TRT controlled studies	
Authors	J. Dumfarth, D. Zimpfer, M. Vögele-Kadletz, J. Holfeld, F. Sihorsch, W. Schaden, M. Czerny, S. Aharinejad, E. Wolner, and M. Grimm.
Title	**Prophylactic low-energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery: A prospective, randomized trial.**
Journal	Ann Thorac Surg, 86(6):1909–1913, December 2008.
Abstract	Background. Wound healing disorders after vein harvest- ing for coronary artery bypass graft surgery increase mor-bidity and lower patient satisfaction. Low-energy shock wave therapy (SWT) reportedly improves healing of diabetic and vascular ulcers by overexpression of vascular endothelial growth fractor and downregulation of necrosis factor kB. In this study, we investigate whether prophylac tic low-energy SWT improves wound healing after vein harvesting for coronary artery bypass graft surgery. Methods. One hundred consecutive patients undergo-ing coronary artery bypass graft surgery were randomly assigned to either prophylactic low-energy SWT (n = 50) or control (n = 50). Low-energy SWT was applied to the site of vein harvesting after wound closure under sterile conditions using a commercially available SWT system (Dermagold; Tissue Regeneration Technologies, Woodstock, GA). A total of 25 impulses (0.1 mJ/mm^2; 5 Hz) were applied per centimeter wound length. Wound heal-ing was evaluated and quantified using the ASEPSIS score. (ASEPSIS stands for Additional treatment, presence of Serous discharge, Erythema, Purulent exudate, Separation of the deep tissue, Isolation of bacteria, and duration of inpatient Stay). Patient demographics, operative data, and postoperative adverse events were monitored. Results. Patient characteristics and operative data in-cluding wound length (SWT 39 ± 13 cm versus control 37 ± 11 cm, p = 0.342) were comparable between the two groups. We observed lower ASEPSIS scores indicating improved wound healing in the SWT group (4.4 ± 5.3) compared with the control group (11.6 ± 8.3, p = 0.0001). Interestingly, we observed a higher incidence of wound healing disorders necessitating antibiotic treatment in the control group (22%) as compared with the SWT group (4%, p = 0.015). No SWT-associated adverse events were observed in the treatment group. Conclusions. As shown in this prospective randomized study, prophylactic application of low-energy SWT im- proves wound healing after vein harvesting for coronary artery bypass graft surgery.
Authors	C. Wang, Y. Kuo, R. Wu, R. Liu, C. Hsu, F. Wang, and K. Yang.
Title	**Extracorporeal shockwave treatment for chronic diabetic foot ulcers**
Journal	J Surg Res, 152:96–103, 3 2008.
Abstract	BACKGROUND: This prospective study compared extracorporeal shockwave treatment (ESWT) with hyperbaric oxygen therapy (HBO) in chronic diabetic foot ulcers. PATIENTS AND METHODS: Seventy-two patients with 72 chronic diabetic foot ulcers were randomly divided into two groups of similar demographics with 34 patients with 36 ulcers in the ESWT group and 36 patients with 36 ulcers in the HBO group. Patients in the ESWT group received 300 + 100/cm^2 impulses of shockwave at 0.11 mJ/cm^2 energy flux density every 2 wk for 6 wk, whereas patients in the HBO group received HBO daily for 20 treatments. The evaluations included clinical assessment of the ulcers with photo-documentation, blood flow perfusion scan, bacteriological examination, histological study, and immunohistochemical analysis. RESULTS: The overall results showed completely

	healed in 31%, improved in 58%, and unchanged in 11% for the ESWT group and 22% completely healed, 50% improved, and 28% unchanged for the HBO group. The ESWT group showed significantly better clinical results and local blood flow perfusion, higher cell concentration, and activity than the HBO group. On immunohistochemical analysis, the ESWT group demonstrated significant increases in endothelial nitric oxide synthase, vessel endothelial growth factor, and proliferation cell nuclear antigen expressions and a decrease in transference-mediated digoxigenin-deoxy-UTP nick end-labeling expression than the HBO group. CONCLUSIONS: ESWT appears to be more effective than HBO in chronic diabetic foot ulcers.
Authors **Title** Journal Abstract	A. M. Larking, S. Duport, M. Clinton, M. Hardy, and K. Andrews. **Randomized control of extracorporeal shock wave therapy versus placebo for chronic decubitus ulceration**. Clin Rehabil, 24(3):222–9, Mar 2010. Objective: To assess whether extracorporeal shock wave therapy increases the rate of healing in chronic decubitus ulceration.Design: Double-blind randomized cross-over study.Setting: A large, long-stay hospital specializing in the management of people with complex neurological disabilities.Subjects: The total population of available patients with chronic neurological conditions and chronic decubitus ulceration who met the inclusion criteria.Interventions: Ulcers were randomized into receiving either the extracorporeal shock wave therapy or the placebo for a four-week period, followed by a two-week 'washout' period followed by a four-week period of the cross-over treatment/placebo. MAIN MEASURES: Measurement of the area of the ulceration. For each observation the average of three measurements were taken.Results: Nine ulcers (in eight patients) were included in the study: five on the buttocks/sacrum/trochanter and four on the feet/ankles. All those with static chronic ulcers showed improved healing starting 6-8 weeks after the start of extracorporeal shock wave therapy, whether treated first with the placebo or the therapy.Conclusions: Extracorporeal shock wave therapy has a potential part to play in the treatment of chronic skin ulceration.
Authors **Title** Journal Abstract	C. Ottomann, B. Hartmann, J. Tyler, H. Maier, R. Thiele, W. Schaden, and A. Stojadinovic. **Prospective randomized trial of accelerated re-epithelization of skin graft donor sites using extracorporeal shock wave therapy.** Journal of the American College of Surgeons, published online 14 July 2010, 7 2010. BACKGROUND: Extracorporeal shock wave therapy may enhance revascularization and repair of healing soft tissue. METHODS: Between January 2006, and September 2007, 28 patients with acute traumatic wounds and burns requiring skin grafting were randomly assigned in a 1:1 fashion to receive standard topical therapy (nonadherent silicone mesh [Mepitel, Mölnlycke Health Care] and antiseptic gel [polyhexanide/octenidine]) to graft donor sites with (n = 13) or without (n = 15) defocused extracorporeal shock wave therapy (ESWT, 100 impulses/cm^2 at 0.1 mJ/mm^2) applied once to the donor site, immediately after skin harvest. The randomization sequence was computer generated, and the patients were blinded to treatment allocation. The primary endpoint was time to complete donor site epithelialization and was determined by an independent blinded observer. RESULTS: Statistical tests indicated no unbalanced distribution of subject characteristics across the two study groups. Mean times to complete graft donor site epithelialization for patients who did and did not undergo ESWT were 13.9 ± 2.0 days and 16.7 ± 2.0 days, respectively (p = 0.0001). CONCLUSIONS: For centers that apply nonadherent gauze dressings and topical antiseptics to skin graft donor sites, application of a single defocused shock wave treatment immediately after skin graft harvest can significantly accelerate donor site epithelialization.

Authors	J. P. Furia, P. J. Juliano, A. M. Wade, W. Schaden, and R. Mittermayr.
Title	**Shock wave therapy compared with intramedullary screw fixation for nonunion of proximal fifth metatarsal metaphyseal-diaphyseal fractures**.
Journal	J Bone Joint Surg Am, 92(4):846–54, Apr 2010.
Abstract	BACKGROUND: The current "gold standard" for treatment of chronic fracture nonunion in the metaphyseal-diaphyseal region of the fifth metatarsal is intramedullary screw fixation. Complications with this procedure, however, are not uncommon. Shock wave therapy can be an effective treatment for fracture nonunions. The purpose of this study was to evaluate the safety and efficacy of shock wave therapy as a treatment of these nonunions. METHODS: Twenty-three patients with a fracture nonunion in the metaphyseal-diaphyseal region of the fifth metatarsal received high-energy shock wave therapy (2000 to 4000 shocks; energy flux density per pulse, 0.35 mJ/mm(2)), and twenty other patients with the same type of fracture nonunion were treated with intramedullary screw fixation. The numbers of fractures that were healed at three and six months after treatment in each group were determined, and treatment complications were recorded. RESULTS: Twenty of the twenty-three nonunions in the shock wave group and eighteen of the twenty nonunions in the screw fixation group were healed at three months after treatment. One of the three nonunions that had not healed by three months in the shock wave group was healed by six months. There was one complication in the shock wave group (post-treatment petechiae) and eleven complications in the screw-fixation group (one refracture, one case of cellulitis, and nine cases of symptomatic hardware). CONCLUSIONS: Both intramedullary screw fixation and shock wave therapy are effective treatments for fracture nonunion in the metaphyseal-diaphyseal region of the fifth metatarsal. Screw fixation is more often associated with complications that frequently result in additional surgery.
TRT non-controlled trials	
Authors	T. A. Davis, A. Stojadinovic, K. Anam, M. Amare, S. Naik, G. E. Peoples, D. Tadaki, and E. A. Elster.
Title	**Extracorporeal shock wave therapy suppresses the early proinflammatory immune response to a severe cutaneous burn injury**.
Journal	International Wound Journal, 6(1):11–21, 1 2009.
Abstract	Following severe burn injury, persistent inflammation perpetuated by surface eschar, bacterial colonisation and neutrophil proteolytic activity can impede normal healing and result in further tissue damage. Extracorporeal shock wave treatment (ESWT) has been shown in the clinical setting to promote the healing of burn and difficult- to-heal wounds; however, the mechanism is unclear. We investigated the role of ESWT on the early proinflammatory response using a severe, full-thickness and highly inflammatory cutaneous burn wound in a murine model. Various wound-healing parameters were measured and leukocyte infiltration quantitated. A panel of 188 candidate genes known to be involved in acute inflammation and wound healing was screened. We show that ESWT of burn wounds 1 hour postwounding significantly blunts polymorphonuclear neutrophil and macrophage infiltration into the wound. ESWT treatment potently attenuates both CC- and CXC-chemokine expression, acute proinflammatory cytokine expression and extracellular matrix proteolytic activity at the wound margin. Given these findings and the clinical success of ESWT, we speculate that ESWT may be a potential therapeutic modality to treat severe wounds wherein excessive inflammatory responses involving increased levels of inflammatory cells, proinflammatory cytokines and proteases may become self-resolving allowing wound healing to progresses by way of normal physiological repair processes.
Authors	S. Edelmann, B. F. Fink, R. E. Fergueson, S. Kirakodu, K. Novak, J. Novak, W. Balke, and

	H. C. Vasconez.
Title	**A study of the biological factors and wound healing of a skin flap model treated with unfocused extracorporeal shockwave therapy**.
Journal	2007.
Abstract	This study was performed to assess the validity of extracorporeal shock wave (ESWT) treatment to promote cell differentiation with neovascularization, thus minimizing the measurable area of necrosis and enhancing epigastric skin flap survival. In addition, we measured the expression level of the mRNAs of the growth factors known to play a major role during normal wound healing angiogenesis using Real-Time PCR. In particular, we studied the expression of basic fibroblast growth factor (bFGF), transforming growth factor beta, (TGF-β), platelet derived growth factor (PDGF), epidermal growth factor (EGF) and vascular endothelial cell growth factor (VEGF) at several time points following the skin flap surgery.1 We studied the localized changes in expression as well as systemic changes that were initiated by the treatment with ESWT.
Authors	E. A. Elster, A. Stojadinovic, J. Forsberg, S. Shawen, R. C. Andersen, and W. Schaden.
Title	**Extracorporeal shock wave therapy for nonunion of the tibia.**
Journal	J Orthop Trauma, 24(3):133–41, Mar 2010.
Abstract	OBJECTIVES:: Delayed and nonunion of the tibia are not uncommon in orthopaedic practice. Multiple methods of treatment have been developed with variable results. The objective of this study was to define disease-specific and treatment-related factors of prognostic significance in patients undergoing shock wave therapy for tibia nonunion. DESIGN:: Retrospective analysis. PATIENTS:: One hundred ninety-two patients treated with extracorporeal shock wave therapy (ESWT) at a single referral trauma center, AUVA-Trauma Center Meidling, a large single-referral trauma center located in Vienna, Austria, in an attempt to determine the feasibility and factors associated with the use of ESWT in the treatment for tibia nonunion. INTERVENTION:: ESWT coupled with posttreatment immobilization, external fixation, or ESWT alone. MAIN OUTCOME MEASURES:: Fracture healing, overall healing percent, and factors associated with ESWT success or failure. RESULTS:: At the time of last follow up, 138 of 172 (80.2 %) patients have demonstrated complete fracture healing. Mean time from first shock wave therapy to complete healing of the tibia nonunion was 4.8 +/- 4.0 months. Number of orthopaedic operations (P = 0.003), shock wave treatments (P = 0.002), and pulses delivered (P = 0.04) were significantly associated with complete bone healing. Patients requiring multiple (more than one) shock wave treatments versus a single treatment had a significantly lower likelihood of fracture healing (P = 0.003). This may be attributable to the finding that a significantly greater proportion of patients with multiple rather than single ESWT treatments had three or more prior orthopaedic procedures (more than one ESWT, 63.9 % versus one ESWT, 23.5 %; P < 0.001). CONCLUSIONS:: ESWT is a feasible treatment modality for tibia nonunion.
Authors	Y.-R. Kuo, C.-T. Wang, F.-s. Wang, Y.-C. Chiang, and C.-J. Wang.
Title	E**xtracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of stz-induced diabetes.**
Journal	Wound Repair Regen, 17:522–530, 3 2009.
Abstract	Extracorporeal shock-wave therapy (ESWT) has a significant positive effect in accelerating chronic wound healing. However, the bio-mechanisms operating during ESWT of wounds remain unclear. This study investigated the effective- ness of ESWT in the enhancement of diabetic wound healing. A dorsal skin defect (area, 6□5 cm) in a streptozotocin-induced diabetes rodent model was used. Fifty male Wistar rats were divided into five groups. Group I consisted of nondiabetic control; group II included

	diabetic control receiving no ESWT; group III includ- ed rats that underwent one session of ESWT (ESW-1) on day 3 (800 impulses at 0.09 mJ/mm^2) postwounding; group IV included rats that underwent two sessions of ESWT (ESW-2) on days 3 and 7; and group V included rats that under- went three sessions of ESWT (ESW-3) on days 3, 7, and 10. The wound healing was assessed clinically. Blood perfusion scan was performed with laser Doppler. The VEGF, eNOS, and PCNA were analyzed with immunohistochemical stain. The results revealed that the wound size was significantly reduced in the ESWT- treated rats, especially in the ESW-2 and ESW-3 groups, as compared with the control ($p < 0.01$). Blood perfusion was significantly increased after ESWT compared with the controls. Histological findings revealed a significant reduc- tion in the topical pro-inflammatory reaction in the ESWT group as compared with the control. In immunohistochemical stain, significant increases in VEGF, eNOS, and PCNA expressions were observed in the ESWT group, especially in the ESW-2 and ESW-3 groups, as compared with the control. In conclusion, treatment with an optimal session of ESWT significantly enhanced diabetic wound healing associated with increased neo-angiogenesis and tissue regenera- tion, and topical anti-inflammatory response.
Authors **Title** Journal Abstract	R. Saggini, A. Figus, A. Troccola, V. Cocco, A. Saggini, and N. Scuderi. **Extracorporeal shock wave therapy for management of chronic ulcers in the lower extremities.** Ultrasound Med Biol, 34(8):1261– 1271, August 2008. Management of chronic ulcers in the lower extremities is still a challenge for patients and health providers. Recent studies showed extracorporeal shock waves (ESW) as effective in stimulating growth factors, inducing angiogenesis and healing of fractures and injuries. This study was planned to investigate the opportunity of introducing the ESW in the treatment of chronic wounds. Thirty consecutive patients with chronic posttraumatic, venous and diabetic ulcers, unresponsive to conservative or advanced dressing treatments, were counseled about the use of ESW as alternative treatment for their wounds. Thirty-two wounds were treated and 16 wounds healed completely within six sessions of ESW. In all of the nonhealed wounds, decrease of the amount of exudates, increased percentage of granulation tissue compared with fibrin/necrotic tissue and decrease of wounds' size were statistically significant after four to six sessions of ESW ($p < 0.01$). Significant decrease of pain was reported ($p < 0.001$). Comparison with a control group of 10 patients with chronic ulcer treated on the basis of regular dressings confirmed the statistical significant improvement in the healing process ($p < 0.01$). ESW therapy seems to be a safe, feasible and cost-effective treatment for chronic ulcers in the lower extremities. Further research and clinical trials are necessary to evaluate dose and time intervals of sessions to standardize a protocol of treatment in the management of chronic wounds.
Authors **Title** Journal Abstract	W. Schaden, R. Thiele, C. Kolpl, M. Pusch, A. Nissan, C. E. Attinger, M. E. Maniscalco-Theberge, G. E. Peoples, E. A. Elster, and A. Stojadinovic. **Shock wave therapy for acute and chronic soft tissue wounds: a feasibility study.** J Surg Res, 143(1):1–12, 2007. BACKGROUND: Nonhealing wounds are a major, functionally-limiting medical problem impairing quality of life for millions of people each year. Various studies report complete wound epithelialization of 48 to 56% over 30 to 65 d with different treatment modalities including ultrasound, topical rPDGF-BB, and composite acellular matrix. This is in contrast to comparison control patients treated with standard wound care, demonstrating complete epithelialization rates of 25 to 39%. Extracorporeal shock wave therapy (ESWT) may

	accelerate and improve wound repair. This study assesses the feasibility and safety of ESWT for acute and chronic soft-tissue wounds. STUDY DESIGN: Two hundred and eight patients with complicated, nonhealing, acute and chronic soft-tissue wounds were prospectively enrolled onto this trial between August 2004 and June 2006. Treatment consisted of debridement, outpatient ESWT [100 to 1000 shocks/cm(2) at 0.1 mJ/mm(2), according to wound size, every 1 to 2 wk over mean three treatments], and moist dressings. RESULTS: Thirty-two (15.4%) patients dropped out of the study following first ESWT and were analyzed on an intent-to-treat basis as incomplete healing. Of 208 patients enrolled, 156 (75%) had 100% wound epithelialization. During mean follow-up period of 44 d, there was no treatment-related toxicity, infection, or deterioration of any ESWT-treated wound. Intent-to-treat multivariate analysis identified age (P = 0.01), wound size < or =10 cm(2) (P = 0.01; OR = 0.36; 95% CI, 0.16 to 0.80), and duration < or =1 mo (P < 0.001; OR = 0.25; 95% CI, 0.11 to 0.55) as independent predictors of complete healing. CONCLUSIONS: The ESWT strategy is feasible and well tolerated by patients with acute and chronic soft tissue wounds. Shock wave therapy is being evaluated in a Phase III trial for acute traumatic wounds.
Authors **Title** Journal Abstract	A. Stojadinovic, E. A. Elster, K. Anam, D. Tadaki, M. Amare, S. Zins, and T. A. Davis. **Angiogenic response to extracorporeal shock wave treatment in murine skin isografts.** Angiogenesis, 11(4):369–380, 2008. Skin grafts are commonly utilized and proven effective methods of open wound coverage. Revascularization through neoangiogenesis is a pivotal mechanism for skin graft integration and durability. Extracorporeal shock-wave treatment (ESWT) has been demonstrated to accelerate wound repair; however, its mechanism-of-action is unclear. We investigated the role of ESWT in early revascularization of full-thickness skin isografts in a murine model. Cohorts of mice were euthanized and skin grafts were harvested 6 h, 2, 4, and 7 days post grafting +/- ESWT. Various aspects of graft neovascularization were measured including gross morphology, quantitative microscopy (vessel number, density), immunohistochemistry (CD31), cDNA SuperArrays for 84 angiogenesis-specific genes, and custom-designed 'Wound Repair' TaqMan Low Density Array (TLDA) cards to assess expression of 188 wound repair genes. We demonstrate that a single administration of ESWT immediately following skin grafting significantly enhances recipient graft revascularization (increased vessel number, size, and density). An augmented early pro-angiogenic and suppressed delayed pro-inflammatory response to ESWT was accompanied by significantly increased expression of both skin graft CD31 and angiogenesis pathway-specific genes, including ELR-CXC chemokines (CXCL1, CXCL2, CXCL5), CC chemokines (CCL2, CCL3, CCL4), cytokines (IL-1 beta, IL-6, G-CSF, VEGF-A), matrix metalloproteinases (MMP3, MMP9, MMP13), hypoxia-inducible factors (HIF-1 alpha), and vascular remodeling kinase (Mst1), as early as 6 h and up to 7 days post grafting and treatment. These findings suggest that early pro-angiogenic and anti-inflammatory effects of ESWT promote tissue revascularization and wound healing by augmenting angiogenesis and dampening inflammation.
Authors **Title** Journal Abstract	O. van der Jagt, W. Schaden, H. T. van Schie, T. Piscaer, J. Waarsing, J. Verhaar, H. Weinans, and J. van der Linden. **Unfocused extracorporeal shockwave therapy diminishes bone loss in rats.** 2007. Extracorporeal Shockwave (ESW) therapy has shown to be effective in the treatment of non-unions and can enhance healing of fresh fractures1. Enhanced proliferation and differentiation of osteoprogenitor cells have been shown in rats after a single ESW treatment2. These studies used focused shockwaves; nowadays unfocused shockwaves can be

	generated, enabling treatment of larger areas without the need for anesthesia. Therefore extracorporeal shockwave therapy might be useful in the treatment of osteoporosis. We evaluated if unfocused electro- hydraulically generated ESW can reduce bone loss and/or enhance fracture healing in ovariectomized and healthy rats. **Materials and Methods** 48 Female Wistar rats, 20 weeks of age were obtained. To induce bone depletion ovariectomy (OVX) was performed. ESW therapy (Dermagold, MTS-Europe GmbH, Konstanz Germany) was given to the antero-lateral side of the right leg, the untreated left leg served as control. Two treatment regimes were used: a single treatment with 2000 pulses, 0.13 mJ/mm2, or two treatments with three weeks in between with 1000 pulses, 0.13 mJ/mm2. The legs were treated 3 (and 6) or 10 (and 13) weeks after OVX. Two days before the first ESW treatment a bilateral fibula osteotomy was performed to evaluate effects on fracture healing. A group with sham-OVX and a fibula osteotomy was treated with 2000 pulses, to evaluate effects in healthy bone. Control groups to check for interactions between the osteotomy and ovariectomy were also evaluated. N=6 for all groups. Under gas anesthesia in-vivo microCT scans of the proximal metaphysis of the treated and untreated legs were made just before ESW treatment and 3, 6 and 10 weeks thereafter. In vivo microCT allows longitudinal follow-up of a single rat making it possible to evaluate dynamic bone changes in a highly detailed manner (voxelsize of 18 microns). Binary datasets of reconstructed images were made using a local threshold algorithm. A region of interest containing the proximal tibia was selected manually (length of 5,4mm), cortical and trabecular bone were automatically separated. Bone morphologic parameters of both were calculated (see Fig. 1). To evaluate the effect of ESW on fracture healing, a cylindrical region of interest 2mm in length was made around the osteotomy. A global threshold was used to determine the amount of mineralized matrix see (Fig. 1). All outcome measures were statistically evaluated using the Wilcoxin signed rank test. **Results** Sham-ovariectomized rats showed enhanced trabecular bone formation after shockwave therapy. Treated legs showed an increase of the trabecular volume fraction of 5% 7 weeks after treatment, whereas the non-treated legs showed a 5% decrease over the same period (p=0.03)(Fig. 2A). The cortical volume did not change significantly. Other bone morphologic parameters were not different in treated and untreated legs. The treated legs of rats suffering bone loss due to OVX that received shockwave therapy 3 weeks after OVX showed aslightly larger bone volume than the contralateral untreated legs, when they were treated with 2000 pulses (Fig. 2B). Cortical bone volume was not different between treated and untreated legs. No statistically significant effect of treatment was found in rats suffering bone loss due to OVX that received shockwave therapy after 10 weeks. There was no difference in mineralized callus formation in the fibula osteotomy between treated and non-treated legs in all treatment groups.
Authors	O. van der Jagt, J. van der Linden, W. Schaden, H. van Schie, T. Piscaer, J. Verhaar, H. Weinans, and J. Waarsing.
Title	**Unfocused extracorporeal shock wave therapy as potential treatment for osteoporosis.**
Journal	J Orthop Res, pages 1528–1533, November 2009.
Abstract	Extracorporeal shock wave therapy (ESWT) influences the differentiation of bone marrow stroma cells towards osteoprogenitors and increases the expression of several growth factors. To assess whether unfocused ESWT might serve as a treatment for osteoporosis, we examined the bone architecture dynamics of ESWT-treated and untreated rat tibiae using in vivo micro-computed tomography (CT) scanning. In addition, the effects of ESWT

	on fracture healing, using a bilateral fibula osteotomy, were examined. Unilateral unfocused ESWT with 2,000 pulses and an energy flux density of 0.16 mJ/mm(2) was applied to the hind leg of ovariectomized and sham-ovariectomized rats. A single treatment with unfocused ESWT resulted in a higher trabecular bone volume fraction (BV/TV) in the proximal tibia of the sham-ovariectomized animals. Three weeks after ESWT, BV/TV was 110% of baseline BV/TV in treated legs versus 101% in untreated contralateral control legs (p = 0.001) and 105% of baseline BV/TV versus 95% at 7 weeks after ESWT (p = 0.0004). In ovariectomized rats, shock wave treatment resulted in a diminished bone loss. At 7 weeks, the BV/TV of the treated legs was 50% of baseline BV/TV, whereas in untreated control legs this was 35% (p = 0.0004). ESWT did not influence acute fracture healing. This study shows that bone microarchitecture can be affected by unfocused shock waves, and indicates that unfocused ESWT might be useful for the treatment of osteopenia and osteoporosis.
Authors	D. Zimpfer, S. Aharinejad, J. Holfeld, A. Thomas, J. Dumfarth, R. Rosenhek, M. Czerny, W. Schaden, M. Gmeiner, E. Wolner, and M. Grimm.
Title	**Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure**.
Journal	J Thorac Cardiovasc Surg, 137(4):963–970, Apr 2009.
Abstract	OBJECTIVES: Direct application of low-energy unfocused shock waves induces angiogenesis in ischemic soft tissue. The potential effects of epicardial shock wave therapy applied in direct contact to ischemic myocardium are uncertain. METHODS: For induction of ischemic heart failure in a rodent model, a left anterior descending artery ligation was performed in adult Sprague-Dawley rats. After 4 weeks, reoperation with (treatment group, n = 60) or without (control group, n = 60) epicardial shock wave therapy was performed. Low-energy shock waves were applied in direct contact with the infarcted myocardium (300 impulses at 0.38 mJ/m(2)). Additionally, healthy animals (n = 30) with normal myocardium were studied. Angiogenesis, ventricular function upregulation of growth factors, and brain natriuretic peptide levels were analyzed. RESULTS: Histologic analysis revealed significant angiogenesis 6 weeks (treatment group: 8.2 +/- 3.7 vs control group: 2.9 +/- 1.9 vessels per field, P = .016) and 14 weeks (treatment group: 7.1 +/- 3.1 vs control group: 3.2 +/- 1.8 vessels per field, P = .011) after shock wave treatment. In the treatment group ventricular function improved throughout the follow-up period (6 weeks: 37.4% +/- 9% [P < .001] and 14 weeks: 39.5% +/- 9% [P < .001]). No improvement of ventricular function was observed in the control group (6 weeks: 28.6% +/- 5% and 14 weeks: 21.4% +/- 5%). Rat brain natriuretic peptide 45 levels were lower in the treatment group compared with those in the control group 6 and 14 weeks after treatment. Vascular endothelial growth factor, Fms-related tyrosine kinase 1, and placental growth factor levels were upregulated after 24 and 48 hours and 7 days in the treatment group. No effects on healthy myocardium were observed. CONCLUSION: Direct epicardial low-energy shock wave therapy induces angiogenesis and improves ventricular function in a rodent model of ischemic heart failure.
Authors	J. Holfeld, D. Zimpfer, A. Thomas, P. Paulus, R. Rosenhek, M. Czerny, W. Schaden, S. Aharinejad, and M. Grimm.
Title	**Direct epicardial shock wave therapy after myocardial infarction improves left ventricular function in pigs.**
Journal	article in press, 8 2010.
Abstract	**Background:** In a recent study we have shown that direct epicardial shock wave therapy (SWT) induces angiogenesis and improves left ventricular ejection fraction (LVEF) in a rat model of ischemic heart failure. The aim of the present study was to proof whether direct epicardial SWT will just as well improve left ventricular function of human sized hearts in pig experiments. To show efficacy for future human application the primary variable was

	LVEF to gain clinically relevant information. **Methods:** A standard model (domestic pigs) for ischemic heart failure induced by LAD ligation was used. Four weeks after LAD ligation, animals underwent re- thoracotomy with (treatment group, n=6) or without (control group, n=5) SWT. Low-energy shock waves were applied in direct contact to cardiac anterior wall (CardioGold®, 300 impulses at 0.38mJ/mm2). Efficacy endpoints were improvement of LVEF and induction of angiogenesis 6 weeks after SWT. Safety endpoints were hemodynamic stability during treatment and myocardial damage related to treatment. **Results:** Four weeks after LAD ligation LVEF was decreased in treatment (43±2.5%, p<.001) and control animals (41±4.2%, p=.012) compared to baseline. LVEF function markedly improved in the treatment group 6 weeks after SWT (62±9.1%, p=.006). No improvement of LVEF was observed in the control group (41±4.2%, p=.358). Quantitative histology revealed significant 2Holfeld et al. Direct Epicardial Shock Wave Therapy after Myocardial Infarction angiogenesis 6 weeks after SWT (treatment group: 8.5±3vessels/field vs. control group: 1.9±0.4vessels/field; p=.004). No acute or chronic adverse effects of SWT were observed. **Conclusion:** Direct epicardial shock wave treatment shows in a porcine model of ischemic heart failure exactly the same positive effects on development of LVEF as previously found in a rat model. Direct epicardial SWT is safe, improves LVEF and induces angiogenesis. This validates the efficacy of this treatment in an animal model which closely resembles ischemic heart failure in humans.