

Acute and chronic wound care

A dermaPACE™ publication summary

Basic science: Studies

- Gutersohn A, Caspari G, and Erbel R. Upregulation of VEGF-mRNA in human umbilical vascular endothelial cells via shock waves. Presentation; *Eur J Heart Failure* 2000;2(Suppl1):42.

Human umbilical vascular endothelial cells were placed into the focus of shock waves at energy flux densities of 0.05, 0.1 and 0.3 mJ/mm² ("modified lithotripter"). After shock wave treatment cells were grown for 24-36h, and tested for VEGF-mRNA. Esw treated cells revealed a significant increase of VEGF-mRNA versus controls. Cell death increased with increasing esw energy levels.

- Wang CJ, Huang SY, and Pai CH. Shock wave enhanced neovascularization at the bone-tendon junction. A study in a dog model. *Am J Foot Ankle* 2002;41:16-22.

Achilles tendon-bone specimen from eight dogs were taken before eswt, as well as 4 and 8 weeks, respectively, after 1000 esw pulses at 0.18 mJ/cm² (Ossatron, HMT). New capillary and muscularized vessels were seen in the 4- and 8-week specimen, but none were seen in the control specimen before shock wave application.

- Wang FS, Yang KD, Chen RF, Wang CJ, and Sheen-Chen SM. Extracorporeal shock wave promotes growth and differentiation of bone-marrow stromal cells towards osteoprogenitors associated with induction of TGF-beta1. *J Bone Joint Surg (Br)* 2002;84-B:457-461.

Esw was applied to the left femur of rats at 0.16 mJ/mm² and in a range of between 250 and 2000 pulses (Ossatron, HMT). Bone marrow cells were harvested after eswt and tested for differentiation towards osteoprogenitors. The mean production of TGF-beta1 in the eswt culture supernatant was 610 pg/ml compared with 283 pg/ml in the control group (p < 0.001). TGF-beta1 induction was dose-dependent, reaching the maximum at 500 pulses and declining sharply at impulse numbers 750 and above.

- Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, and Yang LC. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. *J Orthop Res.* 2003;21(6):984-989.

Shock waves (500 pulses at 0.12 mJ/mm²), directed on the Achilles tendon near the bony insertion in rabbits, produced a significantly higher number of neo-vessels and released angiogenesis related growth markers (eNOS, VEGF, PCNA) compared to the untreated control limb. The effects were observed as early as 1 week after shock-wave treatment and some persisted until up to 12 weeks.

- Wang FS, Wang CJ, Chen YJ, Chang PR, Huang YT, Sun YC, Huang HC, Yang YJ, and Yang KD. Ras induction of superoxide activates ERK-dependent angiogenic transcription factor HIF-1alpha and VEGF-A expression in shock wave-stimulated osteoblasts. *J Biol Chem.* 2004; 279(11):10331-10337.

Esw treatment (OssaTron, HMT, 500 pulses at 0.16 mJ/mm²) of cultures of human osteoblast cells rapidly activated Ras protein, increased superoxide production and VEGF mRNA expression. Culture medium harvested from esw treated osteoblasts increased vessel number in chick chorioallantoic membrane.

- Mariotto S, Cavalieri, Amelio E, Ciampa AR, Carcereri de Prati A, Marlinghaus E, Russo S, and Suzuki H. Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production. *Nitric Oxide*. 2005;12:89-96.

- A suspension of cultured human umbilical vein endothelial cells (HUVEC) were treated with esw (Modulith SLK, Storz, 1000 pulses at 0.03 mJ/mm²). Treatment at low energy esw rapidly enhanced eNOS activity and intracellular NO production. The clinically observed anti-inflammatory action of esw treatment, therefore, should be sustained at least partially by its quick action on eNOS activity.

- Wang CJ. Biological mechanism of musculoskeletal shockwave therapy. *ISMST Newsletter* 2006; 1(1): 5-11.

- Wang CJ, Wang FS, Yang KD, Weng LH, Sun YC, and Yang YJ. The effect of shock wave treatment at the tendon-bone interface. A histomorphological and biomechanical study in rabbits. *J Orthop Res* 2005;23:274-280.

Anterior cruciate ligaments were excised in rabbits and replaced with the long digital extensor. The right knees were treated with 500 pulses of esw (Ossatron, HMT) equivalent to 0.18 mJ/mm², the left knees served as controls. The number of cells with positive immunostains for eNOS, VEGF, PCNA and BMP-2, as well as the number of neovessels in the tendon-bone interface, were significantly higher in the shockwave treated knees. The effects are time dependent over the 24 weeks observation period.

- Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher A, and Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells. *Circulation* 2006;114:2823-2830.

Recruitment of endothelial progenitor cells in hind limb adductor muscles of rats was facilitated with low energy shock wave treatment (experimental version of Biotripter, Dornier, 500 to 2000 pulses at 0.05 mJ/mm²). Histologically, the number of VEGF-positive endothelial cells was significantly increased.

- Meirer R, Brunner A, Deibl M, Oehlbauer M, Piza-Katzer H, and Kamelger FS. Shock wave therapy reduces necrotic flap zones and induces VEGF expression in animal epigastric skin flap model. *J Reconstr Microsurg*. 2007;23:231-236.

Twenty rats were operated on with the epigastric skin flap model, ten animals were treated by esw (EvoTron, SANUWAVE, 500 pulses at 0.11 mJ/mm²). At day seven after the operation, necrotic zones of 4.2% were found in the esw treated group compared with 18.3% in the control group ($p < 0.01$). In tissue samples adjacent to the necrosis areas, increased VEGF expression was observed in the esw treated animals (median 85% versus 47% in controls, $p < 0.1$). For expression of the basic fibroblast growth factor (FGF-2) no difference was found between the two groups.

- Davis TA, Stojadinovic A, Amare K, Anam M, Naik S, Peoples GE, Tadaki D, and Elster EA. Extracorporeal shock wave therapy suppresses the acute early proinflammatory immune response to a severe cutaneous burn injury. *Presentation no. 47; 10th Int Congress of the ISMST, June 6th to 9th, 2007, Toronto, Canada*.

A panel of 184 murine candidate genes known to be involved in acute inflammation and wound healing was screened. Eswt of burn wounds at 1 hr post-wounding significantly blunts polymorphonuclear neutrophil (PMN) and macrophage infiltration into the wound site.

- Krokowicz L, Mielniczuk M, and Siemionow M. Microcirculatory response to shockwave therapy in an acute model. Preliminary report. *Presentation no. 36; 10th Int Congress of the ISMST, June 6th to 9th, 2007, Toronto, Canada*.

Cremaster muscle dissected rats were divided into three groups: non-ischaeamic baseline controls; esw treated with 500 pulses and esw treated with 200 pulses immediately before dissection (DermaPACE, SANUWAVE). Microcirculatory hemodynamic parameters were recorded 1,2,3 and 4 hours after eswt. In the 500 pulse group, a 13% increased functional capillary density was observed over controls. Histological evaluation demonstrated no damage to small vessels and capillaries after esw nor any increase in inflammatory infiltrates.

- Kuo YR, Wu WS, Hsieh YL, Wang FS, Wang CT, Chiang YC, and Wang CJ. Extracorporeal shock wave enhanced extended skin flap tissue survival via increase of topical blood perfusion and associated with suppression of tissue pro-inflammation. *J Surg Res* 2007;143:385-392

Thirty-six rats in a caudally based, random dorsal skin flap model were randomized into three groups: control group I without esw treatment, group II esw treated immediately post-op and group III immediately post-op plus one day following surgery (Ossatron, SANUWAVE, 500 pulses at 14 kV, equivalent to 0.15 mJ/mm²).

Flap tissue blood perfusion was significantly increased three days post-operatively in group II ($p < 0.005$), and flap necrotic area in group II was significantly reduced seven days post-operatively compared with that of the control group ($13 \pm 2.6\%$ versus $42 \pm 5.7\%$, $p < 0.01$). Tissue angiogenesis was up-regulated by esw (substantially increased VEGF and PCNA expressions) and flap tissue inflammatory response was suppressed (reduced leukocyte infiltration from the dermis to subcutaneous-muscular layers of the ischemic flap zones and decreased TNF-alpha expression) in group I compared to the controls. There was only mild response in group II with esw immediately post-operatively and the following day compared to the single dose eswt in group I.