt/indications/

Basic Science of ESWT: Conclusions

- The exact mechanism is not well-defined, SW may activate cells in multiple ways.
- Multiple cell-types activated by shockwaves, including vascular endothelium, stem cells, nerve cells and immune cells, are present in every tissue.
- SW-activated cells initiate a proliferation and anti-inflammatory response
- SW may address the underlying pathology of multiple ischemic and inflammatory conditions.

Thank you!

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