ED1000

A compendium of scientific studies and clinical background of Extracorporeal Shockwave Therapy for Erectile Dysfunction Patients

December 2012

Medispec Ltd.
Clinical Dept.
E-mail: marketing@medispec.com
Phone: +1-301-944-1575
Fax: +1-301-972-6098

Table of Contents:

Introduction

Erectile dysfunction, is the repeated inability to get or keep an erection firm enough for sexual intercourse..

Erectile dysfunction, or ED, can be a total inability to achieve erection, an inconsistent ability to do so, or a tendency to sustain only brief erections. These variations make defining ED and estimating its incidence difficult. An estimated 30 million men in the United States - 10% of the male population experience chronic ED, although as few as 5% seek treatment. It may affect 50% of men between the ages of 40 and 70. Transient loss or inadequate erection affects men of all ages.

According to the National Ambulatory Medical Care Survey (NAMCS), for every 1,000 men in the United States, 7.7 physician office visits were made for ED in 1985. By 1999, that rate had nearly tripled to 22.3.

Damage to nerves, arteries, smooth muscles, and fibrous tissues, often as a result of disease, is the most common cause of ED. Diseases such as diabetes, renal disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular disease and neurological disease account for about 70 percent of ED cases. Between 35 and 50 percent of men with diabetes experience ED.

There are several available treatments options that improve erectile function without treating the cause of the problem, e.g. oral medications (PDE 5-i drugs), hormonal therapy and dopamine agonists, intracavernous injection therapy,Vacuum Constrictions Devices, or surgical treatment for vascular reconstruction, venous blockage to prevent penile venous leak or for implantation of erectile devices.

Yet, none of these options offer cure of the problem but rather ameliorate it.

Currently there are two "curing" options which are in the investigative stage which are gene therapy and bone marrow cell transplantation therapy The main purpose of gene therapy is to induce overexpression of a selected angiogenic ligand (eg, VEGF) that leads to angiogenesis in the ischemic region.
Bone marrow cell transplantation therapy, also may be a useful strategy for angiogenesis because endothelial progenitor cells could be isolated from circulating mononuclear cells in humans and could be shown to be incorporated into neovascularization

We hereby present initial results that suggest that low energy Extracorporeal Shock Wave Therapy might offer a genuine long lasting solution to the ED problem by enhancing penile blood flow.
.
In the last few years many investigators have researched the effect of Extracorporeal Shock Wave Therapy on body potential for neovascularization.
Many articles have been published regarding the effect of shear-stress on neovascularization. Milkiewicz, M. et al. investigated the hypothesis that capillary proliferation in skeletal muscles, induced by a long-term increase in blood flow, which elevated capillary shear stress, is associated with capillary expression of Vascular Endothelial Growth Factor (VEGF).

Young and Dyson studied the effect of therapeutic ultrasound on angiogenesis. They have performed full-thickness excised lesions in the flank skin of adult rats. The wounds were either sham-treated (control group) or were exposed to ultrasound for 5 minutes daily at an intensity of 0.1W/cm2 SATA(frequency either 0.75 MHz or 3.0 MHz). The effect of both treatment modes on the formation of new blood vessels in the lesions was assessed quantitatively using microfocal x-ray techniques. By 5 days following injury there were more blood vessels in equivalent regions of the granulation tissue of the ultrasound – treated wounds than in the control wounds. This suggested that the ultrasound-treated wounds were at a more advanced stage in the repair process. By 7 days after injury there was no significant difference in blood vessel number between the three groups.

Nesser HJ, Karia DH, et al discussed the potential of therapeutic ultrasound utilization in the cardiology field. The bioeffects of ultrasound, such as creation of mechanical vibratons, localized cavitations, microstream formation, physicochemical changes and thermal energy may be exploited to derive therapeutic results. In the area of cardiovascular disease ultrasound could be used for thrombolysis adjunct to coronary interventions, drug delivery, local gene transfer and creating therapeutic lesions. Catheter – based ultrasound could be used for intracoronary thrombolysis, and external ultrasound instrument with transcutaneous delivery could serve to create myocardial lesions, peripheral vessel thrombolysis, and drug and gene delivery. Adjunct administration of microbubbles was found to enhance thrombolysis, and drug and gene therapy.

Reher, P., Doan, N. et al. performed a study aimed at identifying the cytokines and angiogenesis factors induced by Ultrasound in-vitro. Two ultrasound machines were evaluated, a "traditional" (1 MHz pulsed 1:4, tested at 4 intensities), and a "long wave" machine (45 kHz, continuous, also at 4 intensities). The ultrasound was applied on human mandibular osteoblasts, gingival fibroblasts, and peripheral blood mononuclear cells (monocytes). ELISA assay has demonstrated that therapeutic ultrasound stimulates the production of angiogenic factors such as IL-8, bFGF and VEGF. This may be one of the mechanisms through which therapeutic ultrasound induces angiogenesis.

In another study Reher, P., Doan, N. et al evaluated several in-vitro effects of ultrasound that could revert or prevent hypoxia, hypovascularity and hypocellularity observed in osteoradionecrosis. Again "traditional" and "long wave" ultrasound machines were used and tested in various intensities on human gingival fibroblasts, mandibular osteoblasts and monocytes. Results have shown that both ultrasound machines induced increased cell proliferation in fibroblasts and osteoblasts, between 35%-52%. Collagen and non-collagenous protein synthesis were enhanced to levels up to 112%. The angiogenesis related cytokines evaluated were significantly stimulated: IL-8 and bFGF production was enhanced in osteoblasts, and VEGF production was stimulated in all three cell types. The conclusion of this study was that therapeutic ultrasound induces in-vitro cell proliferation, collagen/NCP production, bone formation and angiogenesis.

Many additional in-vitro studies are stressing the enhancing effect of Shock Wave Therapy on neovascularization of living tissues.
In the last years cell therapy with stem and progenitor cells is a new approach to improve neovascularization and function of ischemic tissue. Chemoattractant factors such as SDF-1 and VEGF during acute ischemia attracts circulating progenitor cells (CPCs).

Aicher, A. et al. investigated the effect of extracorporeal shock wave therapy on the attraction of infused human CPCs in a rat model of chronic limb ischemia.
Adductor muscles of the right hid limb of nude rats were treated with 500 shock waves at low energy. The left hid limbs were serving as controls. 24 hours following shock wave therapy labeled CPCs were systemically injected and 48 hours following cell injection, adductor muscles were harvested for immunostaining. Systemically

injected CPCs were significantly more frequently found in the shock wave treated right hind limb muscles as compared to the untreated left control limb (untreated: 1.0±1.1 vs SW: 33.8± 23.2 CPCs per section $P<0.05$; $n>4$). In order to evaluate the functional relevance of SW pretreatment for efficacy of cell therapy, Aicher investigated the changes of blood flow recovery following CPC treatment with and without SW pre-treatment in chronic hind limb ischemia (5 weeks following induction of hind limb ischemia). 24 hours following SW treatment CPCs were injected and 2 weeks later the blood flow was determined by laser Doppler imaging. Results have shown that CPC infusion alone did not significantly increase blood flow recovery in the hind limb ischemia model, whereas CPCs infusion in combination with SW pre-treatment resulted in significant increase in blood flow recovery at 14 days (untreated:0.54±0.149; SW +CPCs: 0.88±0.17; $P<0.01$; $n>4$). Thus, we may conclude that low energy shock wave treatment improves the efficacy of CPC treatment in patients with chronic ischemia.

An additional biological effect of Shock Waves is the induction of differentiation of cardiac primitive cells in vitro.

Di Meglio et al. assessed the hypothesis that SWs can have positive effects on precursors of all cardiac cell populations, namely cardiomyocytes, endothelial, smooth muscle cells and fibroblasts, this is due to the revelation that SW therapy enhances the expression of VEGF and its receptor Flt-1 in human umbilical vein endothelial cells in vitro and proves beneficial in patients with coronary artery disease. Bioptic pieces from normal adult hearts and from explanted ischemic cardiomyopathy hearts were used to obtain the outgrowth of cardiac cells in-vitro.

Precursor and progenitor cells proliferation and expression of differentiation markers were examined both without and after exposition to 800 shock waves at 0.1 mJ/mm2. Results have shown that the growth rate of cardiac cells was slowed down by SW treatment due to the decrease of fibroblast relative number in the cell culture (83% vs. 56%, $p<0.05$). The expression of Flt-1 increased significantly in the primitive cells from both normal and diseased hearts after SW treatment (4-fold and 2-fold, respectively). Similarly, the SW treatment increased nearly 2-fold the expression of smooth muscle actin. The expression of MLC-1 decreased significantly after SW treatment after SW treatment of normal cells and increased in the cells from pathological hearts, while MLC-2 decreased in both cell types. Importantly the number of the primitive cells and expression of differentiation markers were always significantly higher in the control cells from pathological hearts when compared with the normal hearts.

Di Meglio's results indicate that differentiation of primitive cells in the myocardium is markedly enhanced in chronic pathological conditions. The SWs influence positively the differentiation and maturation of cardiomyocytes, endothelial and smooth muscle cells, reducing the relative number of fibroblasts in- vitro, possibly due to the influence on growth factor production and release, enhancing their auto and paracrine action. The effects of shock wave therapy were markedly more prominent in the cells from normal hearts, therefore its use may be recommended in the early stages of heart failure.

Seeman et al. studied the effect of single shock waves on artificially perfused rabbit kidneys. In their study they exposed extracorporeally perfused rabbit kidneys to 5 shock waves at 14 kV. While perfusion flow rate was kept constant, the arterial perfusion pressure was recorded to assess changes in vascular resistance. Results showed that immediately following SW application perfusion pressure decreased by 20-30%, followed by a short relative pressure rise that did not reach pre-treatment values. 15-20min. later arterial perfusion pressure re-attained pre-treatment values. Subsequent to treatment urine flow decreased by over 50%. The observed pressure rise was also induced in non-treated kidneys by perfusion with the effluent of the treated kidneys indicating a humoral mechanism. On the other hand SW application to Formalin-fixed kidneys only caused a marked decrease in the arterial perfusion pressure suggesting that this effect is due to pure mechanical interaction of the SW also found in denaturated kidneys.

Mariotto et al. hypothesized that ESWT increases NO production in cells. This was based on the available data that low density SWs (0.03mJ/mm2) were successfully used for anti-inflammatory treatment of soft tissues, and on the fact that NO plays a critical role in inflammation. Using human Umbilical Vein Endothelial Cells (HUVEC) as a model they observed that ESWs at low energy density rapidly induced enhancement of eNOS activity. In these cells eNOS activity is modulated by tyrosine- and serine phosphorilation. ESW shifted eNOS to a less tyrosine phosphorilated form without affecting its serine-phosphorilation, thus accounting for its rapid enzyme activation. LPS/IFN-gamma treatment of HUVEC cells induced a rapid inhibition of eNOS activity and concomitant NF-kappaB activation which were efficiently counteracted by ESWT. These results indicated that the molecular mechanism of clinically observed anti-inflamatory action of ESW should include tyrosine-dephosphorilation of eNOS, a successive increase in NO production and suppression of NF-kappaB activation.

Ciampa AR et al. suggested a possible molecular mechanism of the anti-inflammatory action of ESWT. In their study they have shown that low energy ESWT quickly increase neural niric oxide synthase (nNOS) activity and basal nitric oxide (no) production in a rat glioma cell line. In addition the treatment of these cells with ESW reverts the decrease of nNOS activity and NO production induced by a mixure of

lipopolysaccharides (LPS), interferon-gamma (IFN-gamma) plus tumor necrosis factor alpha (TNF-alpha). Finally ESW treatment efficiently downregulates NF-kappaB activation and NF-kappaB-dependent gene expression, including inducible NOS and TNF-alpha.

Gotte G. et al. demonstrated that NO can non-enzymatically be formed with a short-time kinetics (min.) by "bombing" with shock waves a solution containing 1 mM hydrogen peroxide and 10 mM L-arginine. This procedure is widening its medical applications with surprisingly positive effects in tissue regeneration and this finding could be one of the initial steps for the understanding of the biochemical responsible for these therapeutical effects.
A large number of animal studies have already demonstrated the biological effect of ESWT on neovascularization.

Wang CJ et al. have shown based on the results of their laboratory that the mechanism of SWs first stimulates the early expression of angiogenesis-related growth factors including eNOS, VEGF and PCNA(proliferating Cell Nuclear Antigen)., then induces the ingrowth of neovascularization that improves blood supply and increases cell proliferation and eventual tissue regeneration to repair tendon or bone tissues. The rise of angiogenetic markers occurred in as early as one week and lasted for approximately 8 weeks while the neovascularization was first noted in 4 weeks and persisted for 12 weeks or longer along with cell proliferation. These findings support the clinical observation that the effect of ESWT appears to be dose-dependent and symptom improvement with time.

In an additional study Wang CJ et al. investigated the effect of SWT on neovascularization of tendon-bone junction. The right limb of 50 NZ white rabbits was treated with SWT to the Achilles tendon near the insertion to the bone. The left limb served as control. Biopsies of the bone-tendon junction were performed 0, 1, 4, 8, and 12 weeks post treatment. The number of neovessels was examined microscopically. Neovascularization was confirmed by angiogenic markers including VEGF, eNOS and endothelial cell proliferation determined by PCNA expression. Results showed that ESWT produced a significantly higher number of neo-vessels and angiogenesis related markers including eNOS, VEGF and PCNA than the control without SW treatment. The eNOS and VEGF began to rise in as early as one week and remained high for 8 weeks, then declined at 12 weeks; whereas the increases in PCNA and neo-vessels began at 4 weeks and persisted for 12 weeks. This led to the conclusion that ESWT in-growth of neovascularization associated with early release of angiogenesis-related markers at the Achilles-tendon-bone junction in rabbits. This neovascularization may play a role to improve blood supply and tissue regeneration at the tendon- bone junction.

In yet an additional study Wang CJ et al. studied the phenomenon of neovascularization at the Achilles tendon-bone junction after low energy shock wave application in eight mongrel dogs. Prior to shock wave application control specimens were taken from the medial one third of the right Achilles tendon-bone unit. 1000 impulses of low energy (14kV, 0.18mJ/mm2) shock wave s were applied to the right Achilles tendon-bone junction. Biopsies taken from the middle one-third of the Achilles tendon –bone junction at 4 weeks and from the lateral one third at 8 weeks have shown: New capillary and muscularized vessels were seen in the specimens obtained in 4 and 8 weeks after SW application but none were seen in the controls. There was considerable geographic variation in the number of the new vessels in the same specimen. Myofibroblasts were not seen in the controls. On the other hand myofibroblasts with haphazard appearance and intermediate orientation fibers were seen in all specimens obtained at 4 weeks and predominantly intermediate orientation myofibroblast fibers at 8 weeks. There were no changes in bone matrix, osteocyte activity and vascularization within the bone.

In addition to the fact that VEGF is a strong mitogen which induces angiogenesis, Gutersohn, A. et al. investigated whether VEGF is elevated after ESWT in HUVEC cells. HUVEC cells were treated with ESWT in different energy levels of 0.02, 0.05, 0.1, and 0.3 mJ/mm2. After shock wave treatment the cells were grown for

24-36 hours. Results have shown that cell death increased with increasing energy dosages. RT-PCR revealed a significant increase in VEGF mRNA in ESWT treated cells in comparison to untreated controls.

They have concluded from this study that Cardiac Shock Wave Therapy can induce VEGF mRNA increase in endothelial cells. They concluded that the beneficial effects on cardiac performance following CSWT may be due to an induction of angiogenesis via VEGF. Thus, CSWT may serve as a new treatment for patients with end stage coronary artery disease.

Nishida, T. (16) et al. also examined the in-vivo and in-vitro effects of ESWT. They applied SWs at HUVEC cells and demonstrated a significant rise in the expression of mRNA of VEGF and its receptor Flt-1 in vitro. A porcine model with chronic myocardial ischemia was made by placing an ameroid constrictor at the proximal segment of the left circumflex coronary artery, which gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction in 4 weeks. Thereafter ESWT to the ischemic myocardial region was performed, which induced a complete recovery of the left ventricular ejection fraction (51±2% to 62±2%), wall thickening fraction (13±3% to 30±3%), and regional myocardial blood flow (1.0±0.2 to 1.4±0.3 mL x min(-1) x g(-1). Neither arrhythmias nor other complications were observed during or after the treatment. SW treatment of the ischemic myocardium was significantly upregulated VEGF expression in vivo.

All the data above demonstrates the biological basis of the enhancing effect of ESWT on tissue neovascularization and regeneration and might serve for treatment of ischemic related erectile dysfunction.

A new Extracorporeal Shockwave therapy device was developed recently which couples the ability of low intensity shock waves to induce angiogenesis to the therapy ED and is becoming a new alternative in the treatment of ED patients. Short and long term results have shown the ability of this new therapy to increase penile blood flow and improve overall erectile function and quality of life of patients.

This booklet summarizes the in vitro, in vivo and clinical studies done on the subject; from the biochemical processes upon shockwaves are triggering the angiogenesis process and the anti-inflammatory ones, following animal studies insuring the safety and effectiveness of the concept, to clinical use in patients.

For further information, please do not hesitate to contact Medispec at: marketing@medispec.com

ED1000

Medispec experience

Does Low Intensity Extracorporeal Shock Wave Therapy Have a Physiological Effect on Erectile Function? Short-Term Results of a Randomized, Double-Blind, Sham Controlled Study

Yoram Vardi,*,† Boaz Appel, Amichai Kilchevsky and Ilan Gruenwald

From the Neuro-Urology Unit, Rambam Healthcare Campus, and the Rappaport Faculty of Medicine, Technion – IIT, Haifa, Israel (YV, BA, AK, IG), and the Department of Urology, Yale-New Haven Hospital, New Haven, Connecticut (AK)

Purpose: We investigated the clinical and physiological effect of low intensity extracorporeal shock wave therapy on men with organic erectile dysfunction who are phosphodiesterase type 5 inhibitor responders.

Materials and Methods: After a 1-month phosphodiesterase type 5 inhibitor washout period, 67 men were randomized in a 2:1 ratio to receive 12 sessions of low intensity extracorporeal shock wave therapy or sham therapy. Erectile function and penile hemodynamics were assessed before the first treatment (visit 1) and 1 month after the final treatment (followup 1) using validated sexual function questionnaires and venoocclusive strain gauge plethysmography.

Results: Clinically we found a significantly greater increase in the International Index of Erectile Function-Erectile Function domain score from visit 1 to followup 1 in the treated group than in the sham treated group (mean ± SEM 6.7 ± 0.9 vs 3.0 ± 1.4, $p = 0.0322$). There were 19 men in the treated group who were initially unable to achieve erections hard enough for penetration (Erection Hardness Score 2 or less) who were able to achieve erections sufficiently firm for penetration (Erection Hardness Score 3 or greater) after low intensity extracorporeal shock wave therapy, compared to none in the sham group. Physiologically penile hemodynamics significantly improved in the treated group but not in the sham group (maximal post-ischemic penile blood flow 8.2 vs 0.1 ml per minute per dl, $p < 0.0001$). None of the men experienced discomfort or reported any adverse effects from the treatment.

Conclusions: This is the first randomized, double-blind, sham controlled study to our knowledge that shows that low intensity extracorporeal shock wave therapy has a positive short-term clinical and physiological effect on the erectile function of men who respond to oral phosphodiesterase type 5 inhibitor therapy. The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with erectile dysfunction.

Key Words: erectile dysfunction, high-energy shock waves, penis, hemodynamics

Abbreviations and Acronyms

ED = erectile dysfunction

EHS = Erection Hardness Score

FMD = flow mediated dilatation

FU1 = followup 1

FU2 = followup 2

IIEF = International Index of Erectile Function

IIEF-EF = International Index of Erectile Function-Erectile Function domain score

LI-ESWT = low intensity extracorporeal shock wave therapy

PDE5i = phosphodiesterase type 5 inhibitors

V1 = visit 1

Submitted for publication October 26, 2011.

Study received institutional ethics review board approval.

Supported by a partial unrestricted grant from Medispec Ltd., Israel that included the use of the focused shock wave probe, Omnispec ED1000.

* Correspondence: Neuro-Urology Unit, Rambam Healthcare Campus, Haifa, Israel (telephone: 00972-4-8542819; FAX: 00972-4-8542883; cell: 00972547655550; e-mail: yvardi@rambam.health.gov.il).

† Financial interest and/or other relationship with Medispec, Ltd.

NUMEROUS therapeutic strategies exist for improving erectile function. While these therapies have been proven to be safe and effective, they are limited for use before the sexual act and do not modify the physiological mechanism of penile erection.[1] Gene and stem cell therapies are current examples of treatment strategies whose therapeutic goals are to restore erectile function as part of the present trend to shift the field of ED treat-

0022-5347/12/1875-1769/0
THE JOURNAL OF UROLOGY®

Vol. 187, 1769-1775, May 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.12.117

ments away from on demand palliative treatments.[2,3]

Adopting this new treatment strategy we began exploring the use of LI-ESWT to achieve this goal.[4,5] Using LI-ESWT as a treatment modality is not new. In 1990 Young and Dyson discovered that therapeutic ultrasound encourages angiogenesis by enhancing the expression of vascular endothelial growth factor.[6–8] This finding led clinicians to begin using shock wave therapy in the treatment of coronary artery disease,[9] bone fractures,[10] calcifying tendonitis[11] and diabetic foot ulcers.[12]

The results of our pioneer pilot study demonstrated that LI-ESWT improved erectile function and penile hemodynamics in men with ED who respond to pharmacotherapy.[4] We also reported that LI-ESWT effectively converted PDE5i nonresponders to responders.[5] While these results were encouraging, our studies were limited by the small sample size and lack of an appropriate control group. To validate our previously published results and to demonstrate whether LI-ESWT has a true physiological effect on the erectile mechanism, we conducted a larger, randomized, double-blind, sham controlled study in men with ED and cardiovascular risk factors who responded to PDE5i.

MATERIALS AND METHODS

The study protocol was reviewed and approved by our institution's Ethics Review Board. All participants gave written informed consent before entering the study.

Screening, Inclusion and Exclusion Criteria

We recruited men with a history of ED for at least 6 months who were already responding to PDE5i from our outpatient ED clinic between July 2009 and October 2010. A total of 77 men underwent an initial screening, including a complete medical history and physical examination (fig. 1). For study inclusion each man had to have an IIEF-EF of 19 or greater while on PDE5i and had to be in a stable heterosexual relationship for more than 3 months. Each man also had to agree to discontinue PDE5i during the entire study period. Men were excluded from analysis if they had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy, were receiving ongoing treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities. Ultimately 10 men met the exclusion criteria.

Study Protocol

The 67 participants who met the inclusion criteria underwent a 4-week PDE5i washout period. At V1 the men were assigned into 2 groups of those who received LI-ESWT (treated group) and those who were given sham therapy (sham group) in a 2:1 ratio using a computer generated table of random numbers. At the same visit each man completed a full IIEF and EHS questionnaire while not on PDE5i. The penile hemodynamics of each man was also evaluated at V1 using our previously described FMD technique in which penile blood flow is measured at rest and after a 5-minute ischemic period using venoocclusive strain gauge plethysmography.[13,14] Each subject then began the 9-week treatment period, which was comprised of 2 treatment sessions per week for 3 weeks that were repeated after a 3-week no treatment interval. A month after the final treatment session (FU1) erectile function and penile hemodynamics were reassessed while the men were still not taking PDE5i (fig. 2).

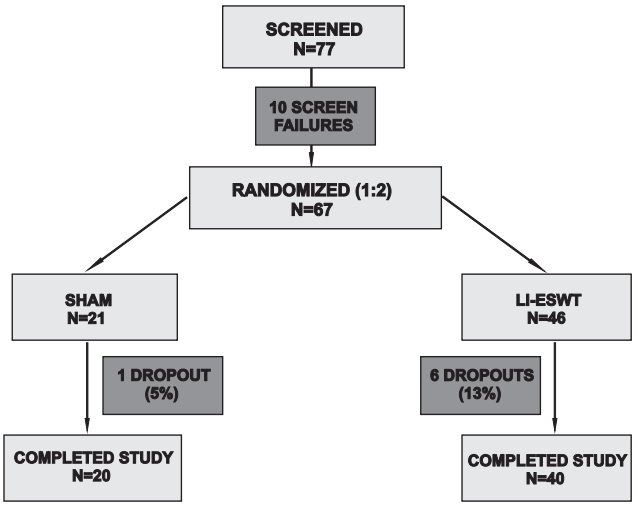


Figure 1. Patient screening and randomization flowchart

Specifics of LI-ESWT

We applied a standard commercial gel normally used for sonography to the penis. The shock waves were delivered to the distal, mid and proximal penile shaft, and the left and right crura using a specialized focused shock wave probe (Omnispec ED1000, Medispec Ltd., Yehud, Israel) as described in our previous studies (fig. 3).[4,5] Since the depth of the shock waves reached both corpora, treatment was delivered on 1 side of the penile shaft only. The 300 shocks at an energy density of 0.09 mJ/mm^2 and a frequency of 120 shocks per minute were delivered at each of the 5 treatment points. Each treatment session was 15 minutes. Due to the low energy density, no local or systemic analgesia was needed.

Followup

To improve the recruitment and compliance rates, all men were eligible to receive an additional treatment course if they were unsatisfied with the initial outcome and had an IIEF-EF of less than 25 at FU1 without PDE5i, regardless of the group to which they were originally assigned. The IIEF of the men who did not undergo additional treatment was reevaluated after 3 months (FU2).

Randomization and Sham Treatment

At randomization each man received a numeric identifier code that was paired to a treatment or sham probe supplied by the manufacturer. The sham probe looked identical to and made the same noise as the treatment probe, but contained a metal plate that prevented the shock wave energy from being applied to the penis. Since the noise and vibration of the probes used in both groups were

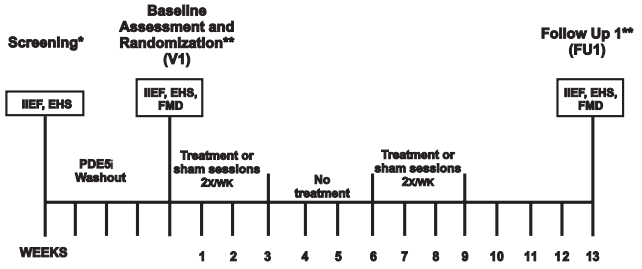


Figure 2. Study flowchart. Single asterisk indicates with PDE5i. Double asterisk indicates without PDE5i.

similar, and the treatment was painless, the operator and subject were blind to the treatment type.

Main Outcome Measures

We used the IIEF-EF to evaluate erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF between V1 and FU1 because this value indicates an improvement of erectile function by at least 1 severity category. The secondary outcome measures were defined as significant increases in the IIEF subcategories, an increase in EHS from 2 or less at V1 to 3 or more at FU1, and an improvement in penile blood flow.

Statistical Analysis

The data were analyzed using statistical software (JMP®, SAS), and the data are expressed as median and range or mean ± SEM. The values of the study parameters from the 2 study groups were compared by Student's t test with pooled variances or the Wilcoxon signed rank test as appropriate. The linear relationship between changes in the IIEF-EF and changes in penile blood flow at FU1 was assessed by Spearman's rank order correlation. A chi-square contingency analysis was used to examine the relationship between the IIEF-EF and penile hemodynamics, with statistical significance set at 5%.

RESULTS

The baseline characteristics of the 2 study groups were similar (table 1). Six (13%) men in the treated group and 1 (5%) man in the sham group did not complete the study protocol (fig. 1). Of these men 3 took PDE5i, 2 could not meet the necessary time commitments, 1 separated from his wife and 1 had a prolonged hospitalization.

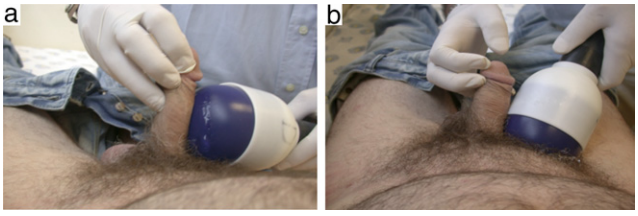


Figure 3. Application of shock wave probe to penile shaft (*a*) and crura (*b*).

Table 1. *Baseline characteristics of the study population at randomization while off PDE5i therapy*

	Sham	Treatment
No. men	20	40
Median age (range)	57 (35–77)	58 (27–72)
Median mos ED (range)	60 (6–240)	42 (6–240)
Concomitant condition (% of men):		
Cardiovascular risk factors*	60	75
Coronary artery disease	10	20
Diabetes mellitus	30	30
Mean ± SEM IIEF-EF domain scores	11.5 ± 0.86	12.6 ± 0.75
Median IIEF-EF domain scores (range)	12.5 (6–17)	13.5 (6–19)
Disease stratification (% of men):†		
Severe dysfunction (IIEF-EF 0–6)	20	12.5
Moderate dysfunction (IIEF-EF 7–12)	30	32.5
Mild to moderate dysfunction (IIEF-EF 13–18)	50	42.5
Mild dysfunction (IIEF-EF 19–24)	0	12.5

All values not significant ($p > 0.05$).

* Including at least 1 of cigarette smoking, hypercholesterolemia, hypertension or obesity.

† Statistical assessment of possible treatment group differences in disease severity distributions of patients could not be performed due to the small numbers in some subgroups.

Efficacy

At FU1 the mean IIEF-EF in the treated group increased by 6.7 points while the score in the sham group increased by 3.0 points ($p = 0.0322$, fig. 4). There were 26 (65%) men in the treated group and 4 (20%) in the sham group who had a 5-point or greater increase in IIEF-EF ($p = 0.0001$). The treated men had significantly improved mean scores in the IIEF subcategories of Sexual Desire ($p = 0.0348$) and Overall Satisfaction ($p = 0.0054$, fig. 4). Of 28 men in the treated group who had an EHS of 2 or less at V1, 19 reported an increase in EHS to 3 or greater at FU1 vs no men in the sham group (fig. 5).

Penile hemodynamics were assessed in 59 of the 60 men who presented at FU1 (1 man in the treated group refused this assessment after treatment). Penile hemodynamics improved significantly in the treated group (table 2, $p < 0.0001$). Furthermore, we noted a strong positive correlation between changes in the IIEF-EF and changes in the resting and maximal post-ischemic penile blood flow at FU1 ($p < 0.0001$). The IIEF-EF and the post-ischemic maximal blood flow improved ($p < 0.001$) in 22 (56%) men in the treated group and 1 (5%) man in the sham group.

Adverse Events

Unlike painful higher intensity shock wave energy used to treat nephrolithiasis and Peyronie disease (0.2 to 1.1 mJ/mm^2), the low intensity shock wave energy (0.09 mJ/mm^2) used in this study was not associated with any pain or side effects such as ecchymoses or hematuria.

Post-Study Followup

A total of 23 men including 16 (80%) from the sham group opted to receive a second series of treatments

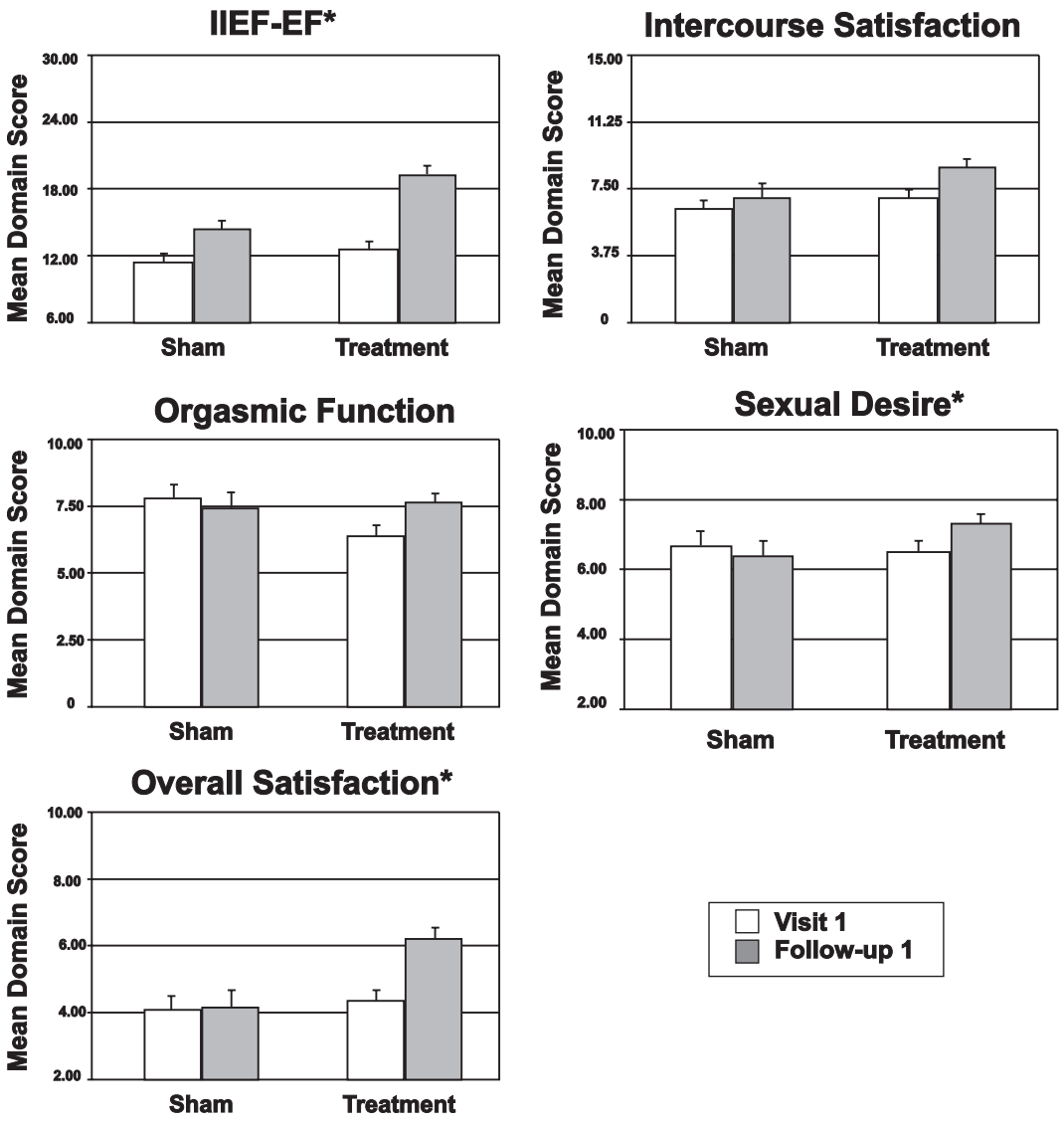


Figure 4. IIEF domain scores (mean ± SEM) for men treated with LI-ESWT or sham therapy at V1 or FU1. Asterisk indicates $p < 0.05$ and represents significance of difference between 2 groups.

without knowing their original group (fig. 6). Mean IIEF-EF of men continuing on to a second round of treatments was 12.2 at FU1, while the remaining 36 men who had followup at 3 months had an additional increase in mean IIEF-EF from 20.7 at FU1 to 22.1 at FU2.

DISCUSSION

Due to the skepticism surrounding this novel treatment, insufficient scientific background and disappointing results of penile shock wave therapy in Peyronie disease, it was crucial to further establish the validity of LI-ESWT by conducting a randomized, double-blind, sham controlled study. We chose to use measurement tools that are validated and widely accepted such as the IIEF and EHS. While validated in men receiving on demand PDE5i, these questionnaires have a high degree of sensitivity and specificity for detecting treatment related changes in the erectile mechanism.[15–17] Since LI-ESWT is a nonpharmacological intervention whose effect is not defined per sexual encounter but during a prolonged period, questionnaires such as the sexual encounter profile were not used.

We postulated that the underlying mechanism of LI-ESWT action is to improve penile hemodynamics. To confirm this hypothesis, objective and quantifiable measures of penile hemodynamics are required. Our experience with nocturnal penile tumescence testing in our first pilot study led us to conclude that nocturnal penile tumescence is not suitable to be used as an investigative tool due to difficulties in interpreting the results in terms of meaningful pa-

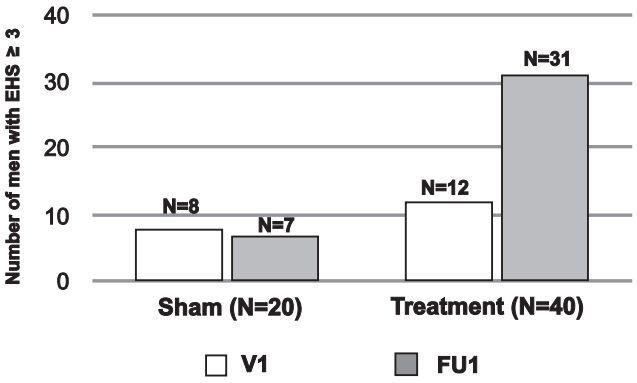


Figure 5. Number of men with EHS 3 or greater at V1 and FU1. For EHS clinical interpretation, grade definitions characterizing penis are grade 1—larger but not hard, grade 2—hard but not hard enough for penetration, grade 3—hard enough for penetration but not completely hard, grade 4—completely hard and fully rigid.

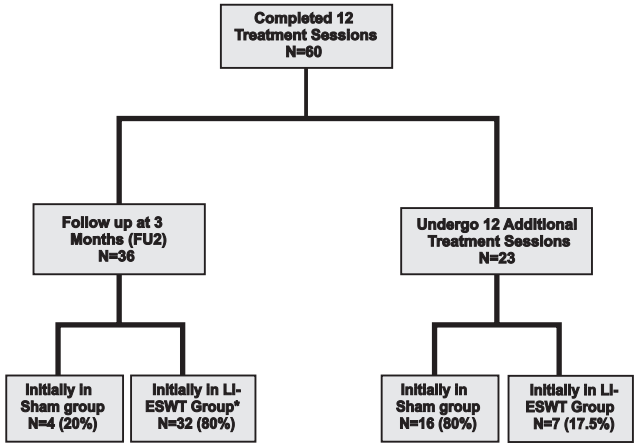


Figure 6. Patient followup after 12 treatment sessions. Asterisk indicates 1 patient (2.5%) was lost to FU2.

rameter changes and changes in penile hemodynamics. We did not use duplex ultrasonography because it mainly measures cavernous artery flow, is operator dependent, and is reliant on the timely response of injected vasoactive agents and patient disposition. Although it is an excellent test to evaluate penile vascular status, duplex ultrasonography may be problematic for the comparison of changes in penile hemodynamics before and after intervention. We used venoocclusive plethysmography to measure penile hemodynamics because it can objectively assess penile perfusion in the flaccid state in a simple and reproducible fashion, it is not operator dependent and it has previously been proven to reflect changes in erectile function after intervention.[13,14] Furthermore, while our group was the first to describe the FMD technique in the penis, it is not principally different from the widely used FMD technique to assess endothelial function in the brachial artery.

The IIEF-EF of the treated men significantly improved at FU1. The increase was not as great as the increases in the IIEF-EF that were reported in studies that introduced the therapeutic effects of PDE5i.[18–20] Admittedly, comparing the efficacies of an on demand treatment to a nonpharmacological rehabilitative intervention that is unrelated to the sexual act is inherently problematic. Unlike the ED naive cases in the first sildenafil studies that had not previously experienced treatment success, those in our study had a different definition of therapeutic success because they already had a positive experience with PDE5i. Furthermore, many of the original PDE5i studies included a mixed ED population, as opposed to our group of men with similar ED risk factors. Our exclusion criteria may also account for the 25% sham effect seen in our study compared to a placebo effect as high as 46% reported in the original PDE5i studies.[21] The results of later studies that excluded patients with psychogenic ED, and examined the effect of PDE5i on men with organic ED and cardiovascular risk factors, are comparable to the results of our study.[22,23] Nevertheless, it is possible that our empirical LI-ESWT protocol is less effective than PDE5i therapy.

Table 2. *Changes in penile blood flow at FU1*

	Resting Blood Flow (ml/min/dl)	Max Blood Flow (ml/min/dl)
Sham:		
Median	0.2	−0.1
Min	−6.7	−9.2
Max	7.6	18.5
Treatment:		
Median	4.6	8.2
Min	−15.5	−17.0
Max	80.2	124.8

All values $p < 0.0001$.

An unexpected finding was the significant improvement in the IIEF Sexual Desire domain scores of the treated men, a finding that has been reported in at least 1 of the previous studies that evaluated pharmacotherapy.[19] While our finding was statistically significant, the clinical importance of a 1-point increase in this score remains unclear.

We did not find statistically significant improvement in the IIEF Sexual Satisfaction domain score. We attribute this lack of improvement to our subjects' previous positive experience with PDE5i. Nevertheless, the IIEF Overall Satisfaction domain score did increase significantly after treatment, indicating a beneficial effect of LI-ESWT.

The EHS data also revealed that more men in the treated group than in the sham group were able to achieve erections sufficiently hard for penetration.

Ease of definition and applicability make the EHS a valuable tool for simple clinical assessment. However, it is statistically ill suited for pre-post and 2-group study designs such as ours.

Physiological evidence that LI-ESWT improves penile hemodynamics comes from the finding that the 2 measures of penile blood flow improved significantly in the treated group and were positively correlated with the increases in IIEF-EF. Moreover, in seeking a success criteria based on clinical and physiological outcomes, we found that of the patients who had a 5-point or greater improvement in the IIEF-EF and improved penile hemodynamics all but 1 came from the treated group. Further supporting our contention that LI-ESWT improves penile hemodynamics is our finding that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes.

While the purpose of this study was to evaluate the physiological effects of LI-ESWT on the penis, our finding that the IIEF-EF remained increased 3 months after the final treatment suggests that the positive physiological effect is preserved. This finding is similar to that of our previous study demonstrating that the subjects' IIEF-EF remained high at the 3 and 6-month followup.[4]

The treatment protocol that we used in all our studies to date was based on that described in the cardiology literature.[24,25] This empirical protocol had not been previously tested in animal or human penile tissue and, therefore, will likely change as more protocols are examined.

Although our final study population was comprised of only 60 men, this number of participants was sufficient to achieve our main goal of determining whether our treatment protocol could yield a genuine physiological effect on cavernous tissue.

To date, no deleterious side effects have been reported in the long-term followup of patients undergoing high intensity penile shock wave therapy for the treatment of Peyronie disease,[26,27] despite findings that such shock waves may lead to the collagenization of corporal smooth muscle in the rat.[28] While our subjects did not report any adverse effects to the treatment, the long-term risk of LI-ESWT on penile tissue has yet to be fully elucidated.

CONCLUSIONS

This is the first randomized, double-blind, sham controlled study in which LI-ESWT has been shown to have a beneficial effect on erectile function in men with ED and cardiovascular risk factors. While we do not know the precise mechanism of action of LI-ESWT, our objective measures lead us to presume that this therapy works by improving penile hemodynamics. We also found that this treatment is feasible and tolerable, and is unique in that it has rehabilitative characteristics. Additional studies with long-term followup are now needed to fully evaluate the efficacy of this new therapy and confirm our findings. These studies must be backed by basic science research whose aims are to fully understand the mechanism of action of this energy. With this additional knowledge, our hope is that LI-ESWT will make its way into the armamentarium of treatment options currently being used in the long-term clinical management of ED.

AKNOWLEDGMENTS

Elliot Sprecher assisted with the statistical analysis and Dr. Arieh Bomzon provided assistance.

REFERENCES

1. LaVignera S, Condorelli RA, Vicari E et al: Endothelial apoptosis decrease following tadalafil administration in patients with arterial ED does not last after its discontinuation. Int J Impot Res 2011; **23:** 200.

2. Melman A, Bar-Chama N, McCullough A et al: hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. Hum Gene Ther 2006; **17:** 1165.

3. Deng W, Bivalacqua TJ, Hellstrom WJ et al: Gene and stem cell therapy for erectile dysfunction. Int J Impot Res 2005; **17:** S57.

4. Vardi Y, Appel B, Jacob G et al: Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 2010; **58:** 243.

5. Gruenwald I, Appel B and Vardi Y: Low-intensity extracorporeal shock wave therapy–a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 2012; **9:** 259.

6. Young SR and Dyson M: The effect of therapeutic ultrasound on angiogenesis. Ultrasound Med Biol 1990; **16:** 261.

7. Nurzynska D, Di Meglio F, Castaldo C et al: Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. Ultrasound Med Biol 2008; **34:** 334.

8. Wang CJ: An overview of shock wave therapy in musculoskeletal disorders. Chang Gung Med J 2003; **26:** 220.

9. Kikuchi Y, Ito K, Ito Y et al: Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris. Circ J 2010; **74:** 589.

10. Haupt G, Haupt A, Ekkernkamp A et al: Influence of shock waves on fracture healing. Urology 1992; **39:** 529.

11. Rompe JD, Rumler F, Hopf C et al: Extracorporal shock wave therapy for calcifying tendinitis of the shoulder. Clin Orthop Relat Res 1995; **321:** 196.

12. Wang CJ, Kuo YR, Wu RW et al: Extracorporeal shockwave treatment for chronic diabetic foot ulcers. J Surg Res 2009; **152:** 96.

13. Dayan L, Gruenwald I, Vardi Y et al: A new clinical method for the assessment of penile

endothelial function using the flow mediated dilation with plethysmography technique. J Urol 2005; **173:** 1268.

14. Vardi Y, Dayan L, Appel B et al: Penile and systemic endothelial function in men with and without erectile dysfunction. Eur Urol 2009; **55:** 979.

15. Mulhall JP, Goldstein I, Bushmakin AG et al: Validation of the erection hardness score. J Sex Med 2007; **4:** 1626.

16. Rosen RC, Riley A, Wagner G et al: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; **49:** 822.

17. Rosen RC, Cappelleri JC and Gendrano N 3rd: The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 2002; **14:** 226.

18. Goldstein I, Lue TF, Padma-Nathan H et al: Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998; **338:** 1397.

19. Porst H, Rosen R, Padma-Nathan H et al: The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 2001; **13:** 192.

20. Brock GB, McMahon CG, Chen KK et al: Efficacy and safety of tadalafil for the treatment of erectile dysfunctions: results of integrated analyses. J Urol 2002; **168:** 1332.

21. Stecher VJ: Near-normalization of erectile function and improvement of psychosocial quality-of-life in men with erectile dysfunction treated with Viagra® (sildenafil citrate). J Sex Med 2005; **2:** 83.

22. Goldstein I, Kim E, Steers WD et al: Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: Multiple Observations in Men with Erectile Dysfunction in National Tadalafil Study in the US. J Sex Med 2007; **4:** 166.

23. Donatucci C, Eardley I, Buvat J et al: Vardenafil improves erectile function in men with erectile dysfunction irrespective of disease severity and disease classification. J Sex Med 2004; **1:** 301.

24. Caspari GH and Erbel R: Revascularization with extracorporeal shock wave therapy: first clinical results. Circulation 1999; **100:** 84.

25. Khattab AA, Broderson B, Schuermann-Kuchenbrandt D et al: Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol 2007; **121:** 84.

26. De Berardinis E, Busetto GM, Antonini G et al: Extracorporeal shock wave therapy in the treatment of Peyronie's disease: long-term results. Arch Ital Urol Androl 2010; **82:** 128.

27. Srirangam SJ, Manikandan R, Hussain J et al: Long-term results of extracorporeal shockwave therapy for Peyronie's disease. J Endourol 2006; **20:** 880.

28. Muller A, Akin-Olugbade Y, Deveci S et al: The impact of shock wave therapy at varied energy and dose levels on functional and structural changes in erectile tissue. Eur Urol 2008; **53:** 635.

ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Low-Intensity Extracorporeal Shock Wave Therapy—A Novel Effective Treatment for Erectile Dysfunction in Severe ED Patients Who Respond Poorly to PDE5 Inhibitor Therapy

Ilan Gruenwald, MD, Boaz Appel, MD, and Yoram Vardi, MD

Neuro-urology Unit, Rambam Healthcare Campus, Haifa, Israel

DOI: 10.1111/j.1743-6109.2011.02498.x

ABSTRACT

Introduction. Low-intensity shock wave therapy (LI-ESWT) has been reported as an effective treatment in men with mild and moderate erectile dysfunction (ED).

Aim. The aim of this study is to determine the efficacy of LI-ESWT in severe ED patients who were poor responders to phosphodiesterase type 5 inhibitor (PDE5i) therapy.

Methods. This was an open-label single-arm prospective study on ED patients with an erection hardness score (EHS) ≤ 2 at baseline. The protocol comprised two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. Patients were followed at 1 month (FU1), and only then an active PDE5i medication was provided for an additional month until final follow-up visit (FU2).

At each treatment session, LI-ESWT was applied on the penile shaft and crus at five different anatomical sites (300 shocks, 0.09 mJ/mm^2 intensity at120 shocks/min).

Each subject underwent a full baseline assessment of erectile function using validated questionnaires and objective penile hemodynamic testing before and after LI-ESWT.

Main Outcome Measures. Outcome measures used are changes in the International Index of Erectile Function-erectile function domain (IIEF-ED) scores, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Results. Twenty-nine men (mean age of 61.3) completed the study. Their mean IIEF-ED scores increased from 8.8 $\pm$ 1 (baseline) to 12.3 $\pm$ 1 at FU1 ($P = 0.035$). At FU2 (on active PDE5i treatment), their IIEF-ED further increased to 18.8 $\pm$ 1 ($P < 0.0001$), and 72.4% ($P < 0.0001$) reached an EHS of ≥ 3 (allowing full sexual intercourse). A significant improvement ($P = 0.0001$) in penile hemodynamics was detected after treatment and this improvement significantly correlated with increases in the IIEF-ED ($P < 0.05$). No noteworthy adverse events were reported.

Conclusions. Penile LI-ESWT is a new modality that has the potential to treat a subgroup of severe ED patients. These preliminary data need to be reconfirmed by multicenter sham control studies in a larger group of ED patients.

Gruenwald I, Appel B, and Vardi Y. Low-intensity extracorporeal shock wave therapy—A novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 2012;9:259–264.

Key Words. Low Intensity Extracorporeal Shock Wave Therapy; Erectile Dysfunction; Penis

Introduction

Erectile dysfunction (ED) is one of the most common disorders of middle-aged men that profoundly affect their quality of life [1]. Although tremendous advances for treating this disorder have been made in the past decade, most currently available treatment modalities still rely on an "on demand" regime, of which up to 35% are unsuccessful [2–4]. From our experience, ED patients who were treated with a phosphodiesterase type 5 inhibitor (PDE5i) tend to search for an alternative

treatment modality that would ameliorate their ED. Hence, there is a need for an effective new treatment concept that would have a durable effect on the spontaneous improvement of erectile function.

We recently reported on the efficacy of a novel therapy, namely, applying low-intensity extracorporeal shock wave therapy (LI-ESWT) to the penis of patients with vasculogenic ED [5]. Results from in vitro and in vivo studies have shown that LI-ESWT induces neovascularization [6–8], and this finding was the theoretical basis for initiating studies on using LI-ESWT for treating ED. The results of our first preliminary research on ED patients who were responsive to PDE5i therapy showed that this treatment modality enhances penile perfusion and substantially improves erectile function [5].

A number of studies have been published on improving efficacy of PDE5i in men who do not respond or respond poorly to PDE5i therapy [9,10], suggesting potential ways to increase the efficacy of PDE5i therapy but not proposing any innovative treatments. Today, patients unsatisfied with response to oral therapy are candidates for either intracavernosal injections or penile implants. As most responders to PDE5i are usually managed by general practitioners in the primary health care setting, poor responders or severe ED patients are mainly referred to urologists and are managed in ED clinics. If LI-ESWT would be proved to be effective in these more severe ED patients, such a unique modality could expand our urological treatment armamentarium in the management of ED. It is against this background that we undertook the current study in which we evaluated the efficacy of LI-ESWT in severe ED men who were poor responders to PDE5i therapy.

Materials and Methods

This was an open-label single-arm prospective pilot study approved by the local ethics committee. The study had a screening phase, a 12-week LI-ESWT phase, applied to the patient's genital area, and a 2-month evaluation phase (Figure 1). Only men over 40 in a stable relationship (>3 months), who were previously diagnosed with ED at our outpatient clinic and were registered as poor responders to PDE5i therapy, were eligible for screening. In order to ensure that these men were poor responders, they were thoroughly questioned in regard to the dosage of the PDE5i, the timing of its intake, and the concomitant sexual stimulation. Men who could not provide definite answers were given four tablets of PDE5i and then asked to return for follow-up after they had completed their treatment. At this follow-up examination, the severe ED and poor responders were identified and then recruited for the study. Our key inclusion criterion was a low erection hardness score (EHS) of zero to two during PDE5i therapy. We excluded men (i) with an unstable medical or psychiatric condition, (ii) with a previous history of a neurological pathology, and (iii) after radical pelvic surgery, irradiations, or hormonal therapy.

At screening, written informed consent and demographic data were obtained from each participant. Assessment of erectile and sexual function during PDE5i treatment was determined using the International Index of Erectile Function-erectile

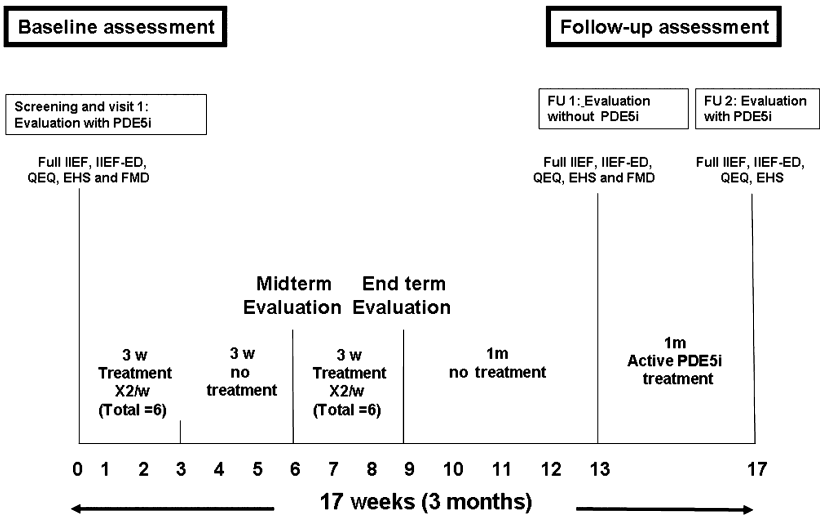


Figure 1 Study flow chart. EHS, erection hardness score; FMD, flow mediated dilatation; FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; PDE5i, phosphodiesterase type 5 inhibitor; QEQ, Quality of Erection Questionnaire.

function domain (IIEF-ED) score, the Quality of Erection Questionnaire (QEQ), and determination of the EHS. We used the flow mediated dilatation (FMD) technique for objective evaluation of the participant's penile hemodynamics and endothelial function [11,12]. After completion of the assessments, the first of the 12 LI-ESWTs was then administered. In the treatment phase, we used the identical treatment protocol that we used in our first study [5]. The treatment protocol consisted of two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. At each treatment session, LI-ESWT was applied on the penile shaft and crus for 3 minutes at five different penile anatomical sites. Each LI-ESWT comprised 300 shocks per treatment point at an energy density of 0.09 mJ/mm^2 and a frequency of 120/min. One month after the end of treatment (FU1), the results of LI-ESWT without PDE5i therapy were evaluated using the identical methods that were used at screening. As the main aim of this study was to assess the effect and benefit of LI-ESWT on this specific population of poor responders, we then provided an active PDE5i medication regime to each study participant, which comprised four tablets of a PDE5i that each man selected according to his best personal experience. One month later (FU2), we reassessed erectile function using the identical methods that were used at screening. The main outcome measures for success were changes in the IIEF-ED, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Statistical Analysis

A repeated-measures analysis of variance (ANOVA) was used to investigate the overall effects of treatment by comparing the effect of LI-ESWT on the study parameters at visit 1 to those from FU1 (net effect without PDE5i therapy) and at visit 1 to those from FU2 (under PDE5i treatment). The Tukey test was used to investigate the specific pairwise differences in the IIEF-ED, the QEQ scores, and the maximum FMD values. ANOVA results are reported as least squares mean ± the pooled standard error of the least squares mean (sem).

The binomial test was used to determine the proportion of treatment successes after treatment at FU1 and FU2 and the significance of the difference between the two proportions.

The changes in the EHS values for each study participant were compared by Bowker's test. For this purpose, the study group was divided into two subgroups: those who achieved a score of three to four on each follow-up visit and those who did not, and then comparing their scores with those that were determined at baseline, where none had scored three or four.

Spearman rank correlation was used to establish the relationship between the changes in the penile hemodynamics and endothelial function and the changes in the IIEF-ED from visit 1 to FU1.

All data were statistically analyzed using JMP Discovery Software (SAS Institute, NC, USA); statistical significance was at 5%.

Results

Thirty-three men entered the study after screening. Four men discontinued due to study noncompliance [2] and protocol violation [2]. The remaining 29 men who met the inclusion–exclusion had a mean IIEF-ED of 8.8 and a median ED duration of 60 months. Other detailed baseline characteristics are displayed in Table 1. The men were middle-aged with coronary heart disease, diabetes mellitus, or cardiovascular risk factors, had severe ED for more than a year, and were incapable of full sexual intercourse.

At FU1, subjects reported improved erectile function, as measured by significantly increased ($P = 0.035$) IIEF-ED (Figure 2), and 10 (34.5%) also reported increased penile rigidity (Figure 3).

Two months after end of the treatment (FU2), while on PDE5i therapy, the mean IIEF-ED increased by 10 points (18.8 ± 1 [standard deviation], $P < 0.0001$) (graph 1). In fact, eight men (27.6%) were normalized according to the IIEF-ED (≥25), and the IIEF-ED domain scores improved in 22 men (75.9%) by at least five points. Twenty-one men (72.4%) reported an EHS value ≥3 ($P < 0.0001$; see Figure 3). On average, the men noted some improvement in their erectile function, 3 weeks after the start of LI-ESWT, which was usually between the sixth and eighth treatment sessions.

Table 1 Baseline patient characteristics

Mean age (years)		61.3	
Age range (years)		41–79	
Cardiovascular risk factors		N	Percent
	Hypertension	24	83.7%
	Hypercholesterolemia	27	93.1%
	Heavy smoker	12	41.4%
	Obesity	8	27.5%
Coronary artery disease		16	55.1%
Diabetes mellitus		21	72.4%

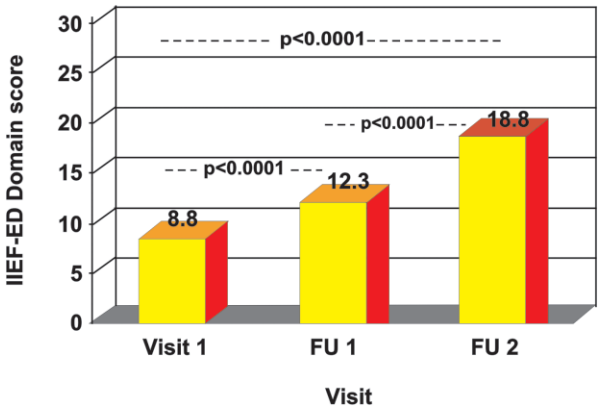


Figure 2 Mean IIEF-ED scores before and after LI-ESWT. FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; LI-ESWT, low-intensity extracorporeal shock wave therapy.

The secondary outcome measures that were used to assess the effect of LI-ESWT on erectile function were the total IIEF and the QEQ scores. Both scores increased significantly from baseline to FU2 (IIEF 30.6 vs. 48.9; QEQ scores: 12.2 vs. 45.5, $P < 0.0001$ for both).

Penile endothelial function improved significantly ($P = 0.0001$) after LI-ESWT, as assessed by the three parameters of penile hemodynamics and endothelial function, namely, maximal postischemic blood flow (Figure 4), basal blood flow, and the area under the flow-time curve (AUC).

We noted a strong correlation between the changes in the IIEF-ED and the changes in those three parameters at baseline and FU1, namely, maximal postischemic blood flow ($P = 0.0087$; Figure 5), basal blood flow ($P = 0.0448$), and AUC ($P = 0.0109$).

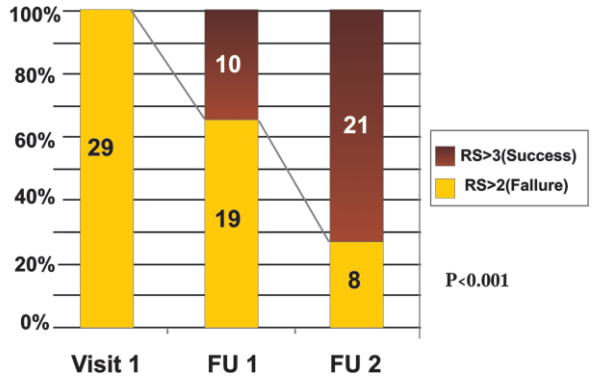


Figure 3 Changes in rigidity scales according to visit. RS, rigidity scale.

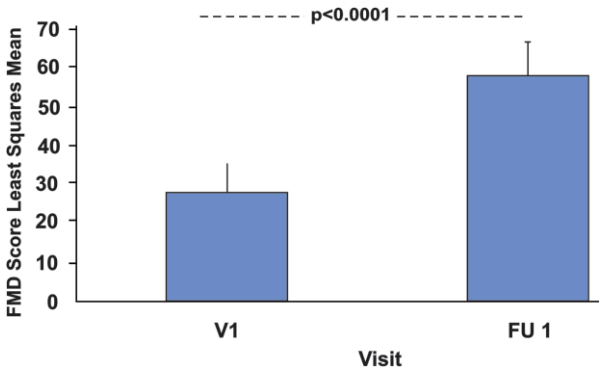


Figure 4 Maximal postischemic blood flow measured at the penis level per visit. FU, follow-up.

None of the men reported pain or any adverse events due to or after the treatment. In fact, the only adverse event was a mild transient allergic reaction to the gel in one man when it was applied at treatment session 2.

Discussion

This is our second report on the effect of LI-ESWT in ED patients. The results of our first

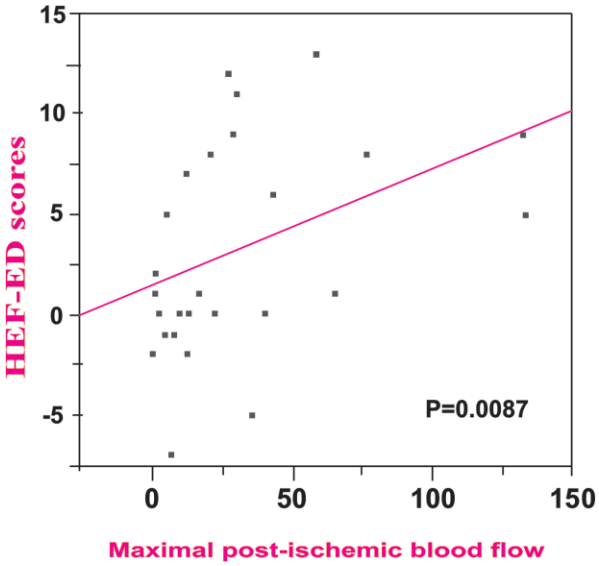


Figure 5 Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED domain scores. Graph 4: Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED score. IIEF-ED, International Index of Erectile Function-erectile function domain.

study showed that this treatment exerts a beneficial effect on 20 ED men who were responders to PDE5is. Here, we report that LI-ESWT is also beneficial when given to 29 poor responders with severe ED and significant cardiovascular risk factors. These results also confirm that this modality exerts a genuine physiological effect on the erectile mechanism when applied directly to the cavernosal tissue.

For this study, we used the identical protocol from our first trial of which the obtained good results did not justify any modification at this time. This does not mean that this treatment protocol is optimal. Hence, additional studies using different protocols need to be done in order to reach the desired clinical outcome.

We recruited men that were already on routine follow-up at our outpatient ED clinic.

Seven were on injection therapy and two were candidates for a penile implant. The others were relatively new patients who were poor or nonresponders to PDE5is and had been referred to our clinic for further treatment. At screening, we interviewed each man using a detailed intake sheet, documented their sexual difficulties in real-life situations, and compared the data with their IIEF-ED. This way, we assured that the study population consisted of true poor or nonresponders and allowed us to simplify the protocol and to assure patient compliance.

Our primary end points were the change in IIEF-ED and in the EHS value. We selected the IIEF-ED as it is the "gold standard" and the most commonly used instrument for evaluating ED. The EHS value was selected as it can precisely make a distinction between those who are able to penetrate and achieve full sexual intercourse from those who are unable to do so. We believe that the EHS value is a reliable measure of the functional capability of our study participants, and because of its simplicity, it should be used more frequently in other ED trials.

The results of the current study showed that the EHS value was three or more in 72.4% of the men after LI-ESWT. This result is remarkable as LI-ESWT significantly improved their response to PDE5i therapy and enabled these nonsexually functioning men to now achieve vaginal penetration and full sexual intercourse. This achievement is also noteworthy because it enabled 34% of these men to function sexually without using any medication. These results are supported by the corresponding improvement in their penile hemodynamics. Both the subjective and objective measurements of erectile function coincide, emphasizing that LI-ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow.

We noticed that most men feel some initial improvement between the sixth and eighth treatment sessions and sometimes a later effect is reported even after the end of treatment.

Limitations of this study are the lack of a sham-controlled arm and the relatively low number of participants. Despite these weaknesses, the substantial changes in the IIEF–ED and the EHS values, as well as the clinically significant effect that was achieved in this group of severe ED patients, cannot be undervalued.

Our finding that this emerging new and exciting treatment modality exerts a beneficial effect in men with severe ED suggests that LI-ESWT could be used as an alternative treatment or as an addition to PDE5i therapy. Noteworthy is our finding that the 21 diabetic patients in our study responded to this energy. As such men are considered a difficult to treat population for ED, this finding raises the question whether LI-ESWT is specifically effective in diabetic ED. Evaluation of the efficacy of LI-ESWT in such men using randomized, double-blind, sham-controlled studies is now needed, and we are in the midst of performing such a study. There is also a need for studies whose aim is to define the optimal treatment protocol in order to be able to offer the best results when using LI-ESWT in ED patients.

Conclusions

These preliminary results of the effect of LI-ESWT in a group of men with severe ED who were nonresponders to PDE5is suggest that LI-ESWT probably has a physiologic effect on the erectile mechanism, a fact that still needs to be reconfirmed in a placebo-controlled manner.

The fact that the magnitude of response is impressive and the objective hemodynamic data showed significant changes posttreatment drives us to believe that there is more than just a placebo effect, especially due to the severity of this study group.

We are aware of the skepticism that this new therapeutic approach may arouse but hope that the data provided in this preliminary study will persuade the reader to at least remain open-minded to this optional treatment strategy. This will probably happen only after better understanding of the

basic physiological effect that this energy has on the cavernosal tissue and the availability of multicenter clinical data.

Acknowledgments

We would like to thank Elliot Sprecher for his contribution to the statistical analyses and to Arieh Bomzon for his huge help in editing the manuscript.

Corresponding Author: Ilan Gruenwald, Neurourology Unit, Rambam Healthcare Campus, Haaliya st, Haifa 9602, Israel. Tel: 0097248542819; Fax: 0097 28542883; E-mail: I_Gruenwald@rambam.health.gov.il

Conflict of Interest: None.

Statement of Authorship

Category 1

(a) Conception and Design
Yoram Vardi; Ilan Gruenwald

(b) Acquisition of Data
Yoram Vardi; Ilan Gruenwald; Boaz Appel

(c) Analysis and Interpretation of Data
Yoram Vardi; Ilan Gruenwald; Boaz Appel

Category 2

(a) Drafting the Article
Ilan Gruenwald

(b) Revising It for Intellectual Content
Ilan Gruenwald; Yoram Vardi

Category 3

(a) Final Approval of the Completed Article
Ilan Gruenwald; Yoram Vardi; Boaz Appel

References

1 Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, Sharlip I, Althof SE, Andersson KE, Brock G, Broderick G, Burnett A, Buvat J, Dean J, Donatucci C, Eardley I, Fugl-Meyer KS, Goldstein I, Hackett G, Hatzichristou D, Hellstrom W, Incrocci L, Jackson G, Kadioglu A, Levine L, Lewis RW, Maggi M, McCabe M, McMahon CG, Montague D, Montorsi P, Mulhall J, Pfaus J, Porst H, Ralph D, Rosen R, Rowland D, Sadeghi-Nejad H, Shabsigh R, Stief C, Vardi Y, Wallen K, Wasserman M. Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2010;7:3572–88.

2 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998;338:1397–404.

3 Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. J Urol 1999;162:722–5.

4 McMahon CG, Samali R, Johnson H. Efficacy, safety and patient acceptance of sildenafil citrate as a treatment for erectile dysfunction. J Urol 2000;164:1192–6.

5 Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 2010;58:243–8.

6 Fisher AB, Chien S, Barakat AI, Nerem RM. Endothelial cellular response to altered shear stress. Am J Physiol Lung Cell Mol Physiol 2001;281:L529–33.

7 Maisonhaute E, Prado C, White PC, Compton RG. Surface acoustic cavitation understood via nanosecond electrochemistry. Part III: Shear stress in ultrasonic cleaning. Ultrason Sonochem 2002;9:297–301.

8 Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett 2002;520:153–5.

9 Gruenwald I, Shenfeld O, Chen J, Raviv G, Richter S, Cohen A, Vardi Y. Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. Eur Urol 2006;50:134–40.

10 Hatzimouratidis K, Moysidis K, Bekos A, Tsimtsiou Z, Ioannidis E, Hatzichristou D. Treatment strategy for "non-responders" to tadalafil and vardenafil: A real-life study. Eur Urol 2006;50:126–32.

11 Dayan L, Gruenwald I, Vardi Y, Jacob G. A new clinical method for the assessment of penile endothelial function using the flow mediated dilation with plethysmography technique. J Urol 2005;173:1268–72.

12 Vardi Y, Dayan L, Apple B, Gruenwald I, Ofer Y, Jacob G. Penile and systemic endothelial function in men with and without erectile dysfunction. Eur Urol 2009;55:979–85.

The effect of Low Intensity Shock Waves on Erectile Dysfunction: 6-month follow up

Y. Vardi, B. Appel, I. Gruenwald, Rambam Health Care Campus , Haifa, Israel

"Best Poster" Prize on Clinical Research ISSM 2012

Objective:

To evaluate the overall efficacy of penile Low Intensity Shock Wave therapy (LI-ESWT) after 6 months in all our patients who participated in different studies.

Methods:

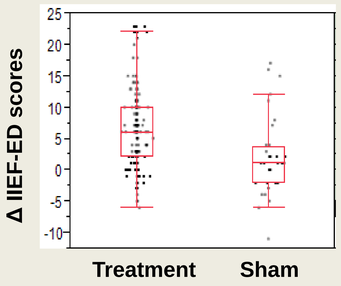
During the past 30 months we have followed up and evaluated the efficacy of LI-ESWT on 191 ED patients (155 treated and 36 Sham). These subjects represent various degrees of ED severity and response to PDE5i therapy. All received the same treatment protocol but they participated in different trials. Follow- up data were collected at the 6 month period after end of treatment and were compared to the patients' baseline scores before treatment.

Results :

- Mean age was 59± 10.3
- Mean ED Duration was 65.1 months.
- 86.4% were cardiovascular patients, 61 (40%) were diabetic of which 50.81% had a significant clinical improvement.
- Mean initial IIEF-ED domain scores: 11.0 (Ttreated-10.98, Sham 11.31)
- Mean initial Total IIEF score: 34.48 .
- No significant differences between sham and treatment regarding medical risk factors
- Based on changes in IIEF-ED Domain scores, 57.4% of all males had a significant clinical improvement 6 months after therapy.

Change in the IIEF-ED domain scores before and after treatment: Comparison to Sham

Changes in IIEF-ED Domain scores (one-way analysis) by treatment

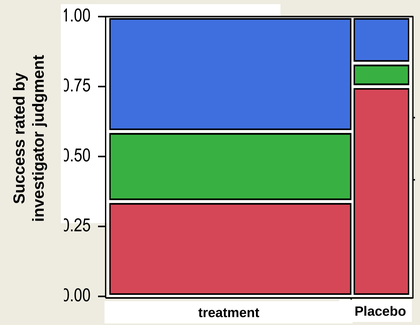


Treated (n=155)- Median score change 6, mean change 6.44

Placebo (n=36) – Median score change 1, mean change 1.77 (P< 0.0001)

Investigator Judgment

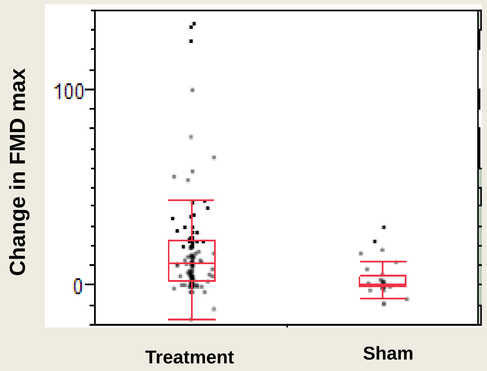
Contingency Analysis of Success By Treatment: Mosaic Plot



	No response	Partial response	Good response	
Treated (%)	34.19	25.16	40.65	100% (n=155)
Placebo (%)	75.00	8.33	16.67	100% (n=36)

Change in Penile Maximal Flow Measured by the Flow Mediated Technique: Treated vs. Sham controlled patients

Change in the Maximal Penile flow (Oneway analysis)



Treatment (n= 110): median change 10.7

Sham (n=29): median change 0.56 (p<0.0001)

Change in IIEF-ED domain score according to ED severity in treated patients:

(n=81) Severe ED (score<10) ……..45.67%

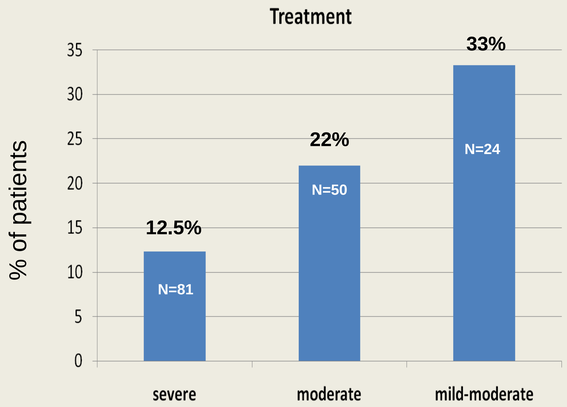
(n=50) Moderate ED (score 11-16) ……..72.00%

(n=24) Mild to moderate (score 17-21)……..45.83%

Success defined as minimal clinical important difference according to ED severity *

**Rosen RC et al: Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011 Nov;60(5):1010-6*

Percent of normalization by severity after shockwave treatment



Conclusions:

In this study we have demonstrated that still after 6 months, applying LI-ESWT directly to the penis has a significant clinical effect for all ED severities, for cardiovascular and diabetic patients and for either responders or non- responders to PDE5i therapy. Further follow up in a larger scale of ED population is needed to fully evaluate the long term effect of this treatment modality.

P-01-087

A MID–TERM ANALYSIS (6 MONTHS) OF THE EFFECT OF PENILE LOW INTENSITY SHOCK-WAVE THERAPY FOR PATIENTS OF VARYING ED ETIOLOGIES AND DIFFERENT DEGREES OF ED SEVERITY

Gruenwald, I.[1]; *Appel, B.*[1]; *Vardi, Y.*[1]
Rambam Healthcare Campus, Haifa, Israel[1]

Objective: To evaluate the overall efficacy of penile Low Intensity Shock Wave therapy (LI-ESWT) after 6 months in patients with a variety of ED etiologies, a range of ED severities and with different responses to PDE5i's.
Methods: During the past 32 months we have followed up and evaluated the efficacy of LI-ESWT on 191 ED patients (155 treated and 36 Sham). These subjects represent a heterogeneous group of ED patients with regard to ED severity and etiology. All received the same treatment protocol but participated in different trials. Follow-up of subjective parameters using validated questionnaires (IIEF-ED Domain score, clinical judgment) was performed 6 months after end of treatment and compared to the patients' baseline scores.
Results: Mean age was 59 ± 10 years, 86% were cardiovascular patients, 50 (40%) were diabetics. Based on changes in IIEF-ED Domain scores, 57.4% of all patients had a significant clinical improvement 6 months after therapy (mean change of 6.44 points in the IIEF-ED Domain score). When sub-dividing the patients to initial severe, moderate and mild ED groups, we found that 46, 72 and 46 percent improved respectively according to minimal clinical improvement criteria. Nineteen percent of the entire group reached normalization.
Conclusion: In this study we have demonstrated that still after 6 months, applying LI-ESWT directly to the penis has a significant clinical effect for all ED severities, for cardiovascular and diabetic patients and for either responders or non-responders to PDE5i therapy.
Policy of full disclosure: an unrestricted grant was provided for this study by medispec.

PS-05-005

THE EFFECT OF A SECOND COURSE OF LOW INTENSITY SHOCK WAVES FOR ED IN PARTIAL OR NON-RESPONDERS TO ONE TREATMENT COURSE

Gruenwald, I. E.[1]; Appel, B.[2]; Vardi, Y.[2]
[1]Haifa, Israel; [2]Rambam Medical Center, Haifa, Israel

Objective: To evaluate the added effect of a second treatment course (2nd round) of penile Low Intensity Shock Wave therapy (LI-ESWT) in patients who underwent an unsuccessful or non-satisfactory 1st course.
Methods: During the past 15 months we treated 84 ED patients of various degrees of ED severity and different etiologies, all received the same treatment protocol. They were offered a 2nd round if the first one was unsatisfactory or if endpoint criteria for success were unmet. These included subjective measures (IIEF-ED Domain scores, clinical judgment) and objective hemodynamic parameters measured by Flow Mediated Dilatation (FMD) test.Evaluation of differences in changes from baseline (V1), one-month after first treatment course (FU1) and one-month after the 2nd round (FU2) was performed with non-parametric Wilcoxon tests.
Results: Twenty-two patients were included, fifteen (68%) had severe ED, mean age 59 y ± 10. After the 2nd round 7/22 (31.8%) achieved an increase of ≥5 points in IIEF-ED Domain score. This positive impact was further supported by the overall improvement in median IIEF-ED Domain scores (from 9.5 at FU1 to 13 at FU2). This 3.5 point-increase at FU2 was significant compared to the poor increase of only 0.5 at FU1 ($P = 0.0235$). According to the investigators' Clinical Global Impression of Change (CGIC) 12/22 (54.5%) improved, resulting in 6 more successful patients at FU2. According to FMD parameters, an additional significant increase of 4.24 ml/mm2 tissue in maximal penile blood flow was recorded ($P = 0.0029$).
Conclusion: We have demonstrated that a 2nd round of LI-ESWT to the penis is beneficial in difficult cases of partial or unsatisfactory response to one round. A larger scale of ED patients who failed LI-ESWT is needed in order to fully evaluate the effect of the 2nd round.
Policy of full disclosure: None.

6. Can Low-Intensity Extracorporeal Shockwave Therapy Improve Erectile Function? A 6-Month Follow-up Pilot Study in Patients with Organic Erectile Dysfunction

Prof Y. Vardi, Dr. B. Appel, Dr. G. Jacob, Dr. O. Massarwi, Dr. I Gruenwald
Neuro-urology unit, Rambam Medical Center, Haifa, Israel

Abstract

Background: Low-intensity extra corporeal shockwave therapy (LI-ESWT) is currently under investigation regarding its ability to promoteneovascularization in different organs.

Objective: To evaluate the effect of LI-ESWT on men with erectile dysfunction (ED) who have previously responded to oral phosphodiesterase type 5 inhibitors (PDE5-I). ***Design, setting, and participants:*** We screened 20 men with vasculogenic ED who Extracorporeal shock wave had International Index of Erectile Function ED (IIEF-ED) domain scores between Low intensity 5–19 (average: 13.5) and abnormal nocturnal penile tumescence (NPT) parameters. Erectile dysfunction Shockwave therapy comprised two treatment sessions per week for 3 wk, which Penis were repeated after a 3-wk no-treatment interval.

Intervention: LI-ESWT was applied to the penile shaft and crura at five different sites.

Measurements: Assessment of erectile function was performed at screening and at 1 mo after the end of the two treatment sessions using validated sexual function questionnaires, NPT parameters, and penile and systemic endothelial function testing. The IIEF-ED questionnaire was answered at the 3-and 6-mo follow-up examinations.

Results and limitations: We treated 20 middle-aged men (average age: 56.1 yr) with vasculogenic ED (mean duration: 34.7 mo). Eighteen had cardiovascular risk factors. At 1 mo follow-up, significant increases in IIEF-ED domain scores were recorded in all men (20.9 ± 5.8 vs 13.5 ± 4.1, $p<0.001$); these remained unchanged at 6 mo. Moreover, significant increases in the duration of erection and penile rigidity, and significant improvement in penile endothelial function were demonstrated. Ten men did not require any PDE5-I therapy after 6-mo follow-up. No pain was reported from the treatment and no adverse events were noted during follow-up.

Conclusions: This is the first study that assessed the efficacy of LI-ESWT for ED. This approach was tolerable and effective, suggesting a physiologic impact on corporeal hemodynamics. Its main advantages are the potential to improve erectile function and to contribute to penile rehabilitation without pharmacotherapy. The short-term results are promising, yet demand further evaluation with larger sham-control cohorts and longer follow-up.

* Corresponding author. Neuro-Urology Unit, Rambam Healthcare Campus, Haifa, Israel.
Tel. +972 4 542819; Fax: +972 4 8542883.
E-mail address: yvard@rambam.health.gov.il (Y. Vardi).

0302-2838/$ – see back matter # 2010 Published by Elsevier B.V. on behalf of European Association of Urology. doi:10.1016/j.eururo.2010.04.004

1. Introduction

In the past decade, phosphodiesterase 5 inhibitors (PDE5-Is) have become available for the treatment of erectile dysfunction (ED). However, their effect is still limited to the sexual act and probably do not improve spontaneous erections. These limitations are probably due to their inability to improve penile blood ßlow for a time period that is sufßicient to allow optimal oxygenation and recovery of cavernosal vasculature. Recently, the effect of long-term daily use of PDE5-Is on endothelial function (EnF) has been shown to induce a short-term improvement in erectile function (EF) but probably not a longstanding one [1–3].

In the search for a new treatment modality that would provide a rehabilitative or curative effect for ED, we looked into technologies that could potentially affect endothelial function and improve penile hemodynamics. We came across some related preliminary publications, particularly from the cardiovascular literature, showing that in vitro as well as in vivo (porcine model) low-intensity extracorporeal shockwave therapy (LI-ESWT) could enhance the expression of vascular endothelial growth factor (VEGF) and its receptor Flt-1 [4,5], and induces neovascularization and improves myocardial ischemia [6]. Newer studies further demonstrated this hemodynamic effect in humans [7,11,12]. Moreover, LI-ESWT was found to be effective not only in the myocardium, but also in other organs with impaired vascularity. Recently, this treatment modality using LI-ESWT was found effective in the treatment of chronic diabetic foot ulcers as compared with hyperbaric oxygen therapy, showing better clinical results and local perfusion [8]. In a prospective randomized trial, LI-ESWT was also effective in improving wound healing after vein harvesting for coronary artery bypass graft surgery [9].

The mechanism of action of LI-ESWT is still unclear. It has been shown that this low intensity energy induces non enzymatic production of physiologic amounts of nitric oxide [10] and activates a cascade of intracellular signaling pathways that lead to the release of angiogenic factors. These encouraging experimental and clinical outcomes provided the theoretic basis for applying this treatment modality to cavernosal tissue in order to improve penile vascular supply and EnF in men with longstanding vasculogenic ED.

2. Patients and methods

The study protocol was reviewed and approved by the local institutional review board and each participant gave his written informed consent.

The methodology used was based on the clinical trials performed in patients with cardiovascular disease using LI-ESWT [11,12]. We adapted the treatment protocol and the probe that was used in these studies for the penis in order to account for the superficial location of the corpora cavernosa and the need to cover the entire corporal surface as well as the crura. Our treatment protocol consisted of two treatment sessions per week for 3 wk, which were repeated after a 3-wk no-treatment interval (Fig. 1).

Shockwaves were delivered by a special probe that was attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). We applied a standard commercial gel normally used for sonography without any local anesthetic effect on the penis and perineum. The penis was manually stretched; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and the left and right crura. The duration of each LI-ESWT session was about 20 min, and each session comprised 300 shocks per treatment point (1500 per session) at an energy density of 0.09 mJ/mm2 and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). During the treatment period, no psychologic intervention or support was provided and patients were required to maintain their normal sexual habits.

2.1. Inclusion/exclusion criteria

We recruited men with a history of ED for at least 6 mo from our outpatient clinic. Each study patient had abnormal 2-night nocturnal penile tumescence (NPT) parameters at screening, had responded positively to PDE5-I therapy (were able to penetrate during sexual intercourse while on on-demand PDE5-I treatment), and had an International Index of Erectile Function ED (IIEF-ED) domain score between 5–19. Each patient agreed to discontinue PDE5-I therapy until the first 1-mo follow-up examination. The exclusion criteria were psychogenic ED (normal NPT parameters), any neurologic pathology, prior radical prostatectomy, and recovery from any cancer within the past 5 yr.

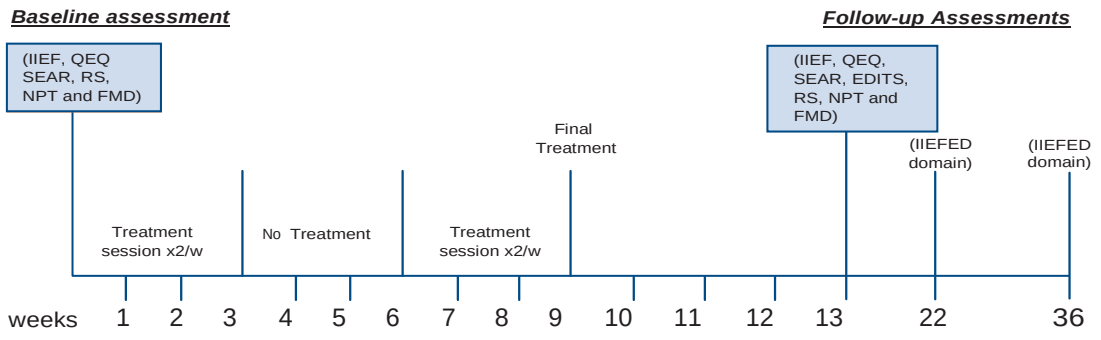


Fig. 1 – Study ßlow chart. IIEF = International Index of Erectile Function; QEQ = Quality of Erection Questionnaire; SEAR = Self-Esteem and Relationship Questionnaire; RS = rigidity score; NPT = nocturnal penile tumescence; FMD = ßlow-mediated dilatation; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction.

2.2. Study protocol

Upon inclusion (visit 1), after a 4-wk PDE5-I washout period, each participant completed several validated sexual function questionnaires:

IIEF, rigidity score (RS), Quality of Erection Questionnaire (QEQ), and the Self-Esteem and Relationship Questionnaire (SEAR). Additionally, penile and forearm EnF testing was done in the last 14 enrolled men using our already-described flow-mediated dilatation (FMD) technique [13,14]. This method uses veno-occlusive strain gauge plethysmography to measure penile and forearm blood flow after a 5-min ischemic period. We used this technique to establish changes in penile EnF by measuring specific indices of endothelial parameters: basal blood flow (P-base), and the maximal postischemic flow. Efficacy was evaluated at 1 mo after end of treatment by completing sexual function questionnaires, determining]NPT parameters, EnF testing, and completing an Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire. For long term evaluation, we used the IIEF-ED domain score at the 3-and 6-mo follow-up examinations. A change in the IIEF-ED domain score of >5 points was used as the main measure of treatment success.

2.3. Statistical analysis

Paired student *t* tests and nonparametric Wilcoxon sign-rank tests were used to examine differences within subjects. Pearson correlation that took into account the changes in systemic EnF was used to examine the relationship between the change in the IIEF-ED scores and the changes in penile EnF at the 1-mo follow-up examination. To this end, we first constructed indices of FMD change using forearm EnF as the reference value before calculating the correlation. The indices were calculated from the difference between the values of the 1-mo and the baseline penile FMD indices, divided by the difference between the 1-mo and the baseline forearm FMD indices. Pearson correlation was also used to examine the degree to which other study parameters or derived indices were related. Lines of best fit were determined and plotted for all correlation analyses. The level of significance for all analyses was set at 5%.

3. Results

This protocol was applied to 20 middle-aged men (mean: 56.1 ± 10.7 yr, range: 33–73 yr) with vasculogenic ED for a mean of 34.7 mo. Eighteen men had one or more cardiovas- cular risk factors.

Table 1 summarizes the pre-and post-therapy scores of all sexual function questionnaires in all study participants. The characteristics of each study participant and the effect of LI-ESWT on their IIEF-ED

Table 1 – Results of sexual function questionnaires before and 1 month after low-intensity extracorporeal shock-wave therapy

p value	% change	Score 1 mo after treatment ± SD	Baseline score ± SD	Test score
<0.001	55	20.9 ± 5.8	13.5 ± 4.1	IIEF ED domain
<0.001	39	54.7 ± 11.7	39.3 ± 8.7	Total IIEF
<0.001	83	61.4 ± 25.8	32.9 ± 18.2	QEQ
<0.001	86	2.7 ± 1.1	1.45 ± 1.0	RS
<0.001	32	46.5 ± 11.3	36.0 ± 10.4	SEAR

IIEF = International Index of Erectile Dysfunction; ED = erectile dysfunction; QEQ = Quality of Erection Questionnaire; RS = rigidity score; SEAR = Self-Esteem and Relationship Questionnaire.

Table 2 – Patient characteristics and the effect of low-intensity extracorporeal shockwave therapy on the International Index of Erectile Function score for each subject from baseline to 6 months after end of treatment

Patient number	Age	ED duration (mo)	ED risk factor s*	IIEF-ED baseline	Δ IIEF-ED at 1 mo	Δ IIEF-ED at 1 mo	Δ IIEF-ED at 1 mo	Δ IIEF-ED at 1 mo
1	47	6	3	18	3	6	5	23"
2	47	24	1	16	7	9	12	28"
3	62	36	3 + 4+ 5	11	12	10	13	24"
4	68	60	3	13	8	8	7	21"
5	54	18	3 + 4+ 5	19	-6	-2	-2	17
6	59	24	3	7	3	6	6	13
7	61	60	3 + 4+ 5	16	11	9	9	25"
8	58	24	2	13	2	2	4	17
9	33	144	1	17	6	6	7	24"
10	54	12	2 + 3	16	1	1	0	16
11	65	24	3	5	22	19	18	23
12	62	12	3 + 4	13	14	16	16	29"
13	59	36	3	13	13	10	10	23
14	46	24	3	5	6	6	6	11
15	33	100	2	11	6	6	10	21
16	73	20	3 + 4	11	-3	-3	-3	8
17	68	24	3 + 5	17	11	11	11	28"
18	63	8	3 + 5	16	9	2	2	18
19	58	15	2 + 3	15	12	9	9	24"
20	53	24	2	17	6	7	7	24"

ED = erectile dysfunction; IIEF = International Index of Erectile function; ED = erectile dysfunction;
* 1 = no risk factors; 2 = miscellaneous risk factors (eg, smoking, medications, surgical procedures); 3 = cardiovascular risk factors (eg, hypertension, hypercholesterolemia, hypertriglyceridemia); 4 = coronary disease; 5 = diabetes mellitus.** Patients with spontaneous erections who did not require phosphodiesterase type 5 inhibitor therapy.

Table 3 – Changes in nocturnal penile tumescence parameters before and 1 month after low-intensity extracorporeal shockwave therapy (n = 18)

Parameter	Baseline (mean ± SD)	1 mo after treatment (mean± SD)
Total number of erection	3.9 ± 2.2	4.6 ± 2.3
Total erection time, h	1.3 ± 1.3	1.4 ± 0.9
Average tip rigidity	37.2 ± 18.9	42.1 ± 22.8
Average base rigidity	47.5 ± 18.1	52.5 ± 22.0
Max rigidity best event, tip	52.6 ± 20.7	61.0 ± 29.6
Max rigidity best event, base	66.9 ± 16.5	68.6 ± 26.6

during the study period are presented in Table 2.

At the 1-mo follow-up examination, the IIEF-ED domain scores signiβicantly increased from 13.5 ± 4.1 to 20.9 ± 5.8 (p < 0.001). The scores of 14 men increased by >5 points and of 7 men by >10 points. The treatment satisfaction scores were also high at the 1-mo follow-up examination (mean score: 23.2). At the 3-and 6-mo follow-up examinations, the improved IIEF-ED domain scores were maintained, and the average increase at the 6-mo follow-up was 7.1 (p = 0.001). A signiβicant improvement in EF was recorded in six men with severe ED at baseline (IIEF-ED domain scores <12); their average IIEF-ED domain score rose from 8.3 to 16.6 at the 6-mo follow-up examination.

Pre-and post-treatment NPT parameters were collected from 18 men (2 patients refused to perform the second NPT). All NPT parameters improved at the 1-mo examina¬tion, especially the rigidity parameters (Table 3).

Penile EnF improved signiβicantly after LI-ESWT (Table 4): basal βlow (7.3 ml/min per deciliter vs 17.8 ml/min per deciliter; p < 0.001) and post-ischemic maximal βlow (12.0 ml/min per deciliter vs 28.9 ml/min per deciliter, p < 0.001). No signiβicant changes were measured in forearm EnF (Table 4). A strong correlation was found between the changes in the IIEF-ED scores and the changes in EnF parameters at the 1-mo follow-up examination (Fig. 2).

At the 3-and 6-mo follow-up examinations, 10 men reported that they had spontaneous erections that were sufβicient for penetration and did not require PDE5-I support before sexual intercourse.

None of the study participants reported any pain during the treatment and follow-up periods, and no adverse effects were recorded.

4. Discussion

All currently available treatments for ED enhance sexual function by improving the quality of erections, yet none are curative. The search for an ED cure is the next step, and should be the goal of this coming decade. Examples of the different therapeutic targets and strategies for curing ED include the Rho/Rho-kinase signaling pathway [15], gene therapy [16], and stem cell regeneration [17]. Advanced treatment protocols for rehabilitating or preserving EnF in men with ED using chronic PDE5-Is have been proposed and are currently undergoing evaluation [1,2,18]. To date, data on the therapeutic beneβits of these treatment protocols to restore spontaneous EF are still scarce.

High-intensity ESWT (lithotripsy) is a well-established treatment for kidney stones. The results of attempts to destroy the βibrotic plaques of Peyronie's disease using this high energy have been published with debatable success, except for pain relief [19,20]. Beneβicial therapeutic effects of moderate intensity also have been reported in certain orthopedic conditions, such as plantar fasciitis, Achilles tendonitis, and tennis elbow, probably due to the attenuating action on inβlammatory processes [21–24].

Table 4 – Changes in βlow-mediated dilatation parameters in both penile and forearm blood βlow before and 1 month after treatment

P value	% change	1 mo	Baseline		Location
0.258	19	4.8 ± 3.3	4.0 ± 2.2	Baseline βlow (ml/min/dl)	Forearm
0.544	-12	10.6 ± 7.4	12.0 ± 9.0	Maximal βlow (ml/min/dl)	
0.004	145	17.8 ± 11.0	7.3 ± 4.7	Baseline βlow (ml/min/dl)	Penis
<0.001	140	28.9 ± 15.2	12.0 ± 8.3	Maximal βlow (ml/min/dl)	

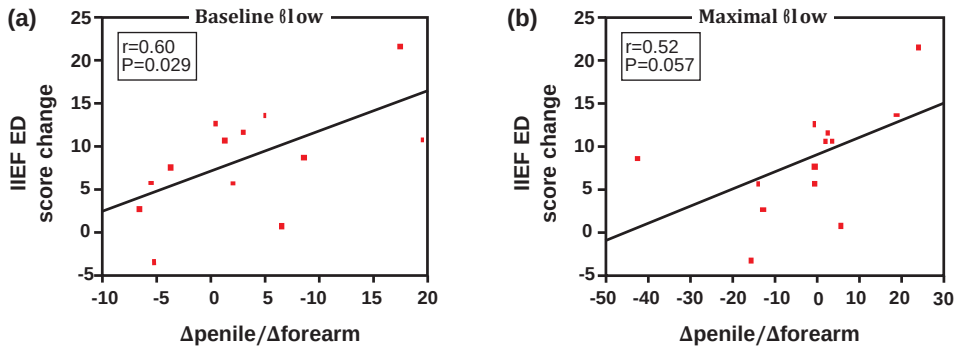


Fig. 2 – Correlation between the adjusted βlow-mediated dilatation indices for (a) baseline and (b) maximal βlow and the changes in the International Index of Erectile Function erectile dysfunction score 1 mo after treatment.

IIEF ED = International Index of Erectile Function—Erectile Dysfunction domain.

More recently, the potential efficacy of LI-ESWT has been investigated in other clinical conditions [6,8,9]. It has been demonstrated that this form of energy triggers the activation of various intracellular signaling pathways and causes upregulation of numerous angiogenic factors to promote neovascularization [4]. In a porcine model of myocardial ischemia, Nishida et al demonstrated that cardiac LI-ESWT induces angiogenesis and markedly ameliorates myocardial ischemia without any adverse effects [5]. In another series of studies, Wang et al. [25,26] demonstrated similar processes in other animal models. The above scientific research led to the assumption that LI-ESWT also might be beneficial in enhancing blood flow in the corpora cavernosa of vasculogenic ED patients.

We structured our treatment protocol on what has been previously used in cardiology for achieving neovascularization. The rationale for including a no-treatment interval in our protocol is based on the finding that biologic responses to LI-ESWT appear to be time-dependent as the peak expression of the neovascularization response occurs 4 wk after treatment [27].

We initially started this investigation as a pilot study in patients with vasculogenic ED. After analyzing the results of the first six men, we were surprised by the positive responses. We decided to increase the number of participants and to include measurements of EnF into our protocol. Another reason for adding EnF was to overcome the problems of comparing pre-and post-therapy NPT parameters and to gain some insight into the underlying hemodynamic mechanism induced by this treatment.

For this purpose, we decided to use our FMD methodol¬ogy, and not Doppler sonography; we wanted to obtain objective, measurable, and comparable hemodynamic results that did not require a pharmacologically-induced vasoactive intervention and to eliminate any operator dependent bias. Our results show impressive objective data that confirm the beneficial effect of LI-ESWT on penile hemodynamics and its correlation with an improved clinical response, as demonstrated by an increase in the IIEF-ED scores 1 mo after LI-ESWT.

Although a considerable placebo effect can be expected with our treatment protocol, our high response rate (>70%) is substantially higher than that of any previously published placebo-controlled trial in men with ED. Moreover, the fact that this effect was maintained without any additional active intervention 6 mo after treatment provides additional evidence that LI-ESWT exerts a genuine physiologic effect on cavernosal tissue. Although our positive results were obtained using validated scientific instruments, we would like to emphasize that the most striking clinical observation was that almost every participant gave a highly positive feedback, sometimes as early as the second treatment session, with the efficacy still present 6 mo later.

This is a proof-of-concept study that was performed to demonstrate the clinical efficacy of LI-ESWT in a small number of highly selected patients with a relatively short follow-up using an adapted empirical protocol. For LI-ESWT to become a recognized curative treatment in patients with ED, large multicenter, long-term, randomized and sham controlled studies should now be performed. Moreover, other LI-ESWT protocols need to be evaluated, and there is a need to better define those patients who respond to this type of treatment and evaluate the duration of its effect. More data also are needed with regard to the possible long-term impact of shockwaves on penile tissue.

4. Discussion

The results of this pilot study emphasize the efficacy and tolerability of penile LI-ESWT in ED. Our short-term results are extremely encouraging, but demand further evaluation. In the future, this could be one of the few nonpharmacologic treatment modalities that are able to improve EF without any adverse effects. Based on our results, LI-ESWT appears to have the potential to be a rapid and curative therapy for ED. Even if the therapeutic effect will be short-lasting, it can be easily repeated. The promising results of this pilot study will hopefully encourage basic research to explore and understand the mechanism of action of this energy on biologic systems, as well as assist in finding further applications of this novel therapeutic modality in other fields of medicine.

Author contributions: Yoram Vardi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gruenwald, Vardi.
Acquisition of data: Gruenwald, Vardi, Appel, Massarwi.
Analysis and interpretation of data: Gruenwald, Vardi, Appel, Jacob.
Drafting of the manuscript: Gruenwald, Vardi.
Critical revision of the manuscript for important intellectual content: Gruenwald, Vardi. Statistical analysis: Gruenwald, Vardi.
Obtaining funding: Vardi.
Administrative, technical, or material support: Gruenwald, Vardi, Appel.
Supervision: Gruenwald, Vardi.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: Medispec Ltd, Israel provided a partial unrestricted grant including use of the electrohydraulic unit (Omnispec ED1000).

Acknowledgement statement: The authors thank Eliot Sprecher for his input in the statistical analysis section.

References

[1] Aversa A, Bruzziches R, Vitale C, et al. Chronic sildenafil in men with diabetes and erectile dysfunction. Expert Opin Drug Metab Toxicol
2007;3:451–64.

[2] Porst H, Rajfer J, Casabe A, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. J Sex Med 2008;5:2160–9.

[3] Vardi Y, Appel B, Ofer Y, Gruenwald I, Dayan L, Jacob G. Effect of chronic sildenafil treatment on penile endothelial function: a randomized, double- blind, placebo controlled study. J Urol
2009;182:2850–5.

[4] Nurzynska D, Di Meglio F, Castaldo C, et al. Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. Ultrasound Med Biol 2008;34:334–42.

[5] Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock Wavetherapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004;110:3055–61.

[6] Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher A, Dimmeler S. Low energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation 2006;114:2823–30.

[7] Kikuchi Y, Ito K, Ito Y, et al. Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris. Circ J 2010;74: 589–91.

[8] Wang CJ, Kuo YR, Wu RW, et al. Extracorporeal shockwave treatment for chronic diabetic foot ulcers. J Surg Res 2009;152:96–103.

[9] Dumfarth J, Zimpfer D, Vo¨ gele-Kadletz M, et al. Prophylactic low energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery: a prospective, randomized trial. Ann Thorac Surg 2008;86:1909–13.

[10] Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett
2002;520:153–5.

[11] Caspari GH, Erbel R. Revascularization with extracorporeal shock wave therapy: first clinical results. Circulation 1999;100:84–9.

[12] Khattab AA, Broderson B, Schuermann-Kuchenbrandt D, et al.
Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol 2007;121:84–5.

[13] Dayan L, Gruenwald I, Vardi Y, Jacob G. A new clinical method for the assessment of penile endothelial function using the flow mediated dilation with plethysmography technique. J Urol 2005; 173:1268–72.

[14] Vardi Y, Dayan L, Appel B, Gruenwald I, Jacob G. Penile and systemic endothelial function in men with and without erectile dysfunction. Eur Urol 2009;55:979–85.

[15] Bivalacqua TJ, Champion HC, Usta MF, et al. RhoA/Rho-kinase suppresses endothelial nitric oxide synthase in the penis: a mechanism for diabetes-associated erectile dysfunction. Proc Natl Acad Sci U S A
2004;101:9121–6.

[16] Melman A, Bar-Chama N, McCullough A, Davies K, Christ G. hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. Hum Gene Ther 2006;17:1165–76.

[17] Deng W, Bivalacqua TJ, Hellstrom WJG, Kadowitz PJ. Gene and stem cell therapy for erectile dysfunction. Int J Impot Res 2005;17:S57–63.

[18] Donatucci CF, Wong DG, Giuliano F, et al. Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. Curr Med Res Opin 2008;24:3383–92.

[19] Hauck EW, Hauptmann A, Bschleipfer T, Schmelz HU, Altinkilic
BM, Weidner W. Questionable efficacy of extracorporeal shock wave therapy for Peyronie's disease: results of a prospective approach. J Urol
2004;171:296–9.

[20] Palmieri A, Imbimbo C, Longo N, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. Eur Urol 2009;56:363–70.

[21] Wang C-J, Chen H-S. Shock wave therapy for patients with lateral epicondylitis of the elbow. Am J Sports Med 2002;30:422–5.

[22] Wang C-J. An overview of shock wave therapy in musculoskeletal disorders. Chang Gung Med J 2003;26:220–32.

[23] Ghandour A, Thomas RH, O'Doherty DP. Extracorporeal shockwave therapy for the treatment of chronic Achilles tendonitis. J Bone Joint Surg Am 2004;86-B:364.

[24] Malay DS, Pressman MM, Assili A, et al. Extracorporeal shockwave therapy versus placebo for the treatment of chronic proximal plantar fasciitis: results of a randomized, placebo-controlled, double-blined, multicenter intervention trial. J Foot Ankle Surg 2006;45:196–210.

[25] Wang C-J, Huang H-S, Pai C-H. Shock wave-enhanced neovascular- ization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg 2002;41:16–22.

[26] Wang C-J, Wang F-S, Yang KD, Weng L-H, Huang C-S, Yang L-C. Shock wave therapy induces neovascularization at the tendon- bone junction: a study in rabbits. J Orthop Surg 2003;21:984–9.

[27] Ciampa AR, Carcereri de Prati A, Amelio E, et al. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett 2005;579:6839–45.

7. Is Low Intensity Shock Wave Therapy A Curative Treatment For Erectile Dysfunction? A-1 Year Follow-up Pilot Study

Presented at the 14th World Meeting of the International Society for Sexual Medicine (Seoul, South Korea, September 2010)

Author: *Prof. Y Vardi*

Institution: Neuro-Urology unit, Rambam Healthcare Campus, Haifa, Israel

Objectives: To evaluate the effect of low intensity extra corporeal shock wave therapy (ESWT) on erectile function, in patients with vasculogenic ED.

Materials and Methods: We included 20 middle-aged patients (56.1±10.7y) with long-standing vasculogenic ED, with a mean IIEF-ED domain score (IIEF-ED) of 13.5 and an abnormal NPT. Excluded were neurogenic, psychogenic or post pelvic- surgery patients. ESWT was applied on the penile shaft and crus for 3 minutes in 5 different penile anatomical sites (intensity of 0.09 mj/mm^2, 300 shocks/site). The treatment included 2 sessions/week for 3 weeks and was repeated after a 3-week no-treatment interval. Assessment of erectile function was performed at screening and at 1,3,6 months after end of treatment using validated ED questionnaires (IIEF, QEQ, SEAR, EDITS, Rigidity score). Objective hemodynamic measurements were performed in 14 patients by penile and forearm endothelial function tests before and one-month after ESWT.

Results: The mean IIEF-ED increased from 13.5 at baseline to 20.6, 20.4 and 21.7 at 1,3 and 6 months. Only 5 patients did not respond to the therapy (IIEF ED increase < 5 points). QEQ improved by 23.8 points (from 32.9 to 55.3, p=0.001) and rigidity score increased from 1.45 to 2.5 (p=0.015). SEAR scores increased from 36 to 45.3 (p=0.002). The EDITS final score was 23.2. A one-year follow of 9 subjects showed improvement from an average of 14.4 to 23.3 in the IIEF. Similar improvements were noted with the other ED questionnaires. Prior to our intervention all subjects were on PDE5i therapy, 5 with poor and 15 with good response. Overall 12 subjects did not require any oral therapy at 3 months. Endothelial function testing one month after treatment showed significant hemodynamic improvement in baseline and maximal penile blood flow (7.7- 18.5 and 12.3- 29.8 ml/min/dl, respectively (p< 0.001). The AUC (expresses penile perfusion) increased from 369.6 to 812.2 units (p< 0.001). No pain or any other side effects were noted nor reported.

Conclusions: This is the first study assessing the efficacy of ESWT for vasculogenic ED. We found this approach to be feasible and tolerable. Its main advantages are the potential to improve erectile function without the need for pharmacotherapy. Short term results are promising yet demand further evaluation using sham control and long-term follow-up that are underway.

Other Applications Using Shockwave

1. Extracorporeal Shock Wave Therapy for the Treatment of Chronic Pelvic Pain Syndrome in Males: A Randomised, Double-Blind, Placebo-Controlled Study

European Urology Supplements, 2009; Vol 7(3); p:159.

Reinhold Zimmermann, Alin Cumpanas ,Florin Miclea, Günter Janetschek.

Abstract

Background

There is no sufficiently validated therapy for chronic pelvic pain syndrome (CPPS).

Objective

To investigate the effects of extracorporeal shock wave therapy (ESWT) in 60 patients suffering from CPPS.

Design, setting, and participants

Sixty patients suffering from CPPS for at least 3 mo were investigated in two groups. Both groups were treated four times (once per week), each by 3000 impulses; group 2 was performed as a sham procedure. The investigation was designed as a placebo-controlled, prospectively randomised, double-blind phase 2 study. Standardised follow-up was performed 1, 4, and 12 wk after ESWT.

Interventions

Low-energy–density ESWT was performed using a perineal approach without anaesthesia. In the placebo group, the same setting was used without shock wave energy transmission.

Measurements

ESWT effects on pain, quality of life (QoL), erectile function (EF), and micturition were evaluated. The parameters were investigated using validated questionnaires (National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI], International Prostate Symptom Score [IPSS], International Index of Erectile Function [IIEF]) and the Visual Analog Scale (VAS) for pain evaluation.

Results and limitations

All patients completed outpatient treatments and follow-ups without any problems. All 30 patients in the verum group showed statistically (highly) significant improvement of pain, QoL, and voiding conditions following ESWT in comparison to the placebo group, which experienced a continuous deterioration of the same parameters during the follow-up period. Perineal ESWT was easy and safe to perform without anaesthesia or any side-effects.

Conclusions

This is the first prospectively randomised, double-blind study to reveal perineal ESWT as a therapy option for CPPS with statistically significant effects in comparison to placebo. ESWT may in particular be interesting because of its easy and inexpensive application, the lack of any side-effects, and the potential for repetition of the treatment at any time.

Take Home Message

With extracorporeal shock wave therapy, it has been possible for the first time to establish a rapid and financially appealing outpatient therapy option for patients with chronic pelvic pain syndrome that uses a standard unit, that does not have side-effects, and that can be repeated as often as required.

Article Outline

1. Introduction

The incidence of chronic pelvic pain syndrome (CPPS) is increasing [1], and [2], and the vast majority of male patients suffer from this abacterial form [3], and [4]. Recently, an incidence of almost 14% was found among >5000 male urologic outpatients, whereas incidence had been estimated to be only 4.5% [5]. The disease reveals substantial morbidity comparable to that of angina pectoris, Crohn's disease, or the status after a heart attack. Disease-typical restrictions are pain sensations most commonly in the prostate, testes, groin, back, pelvic floor, and suprapubic region [6].

The functional CPPS-like symptoms, such as disturbances of micturition and erectile function (EF), can have a crucial diminishing effect on quality of life (QoL) that may be even greater than the pain itself [7], [8], and [9]. The pathophysiology is almost entirely unknown. Previous infections, pelvic floor hypertension, local chemical alterations, and

perfusion disturbances are under discussion [10]. Even the role of the prostate in CPPS is questionable [11], and [12] because women can also develop CPPS-like symptoms [13]. Neurobiologic and psychiatric factors could play a further role. In a murine model, autoimmune prostatitis induced long-lasting pelvic pain, and the origin could clearly be assigned to the prostate [14]. Prolonged smooth muscle contraction in the bladder and prostate resulting from α_1-adrenergic (α_1-ADR) activation may aggravate the symptoms further [15]. The presence of nanobacteria discovered in CPPS sufferers has opened a completely new field of possible aetiologic factors [16].

According to the actual National Institutes of Health (NIH) classification [17], CPPS (type IIIB, Fig. 1) is characterised by the lack of signs of infection in urine and sperm as well as by the specific symptoms (Fig. 2). Routine diagnostic procedure is still debatable, and the clinical diagnosis of CPPS is made in light of complaints, microbiologic findings, and exclusion of more severe, relevant diseases [18].

I Acute bacterial prostatitis	
II Chronic bacterial prostatitis	
III CPPS	
IIIA	Inflammatory CPPS
IIIB	Noninflammatory CPPS
IV Asymptomatic inflammatory prostatitis	

Fig. 1 Prostatitis classification of the National Institutes of Health (NIH).
CPPS = chronic pelvic pain syndrome.

I Acute bacterial prostatitis		Acute (urinary tract) infection
II Chronic bacterial prostatitis		Chronic/repeated (urinary tract) infection
III CPPS		Pelvic area paresthesia/pain >3 mo, no evidence of bacteria
IIIA	Inflammatory CPPS	White blood cells in prostate fluid, urine, seminal fluid
IIIB	Noninflammatory CPPS	No white blood cells in prostate fluid, urine, seminal fluid
IV Asymptomatic inflammatory prostatitis		White blood cells in prostate fluid, urine, seminal fluid, prostatic tissue; no symptoms

Fig. 2 Prostatitis classification of the National Institute of Health (NIH): clinical criteria.
CPPS = chronic pelvic pain syndrome.

No causal or standardised treatment is available at present [19]. Various agents, such as analgesics, antiphlogistics, antibiotics, α-receptor blockers, and 5α-reductase inhibitors (5-ARIs) are used individually and in various combinations [20], and [21]. A certain group of patients may benefit mostly from α-blockers [22], and there is no rational basis for the widespread use of antibiotics [23]. We need to address the lack of evidence or

objective measurement of effectiveness for each of these treatments. Side-effects may predominate over possible treatment effects, thus minimising the benefit to the patient.

Physiotherapy, trigger-point massage, electromagnetic treatment, and acupuncture have already been used for CPPS [24]. Orthopaedic pain syndromes, fractures, and wound healing disorders are successfully treated by low-energy extracorporeal shock wave therapy (ESWT). Shock waves could reduce passive muscle tone and improve the range of movement in upper-arm contractures caused by stroke [25]. Ischaemic dysfunctional myocardial areas could be reperfused by local application of shock waves [26]. In an initial feasibility study, we were able to show that shock waves are easily applicable by perineal approach without side-effects, achieving significant improvement of CPPS-related symptoms, particularly with regard to pain [27]. The encouraging results of this first-ever study necessitated a more objective approach for investigating ESWT by a placebo-controlled, double-blind, randomised trial.

2. Patients and methods

Patients with type IIIB prostatitis (CPPS) of at least 3 mo duration and no evidence of bacteria in urinary and seminal culture tests (criteria according NIH classification) were eligible for the study. Prostate cancer (PCa) was ruled out clinically and serologically prior to therapy. The study protocol (Fig. 3) was approved by the local ethical committee after approval of the general CPPS study by the committees of two medical universities in Germany and Austria. Patients provided informed consent. No other treatments were permitted during the study and follow-up periods.

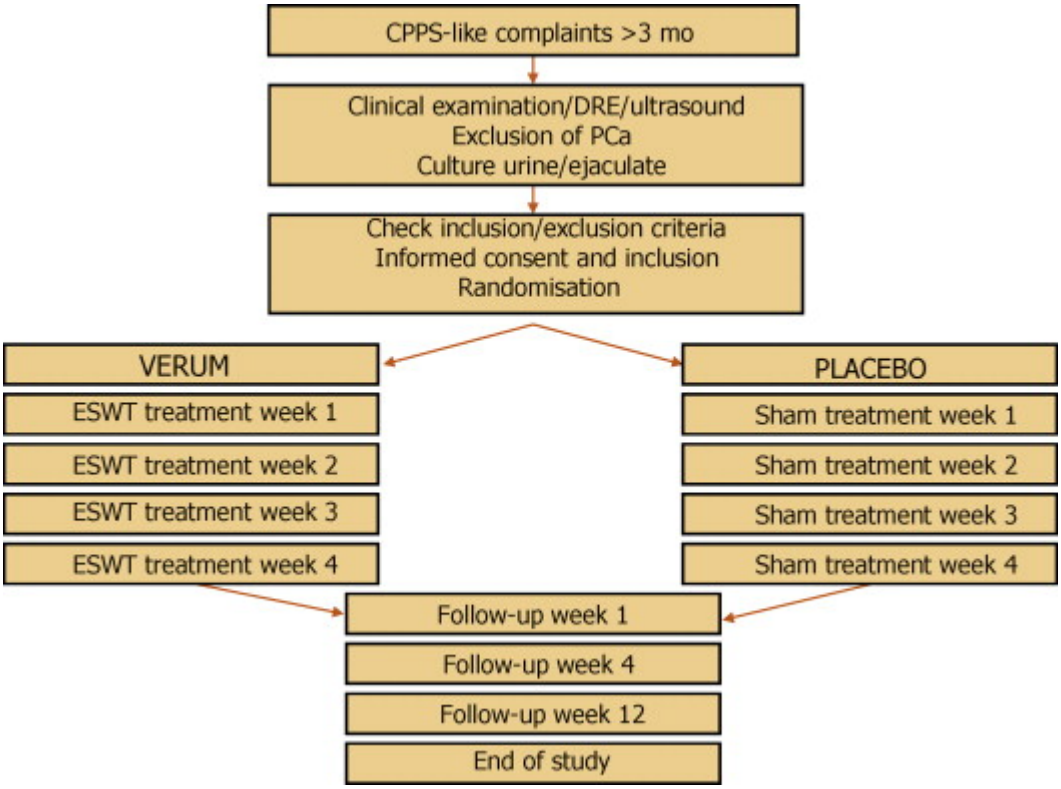


Fig. 3 Extracorporeal shock wave therapy for chronic pelvic pain syndrome: flow chart. CPPS = chronic pelvic pain syndrome; DRE = digital rectal examination; ESWT = extracorporeal shock wave therapy; PCa = prostate cancer.

Prostate-specific antigen (PSA) testing, digital rectal examination (DRE), and transrectal ultrasound of the prostate (TRUS) had been performed prior to study enrolment to rule out other pathologies. All patients were randomised for placement in the verum group or the placebo group prior to treatment. The verum patients received one perineally applied ESWT treatment weekly (3000 pulses each; maximum total energy flow density: 0.25 mJ/mm^2; frequency: 3 Hz) for 4 wk. Treatment parameters were determined by different urologic and nonurologic case studies and publications. The device used for the study was a standard electromagnetic shock wave unit with a focused shock wave source (Duolith SD1, Storz Medical, Tägerwilen, Switzerland). The focus zone penetration depth was in the range of 35–65 mm (Fig. 4), which meant that the shock wave focus could be placed in the prostate and pelvic floor from the perineum easily. The position of the shock wave transducer was changed after every 500 pulses to scan virtually the entire prostatic and pelvic floor region. According to the focus geometry of the transducer head, we could not fail to strike the prostatic region when placing the transducer perineally.

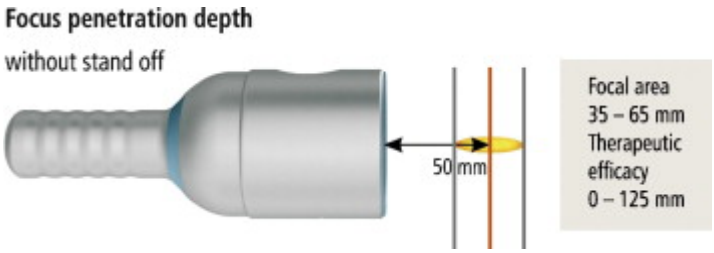


Fig. 4 Characteristics of the transducer.

The placebo treatment was performed with the same therapy head, which was also fitted with a placebo stand-off. This stand-off contained shock wave–absorbing material, a layer of air, and air-filled microspheres. Performance of the placebo stand-off was validated by measuring the output pressure in a laboratory setup. The setting was identical to the verum treatment. The blinding included the specification that neither the patient nor the investigator/follow-up observer was aware of placebo or verum assignment.

The follow-up schema included clinical examinations and the questionnaire-based reevaluation of QoL and complaints at 1, 4, and 12 wk following ESWT. The degree of pain was evaluated using the Visual Analog Scale (VAS, 0–10). CPPS-related complaints were investigated using the NIH-developed Chronic Prostatitis Symptom Index (NIH-CPSI). Micturition conditions were examined using the International Prostate Symptom Score (IPSS); the International Index of Erectile Function (IIEF) was used for self-assessment of potency function.

The data sets were examined by descriptive analysis methods. The characteristic values, such as mean values plus or minus standard errors (SE) and median values, are listed in Table 2 for all investigated times (0, 1, 4, and 12 wk). SE is defined as the standard deviation (SD) divided by the square root of the patient number (ie, 30 per treatment path). In most instances, the data sets are not normally distributed, so the differences in medians are used to assign the effect of therapy. The significance of differences in before and after states were evaluated using the Wilcoxon signed rank test with $p = 0.05$. The Mann-Whitney test was used in case of the significance for the placebo–verum relationship, also with $p = 0.05$. All statistical analyses were carried out using the statistical software package Sigma Stat 3.1 (Systat Software Inc, San Jose, CA, USA).

3. Results

The average age in the verum group was 42 yr (range: 22–52) and in the placebo group was 43 yr (range: 34–61). Because of the wide variety of treatments most patients had received prior to ESWT, it did not seem meaningful to stratify the patients based on these criteria. Prostate volume was not obtained because it had been proven in the preceding feasibility study to be without influence on the treatment outcome.

The placebo group did not show any significant alterations of the median values of IPSS, IIEF, CPSI, and VAS over the follow-up period. In contrast, all these values revealed statistically significant improvement in the verum group. This discrepancy could verify that ESWT is effective in the treatment of CPPS, at least within a limited period of time. Whereas the parameters in the verum group improved continuously after ESWT, the condition of the untreated patients remained stable (CPSI) or even worsened (IPSS, IIEF, VAS), which may reflect the natural course of the disease in the long run.

In the verum group, IPSS improved by 15% after 1 wk and by 25% after 12 wk. IIEF showed an improvement between 5.3% and 10.5% at the same intervals, and the CPSI improved continuously by 16.7%. All patients with a decline in CPSI of ≥5 (n = 13, 43.3%) were exclusively found in the verum group. The VAS showed the clearest improvement (33%) after 1 wk, even reaching 50% after 4 and 12 wk. All alterations were statistically significant with respect to the pretreatment value as well as with respect to the placebo group parameters. No side-effects were observed in any patients during the treatment and follow-up periods. Detailed parameters are shown in Table 1, and Table 2.

Table 1 Changes in parameters for the sham and verum treatment groups

Parameter	Placebo Rel. change % (median values)	Significant changes	Verum Rel. change % (median values)	Significant changes
IPSS (1 wk)–IPSS (pre)	0	No (p = 0.947)	−15.6	Yes ($p \leq$ 0.001)
IPSS (4wk)–IPSS (pre)	0	No (p = 0.631)	−18.8	Yes ($p \leq$ 0.001)
IPSS (12wk)–IPSS (pre)	0	No (p = 0.280)	−25	Yes ($p \leq$ 0.001)
IIEF (1 wk)–IIEF (pre)	0	No (p = 0.959)	10.5	Yes (p = 0.029)
IIEF (4wk)–IIEF(pre)	0	No (p = 0.894)	5.3	Yes (p = 0.034)
IIEF (12wk)–IIEF(pre)	0	No (p = 0.569)	5.3	Yes (p = 0.036)
CPSI (1 wk)–CPSI (pre)	0	No (p = 0.935)	−16.7	Yes ($p \leq$ 0.001)
CPSI (4wk)–CPSI (pre)	2.1	No (p = 0.865)	−16.7	Yes ($p \leq$ 0.001)

CPSI (12wk)–CPSI (pre)	4.2	No (p = 0.935)	−16.7	Yes ($p \leq$ 0.001)
VAS (1 wk)–VAS (pre)	−16.7	No (p = 0.151)	−33.3	Yes ($p \leq$ 0.001)
VAS (4 wk)–VAS (pre)	0	No (p = 0.865)	−50	Yes ($p \leq$ 0.001)
VAS (12 wk)–VAS (pre)	0	No (p = 0.227)	−50	Yes ($p \leq$ 0.001)

CPSI = Chronic Prostatitis Symptom Index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; VAS = Visual Analog Scale.

Table 2 Results: mean values for the sham and verum treatment groups

Parameter	Range: placebo	Normal test: placebo	Mean value: placebo	Median value: placebo	Range: verum	Normal test: verum	Mean value: verum	Median value: verum
IPSS pre	13.0–21.0	Failed	16.10 ± 0.38	16.00	10.0–20.0	Passed	15.83 ± 0.39	16.00
IPSS 1 wk	12.0–22.0	Passed	16.10 ± 0.39	16.00	10.0–17.0	Passed	13.53 ± 0.45	13.50
IPSS4wk	10.0–22.0	Passed	16.27 ± 0.43	16.00	9.0–16.0	Passed	12.90 ± 0.30	13.00
IPSS 12 wk	12.0–24.0	Failed	17.03 ± 0.55	16.00	10.0–15.0	Passed	12.53 ± 0.31	12.00
IIEF pre	11.0–23.0	Passed	17.13 ± 0.68	18.00	12.0–23.0	Passed	18.27 ± 0.60	19.00
IIEF1 wk	10.0–22.0	Failed	17.13 ± 0.61	18.00	16.0–23.0	Failed	20.17 ± 0.42	21.00
IIEF4wk	11.0–21.0	Failed	17.33 ± 0.57	18.00	14.0–23.0	Failed	20.07 ± 0.44	20.00
IIEF 12 wk	10.0–22.0	Failed	16.83 ± 0.59	18.00	16.0–23.0	Passed	20.17 ± 0.32	20.00
CPSI pre	21.0–32.0	Failed	25.07 ± 0.48	24.00	7.0–27.0	Failed	23.20 ± 0.66	24.00
CPSI 1 wk	16.0–33.0	Failed	24.77 ± 0.56	24.00	5.0–24.0	Failed	19.93 ± 0.58	20.00
CPSI 4 wk	22.0–34.0	Failed	24.97 ± 0.44	24.50	6.0–25.0	Failed	19.53 ± 0.57	20.00
CPSI 12 wk	21.0–32.0	Failed	25.00 ± 0.50	25.00	6.0–24.0	Failed	19.70 ± 0.67	20.00

VAS pre	4.0–8.0	Failed	5.73 ± 0.20	6.00	1.0–7.0	Failed	5.33 ± 0.26	6.00
VAS 1 wk	3.0–8.0	Failed	5.30 ± 0.22	5.00	1.0–6.0	Failed	3.63 ± 0.22	4.00
VAS 4 wk	3.0–8.0	Failed	5.73 ± 0.20	6.00	1.0–5.0	Failed	3.03 ± 0.20	3.00
VAS12wk	2.0–8.0	Failed	6.13 ± 0.26	6.00	1.0–6.0	Failed	3.13 ± 0.28	3.00

CPSI = Chronic Prostatitis Symptom Index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; VAS = Visual Analog Scale.

4. Discussion

Because of the lack of efficacy of the majority of drug-based therapies, new options for CPPS treatment are of broad interest. Individual therapies are being increasingly scrutinised in relation to their effects. Regrettably, the pathophysiologic backgrounds remain unclear at present, which makes the search for the most effective therapy even more difficult and necessitates a multimodal therapy approach [28], and [29].

CPPS is assumed either to be a myofascial pain syndrome or to involve neurologic components, thus leading to dysfunctional effects. Many of the complaints may be closely associated with the autonomic nervous system and the interplay between smooth and cross-striated muscles. Previous inflammations occurring via the sympathetic end plate may lead to pain via nociceptive nerve endings and receptors. The prostate seems to have at least a particular role in the pathophysiology of CPPS.

Certain kinds of psychological stress may provoke abnormal electromyographic activity and myofascial pain syndromes. Different coping and environmental factors are of outstanding importance for the successful adjustment of patients with CPPS [30].

Generally, the effects of extracorporeal shock waves on living tissue consist of transformation of mechanical signals into biochemical or molecular-biologic signals that again induce particular alterations within cells (mechanotransduction). Many possible ESWT effects are currently under discussion: Hyperstimulation of nociceptors and interrupting the flow of nerve impulses could lead to pain alleviation. ESWT is able to increase local microvascularisation as well as reduce muscle tone and spasticity.

Shock waves can possibly influence the neuroplasticity of the human pain memory: The prolonged lack of effective pain therapy could lead to a reinforcement of negative impulses (pain) in the brain. Long-term fixation of these impulses could result in the development of a particular *pain memory*. By triggering minimal pain impulses, ESWT could break through this negative-conditioned pain memory by *resetting* the pain [31]—an approach based on the neuron-holographic brain model. It defines the healing effects of ESWT by selective erasing of pathologic reflex patterns and might explain the possibility of influencing areas of pain localised at a distance from the treatment locus.

The results obtained concur with numerous investigations, particularly in the field of orthopaedics. There is a relatively long history of ESWT for painful illnesses of different

origins, particularly for chronic plantar fasciitis, which is at present probably the best-evaluated ESWT indication [32], [33], [34], [35], and [36]. The manner of application, clinical results, and range of side-effects are largely concordant to our present investigation. Besides orthopaedics, there are no similar studies about painful illnesses to which we could refer. In urology and for CPPS, very few comparable studies are to be found regarding shock wave application or study design. Therefore, we cannot really refer to comparable urologic applications.

In contrast with our first study, subjective urination conditions improved significantly for the entire follow-up period of 12 wk. Subjectively perceived urination quality is obviously impaired by CPPS. According to IPSS, the patients showed mainly obstructive symptoms. The interpretation of this effect is of course limited because IPSS reveals only subjective changes. Therefore, we will include in future uroflowmetry and urodynamic evaluation for a subgroup of patients to objectify these results.

The improvement of the IIEF was another unexpected result. It may be explained by the comprehensible fact that the general improvement in QoL also has a positive impact on sexual function, which is well known to be markedly reduced among CPPS patients [37]. Pain reduction can naturally support the functionality of erection and the individual capacity for enjoying sexuality in general. Furthermore, some facts do indeed suggest that local (penile) application of shock waves could possibly have positive effects on erectile tissue.

The most important parameter both clinically and with respect to daily life was pain, which we were able to reduce significantly in this study. Satisfyingly, the effect of the pain reduction continued over the entire follow-up period and was even intensified after 4 and 12 wk.

As expected, pain alleviation led to an improvement in CPPS-specific QoL. The CPSI could be improved for the whole follow-up time, whereas the symptoms of the patients in the placebo group became even worse. According to recent literature, an improvement of approximately 30% of the pain scale represents a clinically important difference [38] that makes the improvement achieved in this study relevant for daily life. A six-point decline in the CPSI total score represents the optimal threshold for predicting treatment response [39]. By using ESWT as a monotherapy, we were able to reach a mean five-point decline—not optimal according to the mentioned definition but nevertheless having clinical importance for the patients [40]. It is of particular importance that all patients showing a CPSI score decline of ≥5 (43.3%) were exclusively in the verum group, a fact that we think underscores the effectiveness of shock wave treatment.

The anticipated placebo effect could not be observed in this investigation. The reasons for this lack remains speculative, particularly because the study was conducted in a strict double-blind setting. The efficacy of blinding, however, has not been assessed.

Many studies have shown that directing the shock waves to the most tender point in comparison to exclusive ultrasound targeting leads to the best results [32]. This fact and the verification of intra-/periprostatic shock wave focus, when the transducer is placed perineally (as obtained in our previous feasibility study), allowed us to omit ultrasound guidance, which simplified the ESWT sequence considerably.

For the present study, the follow-up duration has so far been restricted to 12 wk. We are continuing to evaluate the patients at 6 and 12 mo after the end of ESWT treatment to obtain long-term results, particularly because of the good results and because most shock wave therapies usually require a longer period of time to show clinically significant effects on pain relief.

As proven in many investigations, the total applied ESWT energy significantly influences the final outcome. Therefore, ESWT effect can be considered dose dependent [33]. Our treatment schedule is partly empirical but similar to various nonurologic schematas, with proven efficiency and a very low or absent side-effect rate [32], [34], [35], and [36]. In urology, we do not have comparable investigations to refer to besides our own study [27]. In future, the treatment regime will be adapted in the light of the results observed at any stage of follow-up to obtain more objective treatment procedures. It might be possible, for example, to extend the intervals between the treatments by a significant extent to intensify the time-dependent tissue influence of ESWT and prolong the treatment effects. Because of the lack of any therapy-specific side-effects and the ease of application, it would be possible in theory to repeat the ESWT cycle at any time. Therefore, patients whose complaints become worse again after ESWT will be treated by a second cycle in the context of a separate study.

The major strength of this study is certainly the randomised, double-blind design, including the placebo-controlled group. Additionally, this investigation has not been performed by the original workgroup that introduced ESWT for CPPS into clinical practice but by an independent centre with members who had no personal interest in the establishment of this new therapy.

5. Conclusions

ESWT could be of significant importance in the treatment of CPPS (type IIIB prostatitis) because of the straightforwardness of its application and the lack of any appreciable side-effects. With ESWT, it has been possible for the first time to establish a rapid and therefore financially appealing outpatient CPPS therapy option (1) that uses a standard unit, (2) that can be repeated as often as required, and (3) that requires little expenditure in terms of either time or personnel. An additional advantage lies with the local application to the affected region compared with the systemic load caused by drugs (eg, analgesics), which typically leads to not-inconsiderable side-effects, especially when administered over longer periods of time.

References

- *[1] M.M. Collins, R.S. Stafford, M.P. O'Leary, M.J. Barry. How common is prostatitis? A national survey of physicians visits. J Urol 159 (1998) (1224 - 1228)*
- *[2] A.M. Duloy, E.A. Calhoun, J.Q. Clemens. Economic impact of chronic prostatitis. Curr Urol Rep 8 (2007) (336 - 339) Crossref.*
- *[3] J.C. Nickel. Classification and diagnosis of prostatitis: a gold standard?. Andrologia 35 (2003) (160 - 167) Crossref.*
- *[4] M.A. Pontari, M.R. Ruggieri. Mechanisms in prostatitis/chronic pelvic pain syndrome. J Urol 179 (Suppl 5) (2008) (S61 - S67) Crossref.*

- [5] R. Bartoletti, T. Cai, N. Mondaini, et al., Italian Prostatitis Study Group. Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multicenter case-control observational study. J Urol 178 (2007) (2411 - 2415) Crossref.
- [6] D.A. Shoskes, R. Berger, A. Elmi, J.R. Landis, K.J. Porpert, S. Zeitlin, Chronic Prostatitis Collaborative Research Network Study Group. Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. J Urol 179 (2008) (556 - 560) Crossref.
- [7] A.J. Schaeffer. Epidemiology and evaluation of chronic pelvic pain syndrome in men. Int J Antimicrob Agents 31 (Suppl 1) (2008) (108 - 111) Crossref.
- [8] J. Walz, P. Perotte, G. Hutterer, et al.. Impact of chronic prostatitis-like symptoms on the quality of life in a large group of men. BJU Int 100 (2007) (1307 - 1311) Crossref.
- [9] S.W. Lee, M.L. Liong, K.H. Yuen, et al.. Adverse impact of sexual dysfunction in chronic prostatitis/chronic pelvic pain syndrome. Urology 71 (2008) (79 - 84) Crossref.
- [10] M.A. Pontari. Chronic prostatitis/chronic pelvic pain syndrome. Urol Clin North Am 35 (2008) (81 - 89) Crossref.
- [11] H. Hedelin, M. Fall. Controversies in chronic abacterial prostatitis/chronic pelvic pain syndrome. Scand J Urol Nephrol 42 (2008) (198 - 204) Crossref.
- [12] R.E. Berger, M.A. Ciol, I. Rothman, J.A. Turner. Pelvic tenderness is not limited to the prostate in chronic prostatitis/chronic pelvic pain syndrome (CPPS) type IIIA and IIIB: comparison of men with and without CP/CPPS. BMC Urol 7 (2007) (17) Crossref.
- [13] M. Marszalek, C. Wehrberger, C. Temml, A. Ponholzer, I. Berger, S. Madersbacher. Chronic pelvic pain and lower urinary tract symptoms in both sexes: analysis of 2749 participants of an urban health screening project. Eur Urol 55 (2009) (499 - 508) Abstract, Full-text, PDF, Crossref.
- [14] C.N. Rudick, A.J. Schaeffer, P. Thumbikat. Experimental autoimmune prostatitis induces chronic pelvic pain. Am J Physiol Regul Integr Comp Physiol 294 (2008) (R1268 - R1275) Crossref.
- [15] J.C. Nickel. Role of alpha1-blockers in chronic prostatitis syndromes. BJU Int 101 (Suppl 3) (2008) (11 - 16) Crossref.
- [16] Z. Zhou, L. Hong, X. Shen, et al.. Detection of nanobacteria infection in type III prostatitis. Urology 71 (2008) (1091 - 1095) Crossref.
- [17] J.N. Krieger, L.J. Nyberg, J.C. Nickel. NIH consensus definition and classification of prostatitis. JAMA 282 (1999) (236 - 237) Crossref.
- [18] W. Weidner, R.U. Anderson. Evaluation of acute and chronic bacterial prostatitis and diagnostic management of chronic prostatitis/chronic pelvic pain syndrome with special reference to infection/inflammation. Int J Antimicrob Agents 31 (Suppl 1) (2008) (91 - 95) Crossref.
- [19] W. Weidner, F.M. Wagenlehner, M. Marconi, A. Pilatz, K.H. Pantke, T. Diemer. Acute bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: andrological implications. Andrologia 40 (2008) (105 - 112) Crossref.
- [20] K.J. Porpert, R.B. Alexander, C.J. Nickel, et al.. The Chronic Prostatitis Collaborative Research Network. Design of a multicenter randomized clinical trial for chronic prostatitis/chronic pelvic pain syndrome. Urology 59 (2002) (870 - 876)

- [21] J.C. Nickel, J. Downey, D. Ardern, J. Clarke, K. Nickel. Failure of monotherapy strategy for difficult chronic prostatitis/chronic pelvic pain syndrome. J Urol 172 (2004) (551 - 554) Crossref.
- [22] J.C. Nickel. Treatment of chronic prostatitis/chronic pelvic pain syndrome. Int J Antimicrob Agents 31 (Suppl 1) (2008) (S112 - S116)
- [23] B.C. Taylor, S. Noorbaloochi, M. McNaughton-Collins, et al.. Urologic Diseases in America project. Am J Med 121 (2008) (444 - 449) Crossref.
- [24] R.U. Anderson, D. Wise, T. Sawyer, C. Chan. Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. J Urol 174 (2005) (155 - 160) Crossref.
- [25] P. Manganotti, E. Amelio. Long term effect of shock wave therapy on upper limb hypertonia in patients affected by stroke. Stroke 36 (2005) (1967 - 1971) Crossref.
- [26] Y. Fukumoto, A. Ito, T. Uwatoku, et al.. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis 17 (2006) (63 - 70) Crossref.
- [27] R. Zimmermann, A. Cumpanas, L. Hoeltl, G. Janetschek, A. Stenzl, F. Miclea. Extracorporeal shock-wave therapy for treating chronic pelvic pain syndrome: a feasibility study and the first clinical results. BJU Int 102 (2008) (976 - 980) Crossref.
- [28] M.A. Pontari. Etiologic theories of chronic prostatitis/chronic pelvic pain syndrome. Curr Urol Rep 8 (2007) (307 - 312) Crossref.
- [29] N.B. Dhar, D.A. Shoskes. New therapies in chronic prostatitis. Curr Urol Rep 8 (2007) (313 - 318) Crossref.
- [30] J.C. Nickel, D.A. Tripp, S. Chuai, et al., NIH-CPCRN Study Group. Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. BJU Int 101 (2008) (59 - 64)
- [31] O.J. Wess. A neural model for chronic pain and pain relief by extracorporeal shock wave treatment. Urol Res 36 (2008) (327 - 334) Crossref.
- [32] H. Gollwitzer, P. Diehl, A. von Korff, V.W. Rahlfs, L. Gerdesmeyer. Extracorporeal shock wave therapy for chronic painful heel syndrome: a prospective, double blind, randomized trial assessing the efficacy of a new electromagnetic shock wave device. J Foot Ankle Surg 46 (2007) (348 - 357) Crossref.
- [33] D.S. Malay, M.M. Pressman, A. Assili, et al.. Extracorporeal shockwave therapy versus placebo for the treatment of chronic proximal plantar fasciitis: results of a randomized, placebo-controlled, double-blinded, multicenter interventional trial. J Foot Ankle Surg 45 (2006) (196 - 210) Crossref.
- [34] J.D. Rompe, C. Schoellner, B. Nafe. Evaluation of low-energy extracorporeal shock-wave application for treatment of chronic plantar fasciitis. J Bone Joint Surg Am 84 (2002) (335 - 341)
- [35] J.D. Rompe, A. Meurer, B. Nafe, A. Hofmann, L. Gerdesmeyer. Repetitive low-energy shock wave application without local anesthesia is more efficient than repetitive low-energy shock wave application with local anesthesia in the treatment of chronic plantar fasciitis. J Orthop Res 23 (2005) (931 - 941)
- [36] J.D. Rompe, J. Decking, C. Schoellner, B. Nafe. Shock wave application for chronic plantar fasciitis in running athletes. A prospective, randomized, placebo-controlled trial. Am J Sports Med 31 (2003) (268 - 275)

- *[37] S. Aubin, R.E. Berger, J.R. Heiman, M.A. Ciol. The association between sexual function, pain, and psychological adaptation of men diagnosed with chronic pelvic pain syndrome type III. J Sex Med 5 (2008) (657 - 667) Crossref.*
- *[38] J.T. Farrar, J.P. Young Jr., L. La Moreaux, J.L. Werth, R.M. Poole. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94 (2001) (149 - 158) Crossref.*
- *[39] K.J. Propert, M.S. Litwin, Y. Wang, et al.. Chronic Prostatitis Collaborative Research Network (CPCRN): responsiveness of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). Qual Life Res 15 (2006) (299 - 305) Crossref.*
- *[40] J.C. Nickel, J.*

2. Extracorporeal Shockwave Therapy for Chronic Skin Lesions

Authors:
*W. Schaden, C. Kölpl, A. Valentin, M. Pusch, R. Thiele**

Institution:
Trauma Center Meidling, Vienna, Austria
* Zentrum für extracorporale Stosswellentherapie, Berlin

Abstracts of the 8th Congress of the ISMST

Introduction:
Treating infected non-unions with soft tissue problems with ESWT we observed that there was also a positive effect on the skin. In most of the patients an extremely rapid healing of the wounds was observed. After successful animal trials performed at the department of plastic and reconstructive surgery of the University of Innsbruck we started our pilot trial.

Material and Methods:
Since September 2004, 102 patients with 104 chronic skin lesions were treated by means of ESWT. A special therapy head to defocus the shockwaves was constructed. All therapies were performed without any kind of anesthesia as an outpatient treatment. We used the same form of dressing after ESWT that was applied before. the treatment. Depending on the surface of the defect different number of pulses were applied. The patients were treated in 1 up to 6 sessions depending to their tendency of regeneration and epithelialization.

Reason for skin lesion:
Posttraumatic 44
Venous ulcer 25
Arterial ulcer 15
Postoperative 10
Decubital Ulcer 5
Burning wounds 5
Total 104

Results:
Out of the 104 patients 77 (74%) showed complete healing, 11 (10%) had more than 50% of epithelialization and 7 (7%) had less than 50%. 9 (10%) patients were lost of follow up. The treatment was tolerated by all patients without any kind of anesthesia. No adverse effects have been observed. In none of the cases an increase of symptoms was reported. After further pilot studies evaluating the most efficient treatment parameters, prospective randomized trials have to be performed to proof safety ness and efficacy of shockwave therapy in this new medical field.

3. Skin perfusion model in rats

First ATRAD Congress on Shockwave Treatment For musculoskeletal Pain; 20 September 2008, Berlin; Abstracts; Association For Radial Pain Therapy

Ludger Gerdesmeyer, Hans Gollwitzer, Rainer Mittermayr

Dept. of Endoprothesis and Spine Surgery, MARE Clinic Kiel, Kiel, Germany
Dept. of Orthopaedic Surgery and Sportstraumatology, Technical University Munich, Germany

Introduction:
Shockwaves were initially used to treat wound healing disorders.
First results showed good outcomes. Radial shockwaves were not applied in wound healing until now.
Methods:
In an epigastric skin flap model the effect of radial extracorporeal shockwaves was investigated in rats (Male Sprague Dawley rats weighing 300 to 350 g).
A total of 25 subjects randomly received assigned treatment. All subjects underwent surgery to create a specific skin flap with reduced perfusion due to ligation of the epigastric artery and vein. After surgery the subjects were assigned into 3 groups. The first group received 300 shockwaves with an ED of 0.13 mJ and 2Hz, the second group received 600 shockwaves with an ED of 0.13 mJ and 4 Hz, the third group received a placebo. To quantify the effect, planimetry and laser Doppler imaging (LDI) were performed 7 days after intervention and compared to baseline.
Results:
Baseline showed homogeneity regarding all criteria. Seven days after treatment rats receiving a total of 600 SW at 0.13 mJ showed significantly better outcomes compared to placebo and rats receiving 300 SW at 0.13 mJ. These significantly better outcomes after 600 SW at 0.13 mJ were found in both criteria (Planimetry and LDI). The group receiving 300 SW at 0.13 mJ showed slightly better outcomes but they were not significant compared to placebo. Only minor side effects such as petechial bleeding and edema were observed.
Discussion:
These findings demonstrate positive effects in a rat model. The clinical effect size remains unknown and needs to be determined.
Conclusion:
rESWT is an effective and safe method to treat wound healing with impaired perfusion conditions after surgery. The effect size reaches clinical relevance. These initial findings have to be verified in further studies. Clinical feasibility trials could start to calculate the clinical effect size of radial shockwaves in perfusionrelated wound healing disorders.

4. Extracorporeal Shockwave Therapy (ESWT) for Diabetic Wounds

First ATRAD Congress On Shockwave Treatment Formusculoskeletal Pain; 20 September 2008, Berlin;Abstracts; Association For Radial Pain Therapy

Gerald Zöch
Surgical Dept., SMZ -Ost Donauspital, Vienna, Austria

Introduction:
It is proven that ESWT improves and accelerates wound healing.
This trial investigates the safety and efficacy of this method for diabetic wounds.
Methods:
Between July 2007 and April 2008 eighteen patients with twenty-one foot lesions (Stage I A and II A respectively according to the Armstrong - Score) were treated with ESWT. Treatment consisted in debridement, ESWT (EMS Swiss DolorClast®), 2 -times a week with 400 - 1000 shocks/cm2 at 0,1 mJ/mm2 and moist dressings. The materials used were not changed during ESWT treatment. The wound size was calculated by WHAT® technique.
Results:
The treatment caused no pain and no infection occurred. The mean size of the wounds was: after one week 66,7%, after two weeks 58,7% and after three weeks 35,3% of the size before ESWT. Complete healing was achieved in 16 of 21 wounds (14 patients) after 6 weeks (range 3 - 11 weeks). Four patients dropped out for reasons not related to the therapy.
Discussion:
This study indicated ESWT as an additive therapy to standard wound management. It can be applied safely and effectively. Neither anesthesia nor hospitalization
is necessary.
Conclusion:
Although it was no randomized trial the preliminary results indicate the effect of ESWT in improving wound-repair in non-infected and non-ischemic diabetic wounds.

5. Effect of shock waves on the healing of partial-thickness wounds in piglets.

J Surg Res. 1990 Jul; 49(1):45-8.

Haupt G, Chvapil M.

University of Arizona Health Sciences Center, Department of Surgery, Tucson 85724.

During the last 20 years, the role of various physical factors in wound healing has been widely studied and recognized. With the use of shock waves for the treatment of urolithiasis, a new mechanical medium has been introduced into medicine. The influence of shock waves on the reepithelialization of partial-thickness wounds was studied in four Yorkshire piglets by a quantitative morphometric method. Wounds were inflicted either in intact skin (three pigs) or in skin irradiated with 1500 rads to achieve delayed healing. A significant enhancement in normal or delayed healing was found with low-dose treatment (10 SW at 14 kV). High-dose application of shock waves (100 SW at 18 kV) resulted in inhibition of the rate of reepithelialization of the wounds. Shock waves of intermediate energies were without effect. The stimulating effect of low-energy shock waves coincides with significantly increased vascularization of the upper dermis and thicker layer of the newly formed epithelial cells covering the wound.

6. Extracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes

Wound Repair and Regeneration, Volume 17, Number 4, July/August 2009 , pp. 522-530(9)

Kuo, Yur-Ren; Wang, Chun-Ting; Wang, Feng-Sheng[1]; Chiang, Yuan-Cheng[2]; Wang, Ching-Jen[3]

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 effectiveness 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 included 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 underwent 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 reduction 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 regeneration, and topical anti-inflammatory response.

7. Is There A Role For ESWT In Wound Care?

Podiatry Today; 19(7) ; Jul 01 2006

By John S. Steinberg, DPM, Lt. Col. Alexander Stojadinovic, MD, LCDR Eric Elster, MD, Lt. Col.(P) George Peoples, MD, and Chris E. Attinger, MD

Over the past several years, there has been a developing body of knowledge regarding the clinical applications of extracorporeal shockwave therapy (ESWT). The latest area of clinical investigation for this technology is in the arena of wound healing. Researchers are now studying ESWT as a new approach to wound healing with a particular emphasis on complex soft tissue wounds with and without underlying bone disruption. Hopefully, this article will serve as an introduction to this new topic and we hope the evidence-based data will soon follow as the ongoing clinical trials progress.

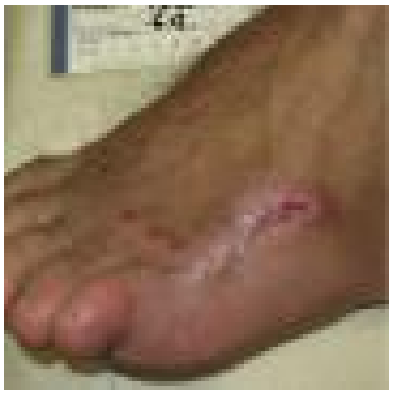
Preliminary clinical trials show that the core technology of unfocused ESWT (Tissue Regeneration Technologies) significantly enhances and accelerates the healing of complex soft tissue wounds in comparison to standard methods of treatment. Experience to date with ESWT indicates it is uniquely suited to the challenge of efficiently and effectively treating a variety of complex wound types, including military combat wounds. If proven in the proposed definitive field testing, such a system would offer new treatment options for some of our most challenging non-healing wound types.

Clinicians have used ESWT successfully to disintegrate kidney stones since 1981. The high efficacy and few adverse effects associated with this treatment made it the standard of care worldwide. Then shockwave therapy became a standard treatment for various common orthopedic conditions such as plantar fasciitis, tendinosis calcarea of the shoulder and tennis elbow.[1] Further research has demonstrated shockwave therapy's effectiveness in treating nonunion fractures in long bones and aseptic bone necrosis in humans.[2-4] Unlike the treatment of kidney stones, the fundamental therapeutic objective of orthopedic shockwave application is not to destroy tissue but to stimulate tissue regeneration.[5,6]

Researchers have shown that treatment with ESWT increases the release of critical wound growth factors and promotes vessel in-growth. The resulting improved circulation within the wound can have certain benefits in a variety of wound etiologies. Animal studies indicate that local delivery of shockwave therapy stimulates early expression of angiogenesis-related growth factors, including endothelial nitric oxide synthase, vessel endothelial growth factor and proliferating cell nuclear antigen. This results in new vessel in-growth that improves blood supply, increases cell proliferation and accelerates tissue regeneration and healing.[1,7-9]

Ludwig, et. al., described the beneficial effect of ESWT on wound healing in 1990.[10] During the course of treating nonunion or delayed osseous union of bone fractures, researchers discovered that both the disrupted bone as well as overlying soft tissue wounds healed rapidly.[3] Subsequently, an extensive body of peer-reviewed literature emerged, demonstrating that one could apply ESWT safely and with minimal risk to treat patients with a variety of complex surgical problems, including nonunion of long bone fractures with or without osteomyelitis, aseptic femoral head necrosis, pseudoarthroses

and osteochondritis dissecans.[10-15] The observed antibacterial effects of extracorporeal shockwaves are highly relevant to the increased risk of infection common to non-healing wounds.



Understanding the Different Mechanisms of ESWT

While the ESWT technology is quite different from current standards of soft tissue wound care, it is conceptually similar in its potential wound benefits. Extracorporeal shockwave therapy appears to increase local wound vascular density and blood flow as well as the rate of granulation tissue production while reducing bacterial counts. This would clearly accelerate healing time and promote the eradication of preexisting bacterial overgrowth. Extracorporeal shockwave therapy has shown potential for spontaneous epithelialization with a reduced need for secondary suturing, skin graft or flap closure.

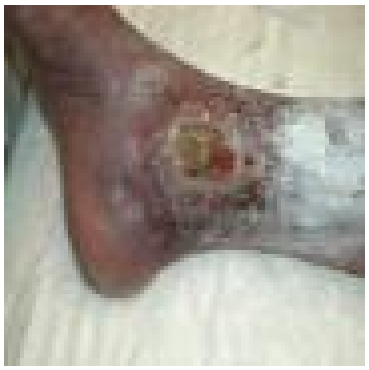
Extracorporeal shockwave therapy generates an acoustic pressure wave that penetrates human tissue through a liquid medium. One can focus the energy wave to a point or distribute it over a broad therapeutic front. Initially, researchers believed ESWT mechanically induced micro-sized fractures in bone tissue. However, it is now widely accepted that ESWT induces a reproducible biological response in target and surrounding tissue, releasing wound growth factors locally, stimulating stem cells and producing an antibacterial effect on biofilms (clusters of bacteria with a protective coating). Accordingly, ESWT facilitates vascular in-growth, re-epithelialization and complete wound closure.

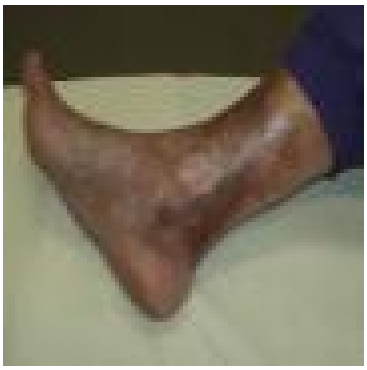
Current versions of ESWT in clinical use are based on the technology of an electrohydraulic shockwave. To achieve this, one would position a spark plug with two opposing electrodes under water in an ellipsoid reflector, releasing an electrical discharge in the focal point F1 (between opposing electrodes). The opposing electrodes are connected to a capacitor, which one charges to the maximum voltage and then abruptly discharges. The underwater discharge causes the explosive formation of a plasma channel, which results in evaporation of the water surrounding the opposing electrodes.

The primary spherical shockwave that is released at F1 expands in the surrounding water and the walls of the ellipsoid reflector reflect the shockwave. Due to the geometric properties of an ellipsoid reflector, all shockwaves generated at the opposing electrodes (F1) are reflected to a small area at a fixed distance away (known as the focal point or F2) from the opposing electrodes. Therefore, during an ESWT procedure, one should carefully align the device shock head and the patient, ensuring the target area to be treated is located at F2 where F2 is typically the point of maximum pressure.

In considering the application of ESWT to wound care, the technology must be adapted into a wide focus treatment area rather than the highly focused devices currently in use. To achieve shockwaves that are “roughly plane” to the treatment area, the reflector utilized in the wound treatment device applicator is made of a generalized parabolic reflector.

Placing the tips of the electrode (F1) in an exact parabolic reflector will result in a plane wave which emits after the reflection of the primary spherical wave. The focal point (F2) of these plane waves is, by definition, “unfocused” or “defocused,” meaning a focal point (F2) no longer exists. Therefore, the shockwave characteristics for the parabolic reflector could be defined as plane waves or, in other words, parallel rays. By using the generalized parabolic reflector, the plane waves are bent slightly toward the central acoustic axis. Therefore, the waves are unfocused, nearly parallel and a focal point (F2) does not exist. The energy density realized by the generalized parabolic reflector is higher than with an exact parabolic reflector and the acoustic field stimulates a large area.





How Clinicians Would Use ESWT To Treat Wounds

While all of this sounds quite complex, the actual use of the ESWT device in the wound patient is quite simple. One would prepare the patient with appropriate sharp debridement and local wound care. Then place the ESWT applicator head over the wound, utilizing ultrasonic gel and plastic draping to prevent any cross-contamination of the device.

The current study protocol utilizes 100 shocks per 1 cm^2 of wound so the treatment lasts just one to two minutes. The most sensation the patient may notice is the sound of the ESWT machine as it generates the shockwaves and bright flashes of light that correspond to those waves.

Currently, several shockwave devices are FDA approved to treat kidney and ureteral stones, chronic heel pain (plantar fasciitis) and tennis elbow (lateral epicondylitis). The devices have proven useful in treating Achilles and patellar tendonitis as well as challenging and difficult to treat delayed osseous union or nonunion fractures as well as avascular necrosis. Under European CE medical device approval, ESWT is routinely used by physicians to treat chronic non-healing soft tissue wounds, ischemic heart disease, arthritis, burns and periodontal disease successfully.

What Does The Research Indicate?

Clinical research conducted by Schaden at the Meidling Trauma Center in Vienna, Austria and at the Berlin Center for Extracorporeal Shock Wave Therapy suggest that ESWT is very effective in treating acute and chronic skin lesions such as venous and arterial ulcers, decubitis ulcers, post-traumatic wounds and burns.[15] The study was presented in May at the 9th International Society for Musculoskeletal Shockwave Therapy in Rio de Janiero. The study involved 200 patients including 65 with post-traumatic lesions, 25 venous ulcers, 28 arterial ulcers, 13 decubitus ulcers and five burn injuries.[15]

Researchers utilized a DermaGold™, MultiWave™ MTS 180 (Tissue Regeneration Technologies). Since surface defects are often involved, researchers modified the shockwave head so the shockwave would no longer be focused in a small plane to the treatment area. Clinicians used low energy flux densities and, depending on the size of the defect, the number of pulses varied between a few hundred to several thousand. Researchers administered no antibiotics (unless the patient was already taking them), anesthesia or debridements in the study.

Between September 2004 and January 2005, researchers used ESWT to treat 104 non-healing soft tissue wounds in 102 patients (50 male and 52 female patients with a median age of 61 years) with ESWT. They received 100 to 1,000 shocks/cm^2 at 0.1 mJ/mm^2, according to the size of the wound. The researchers administered the treatments weekly or every other week based on the rate of regeneration over one to six treatments (with a mean of three treatments). The rate of epithelialization was carefully documented. The mean treatment time was three minutes per session.

e pre-ESWT wound dressing therapy was not modified for the purpose of this study and continued after patients were treated with ESWT. For clean wounds/ ulcers, researchers employed wet-to-wet dressings with Tender-Wet®. Wounds with heavy secretions received Seasorb® or Comfil®, and the researchers used Aquacel Ag® for wounds with necrotic tissue.

Despite the fact that the wounds had bacterial contamination, no patients received antibiotic therapy during ESWT. No anesthesia was necessary in any of the patients studied as the shockwave was defocused and delivered over a broad treatment front. Researchers administered all ESWT on an outpatient basis and patients tolerated it well without any adverse side effects. Nine patients did not complete treatment and constituted study dropouts. (See “A Closer Look At Healing Rates Of Wounds Treated With ESWT” above.)

During a three- to 12-week period of monitoring, 81 percent of wounds healed completely with 12 percent demonstrating incomplete healing but greater than 50 percent epithelialization.

Throughout the course of this pilot study, none of the wounds deteriorated with ESWT. Interestingly, obviously colonized wounds at the outset of treatment improved without antibiotics after the first treatment session, presumably due to the bactericidal effect of shockwave therapy. No wound infection developed in this patient cohort. Surprisingly, even chronic venous stasis and arterial insufficiency ulcers demonstrated rapid wound healing with ESWT as 19 (53 percent) of 36 patients healed completely within six to 12 weeks while 10 (28 percent) patients had epithelialized over 50 percent of the treated

wound surface area. No patient in this study experienced any deterioration of the treated wound.

Where Is The Current Research On ESWT Headed?

Based on these encouraging results and other studies throughout the world, an FDA-sponsored diabetic foot ulcer study began in the United States earlier this year. Chris Attinger, MD, and John Steinberg, DPM, of the Limb Center at Georgetown University, have begun enrolling patients into this randomized, controlled trial for diabetic foot wounds using the wide focused ESWT technology. Several other sites will begin enrolling patients in this study as this article is published.

Very promising research involving similar ESWT technology is currently proposed for military combat wounds. Eric Elster, MD, George Peoples, MD, and Alexander Stojadinovic, MD, are leading the way in a pivotal randomized trial that will evaluate the efficacy of the technology in the management of acute traumatic wounds of the extremity with an emphasis on combat wounds.

Clearly, the possible utility of this technology is just in the process of emerging into wound care. The ongoing and future clinical trials, which employ randomization and specific wound types, should yield definitive clinical evidence on whether ESWT can play a role in healing the problem wound. We look forward to seeing the results of the clinical trials for proper assessment of the position that this may take within the current treatment protocols.

References:

1. Wang, C-J. An Overview of Shock Wave Therapy in Musculoskeletal Disorders. Chang Gung Med J 26:220-32, 2003.
2. Wang CJ, Chen HS, Chen CE, Yang KD. Treatment of nonunions of long bone fractures with shock waves. Clin. Orthop. 2001; 387; 95-101, 2001.
3. Schaden W, Fischer A, Seiler A. Extracorporeal shock wave therapy of non-union or delayed osseous union. Clin. Orthop (387) 90-94, 2001.
4. Ludwig J, Lauber S, Lauber HJ, Dreisilker U, Hotzinger H. High-energy shock wave treatment of femoral head necrosis in adults. Clin Orthop (387), 119-125, 2001.
5. Wang CJ, Yang KD, Chen RF, Wang FS, Sheen-Chen SM. Extracorporeal shockwave promotes growth and differentiation of bone marrow stromal cells towards osteoprogenitors associated with induction of TGF-beta 1 and VEGF Induction J Bone Joint Surg Br 84(2002b), 457-461.
6. Wang CJ, Huang HY, Pai CH. Shock wave enhanced neovascularization at the bone tendon junction. A study in a dog model. J Foot Ankle Surg, 41(1); 16-22, 2002a.
7. Nishida T, Shimokawa H, Oi K, et. al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia induced myocardial dysfunction in pigs in vivo. Circulation (110) 3055-3061, 2004.
8. Meirer R, Kamelger FS, Huemer GM, Wanner S, Piza-Katzer H. Extracorporal shock wave may enhance skin flap survival in an animal model. Br. J of Plastic Surgery, 58, (1) 53-57, 2005.
9. Haupt G, Chvapil M. Effect of Shock Waves on the Healing of Partial-Thickness Wounds in Piglets, J. of Surgical Research 49, 45-48, 1990.
10. Ludwig J, Lauber S, Lauber J, Hotzinger H. Shockwave treatment of femur necrosis

in the adult. Z Orthop Ihre Grenzgeb. Jul-Aug; 137(4):2-5, 1999.
11. Lauber S. High energy extracorporeal shockwave therapy in femur head necrosis. Z Orthop Ihre Grenzgeb. Sep-Oct; 138(5):3-4, 2000.
12. Thiele R, Marx S, Ludwig J, Herbert C. Extracorporeal Shockwave Therapy for Adult Osteochondritis dissecans of the Femoral Condyle and the Talus. 7th Congress of the International Society for Musculoskeletal Shockwave Therapy, Kaohsiung April 1-4, 2004.
13. Gerdesmeyer L, von Eiff C, Horn C, Henne M, Roessner M, Diehl P, Gollwitzer H. (2005), Antibacterial effects of extracorporeal shock waves, Ultrasound in Med. & Biol. Vol. 31, pp 115-119, 2005.
14. Hilton L. Study Shows Shock Wave Therapy Helps Heal Various Skin Lesions. Dermatology Times, 26(9), 2005.
15. Schaden W, Kölpl C, Valentin A, Pusch M, Thiele R. Extracorporeal Shockwave Therapy for Chronic Skin Lesions. 8th International Congress of the ISMST, May 29th - June 1st 2005, Vienna, Austria.

8. Prophylactic low-energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery: a prospective, randomized trial.

Ann. Thorac. Surg. Vol: 86; 2008 Dec; pp: 1552-6259

Julia Dumfarth; Daniel Zimpfer; Margit Vögele-Kadletz; Johannes Holfeld; Florian Sihorsch; Wolfgang Schaden; Martin Czerny; Seyedhossein Aharinejad; Ernst Wolner; Michael Grimm

BACKGROUND: Wound healing disorders after vein harvesting for coronary artery bypass graft surgery increase morbidity 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 kappaB. In this study, we investigate whether prophylactic low-energy SWT improves wound healing after vein harvesting for coronary artery bypass graft surgery. METHODS: One hundred consecutive patients undergoing 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 healing 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 including 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 improves wound healing after vein harvesting for coronary artery bypass graft surgery.

9. Angiogenic response to extracorporeal shock wave treatment in murine skin isografts

Angiogenesis; 2008 Dec; 11(4): 369-80

Alexander Stojadinovic[1, 2], Eric A. Elster[2, 3, 4], Khairul Anam[3], Douglas Tadaki[2, 3], Mihret Amare[3], Stephen Zins[3] and Thomas A. Davis[1, 3]

(1) Combat Wound Initiative Program, Department of Surgery, Walter Reed Army Medical Center, Washington, DC, USA

(2) Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

(3) Regenerative Medicine Department, Combat Casualty Care, Naval Medical Research Center, Room 2A10, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA

(4) Combat Wound Initiative Program, Department of Surgery, National Naval Medical Center, Bethesda, MD, USA

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-1β, IL-6, G-CSF, VEGF-A), matrix metalloproteinases (MMP3, MMP9, MMP13), hypoxia-inducible factors (HIF-1α), 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.

Basic Science Research

In-Vitro and In-Vivo Studies

1. Endothelial cellular response to altered shear stress.

Aron B. Fisher, Shu Chien, Abdul I. Barakat, and Robert M. Nerem.

Am J Physiol Lung Cell Mol Physiol 281: L529-L533, 2001;

Endothelial cells are normally exposed constantly to mechanical forces that significantly influence their phenotype. This symposium presented recent information concerning endothelial cell responses to shear stress associated with blood flow. Endothelial cell shear stress mechanosensors that have been proposed include membrane receptor kinases, integrins, G proteins, ion channels, intercellular junction proteins, membrane lipids (e.g., those associated with caveolae), and the cytoskeleton. These sensors are linked to signaling cascades that interact with or result in generation of reactive oxygen species, nitric oxide, and various transcription factors among other responses. Endothelial cells adapt to sustained shear stress, and either an increase or decrease from normal shear leads to signaling events. In vitro models for the study of endothelial cell responses must consider the pattern of shear stress (e.g., steady vs. oscillatory flow), the scaffold for cell growth (e.g., basement membrane or other cell types such as smooth muscle cells), and the extent of flow adaptation. These cellular responses have major relevance for understanding the pathophysiological effects of increased shear stress associated with hypertension or decreased shear stress associated with thrombotic occlusion.

2. Physical shock wave mediates membrane hyperpolarizationand Ras activation for osteogenesis in human bone marrow stromal cells.

Wang, F.S.,Wang, C.J., Huang, H.J., Chung, H., Chen, R.F., Yang, K.D.:

Biochem. Biophys. Res. Commun. 287, 648–655 (2001)

Physical shock wave (SW) has shown effectiveness on promotion of bone growth. We have recently demonstrated that SW could promote bone marrow stromal cell differentiation toward osteoprogenitor associated with induction of TGF- 1. We have further demonstrated that SW-induced membrane hyperpolarization and Ras activation acted an early signal for the osteogenesis in human bone marrow stromal cells. An optimal dose of SW treatment at 0.16 mJ/mm2 for 500 impulses induced a rapid membrane hyperpolarization in 5 min, activation of Ras in 30 min, and cell proliferation in 2 days. The SW-promoted cell growth was related to osteogenesis as demonstrated by increase of bone alkaline phosphatase activity in 6 days and osteocalcin mRNA expression in 12 days. In support that SW-induced Ras activation mediated osteogenesis of human bone marrow stromal cells, we further demonstrated that transfection of bone marrow stromal cells with a dominant negative Ras mutant (Asn-17 rasH) abrogated the SW enhancement of osteogenic transcription factor (CBFA1) activation, osteocalcin mRNA expression, and bone nodule formations. These results suggest that physical SW promotes bone marrow stromal cell differentiation toward osteogenic lineage via membrane hyperpolarization, followed by Ras activation and specific osteogenic transcription factor CBFA1 expression. A link between physical SW and biomembrane perturbation-mediated Ras activation may highlight how noninvasive physical agents could be used to promote fracture healing and to rescue patients with osteoporosis and osteopenic disorders in the future

3. Ras induction of superoxide activates ERK-dependent angiogenic transcription factor HIF-1 alpha and VEGF-A expression in shock wave-stimulated osteoblasts.

Feng-Sheng Wang, Ching-Jen Wang, Yeung-Jen Chen, Per-Rong Chang, Yu-Ting Huang, Yi-Chih Sun, Hueng-Chen Huang, Ya-Ju Yang, Kuender D Yang Department of Medical Research, Chang

Gung Memorial Hospital, Kaohsiung 833, Taiwan.
J Biol Chem. 2004 Mar 12;279 (11):10331-7 14681237 (P,S,E,B) Cited:1

Vascular endothelial growth factor (VEGF) released by osteoblasts plays an important role in angiogenesis and endochondral ossification during bone formation. In animal studies, we have reported that shock waves (SW) can promote osteogenic differentiation of mesenchymal stem cells through superoxide-mediated signal transduction (Wang, F. S., Wang, C. J., Sheen-Chen, S. M., Kuo, Y. R., Chen, R. F., and Yang, K. D. (2002) J. Biol. Chem. 277, 10931-10937) and vascularization of the bone-tendon junction. Here, we found that SW elevation of VEGF-A expression in human osteoblasts to be mediated by Ras-induced superoxide and ERK-dependent HIF-1alpha activation. SW treatment (0.16 mJ/mm(2), 1 Hz, 500 impulses) rapidly activated Ras protein (15 min) and Rac1 protein (30 min) and increased superoxide production in 30 min and VEGF mRNA expression in 6 h. Early scavenging of superoxide, but not nitric oxide, peroxide hydrogen, or prostaglandin E(2), reduced SW-augmented VEGF-A levels. Inhibition of superoxide production by diphenyliodonium, an NADPH oxidase inhibitor, was found to suppress VEGF-A expression. Transfection of osteoblasts with a dominant negative (S17N) Ras mutant abrogated the SW enhancement of Rac1 activation, superoxide synthesis, and VEGF expression. Further studies demonstrated that SW significantly promoted ERK activation in 1 h and HIF-1alpha phosphorylation and HIF-1alpha binding to VEGF promoter in 3 h. In support of the observation that superoxide mediated the SW-induced ERK activation and HIF-1alpha transactivation, we further demonstrated that scavenging of superoxide by superoxide dismutase and inhibition of ERK activity by PD98059 decreased HIF-1alpha activation and VEGF-A levels. Moreover, culture medium harvested from SW-treated osteoblasts increased vessel number of chick chorioallantoic membrane. Superoxide dismutase pretreatment and anti-VEGF-A antibody neutralization reduced the promoting effect of conditioned medium on angiogenesis. Thus, modulation of redox reaction by SW may have some positive effect on angiogenesis during bone regeneration.

4. Shock waves treatment induces differentiation of cardiac primitive cells in vitro

F. Di Meglio, D. Nurzynska1, C. Castaldo, A. Arcucci, E. Marlinghaus, S. Russo, S. Montagnani.

Universita degli Studi di Napoli Federico II, Scienze Biomorfologiche e Funzionali, Naples, Italy; Applied Research Center, Kreuzlingen, Switzerland. Presented at the WCC 2006

The identification of resident stem cells and progenitors of cardiomyocytes, endothelial and smooth muscle cells in the adult human heart has triggered the studies of new treatment options influencing their proliferation, migration and differentiation. It has been recently made known that shock waves (SW) therapy enhances the expression of VEGF and its receptor Flt-1 in human umbilical vein endothelial cells in vitro and proves beneficial in patients with coronary artery disease. We assessed the hypothesis that shock waves can have positive effects on precursors of all cardiac cell populations, namely cardiomyocytes, endothelial, smooth muscle cells and fibroblasts.

We used bioptic pieces from normal adult hearts (n=10) and from human hearts explanted due to the ischemic cardiomyopathy (n=14) to obtain the outgrowth of cardiac cells in vitro. The precursors and progenitors of cells of cardiac lineages were identified and quantified by immunocytochemistry. The cell proliferation and expression of differentiation markers were then examined by immunocytochemistry and western blot, both without and after exposition to 800 shots of SW at 0,1 mJ/mm2.

The growth rate of cardiac cells was slowed down by the SW treatment due to the decrease of fibroblast relative number in the cell culture (83% vs. 56%, $p < 0.05$). The expression of Flk-1 increased significantly in the primitive cells from both normal and diseased hearts after SW treatment (4-fold and 2-fold, respectively). Similarly, the SW treatment increased nearly 2-fold the expression of smooth muscle actin, while the increase of α-sarcomeric actin and MHC expression was not significant. The expression of MLC-1 decreased significantly after SW treatment of normal cells and increased in the cells from pathological hearts, while MLC-2 decreased in both cell types. Importantly, the number of primitive cells and expression of differentiation markers were always significantly higher in the control cells from pathological hearts when compared with the normal hearts.

The results indicate that differentiation of primitive cells in the myocardium is markedly enhanced in chronic pathological conditions. The SW treatment influences positively differentiation and maturation of cardiomyocytes, endothelial and smooth muscle cells, reducing the relative number of fibroblasts in vitro, possibly due to the influence on growth factor production and release, enhancing their auto- and paracrine action. The effects of SW therapy were markedly more prominent in the cells from normal hearts, therefore its use may be recommended in the early stages of heart failure.

5. Shock Waves Activate In Vitro Cultured Progenitors And Precursors Of Cardiac Cell Lineages From The Human Heart.

Daria Nurzynska, Franca Di Meglio, Clotilde Castaldo, Alessandro Arcucci, Ernst Marlinghaus, Sergio Russo, Bruno Corrado, Luca de Santo, Francesco Baldascino, Maurizio Cotrufo, Stefania Montagnani

Ultrasound Med Biol. 2007 Oct 1

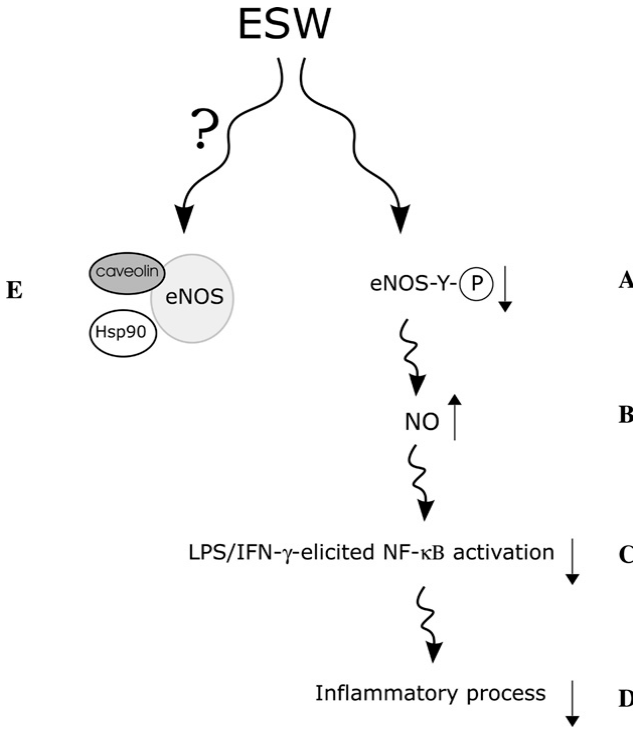
Postischemic cardiomyopathy remains one of the disorders in urgent need of effective noninvasive therapy. It is currently accepted that the isolation, expansion and application of resident cardiac stem cells may hold therapeutic promise for the future. Recently, it has been demonstrated that shock waves (SW) could enhance the expression of vascular endothelial growth factor (VEGF) and its receptor, Flt-1. As the development of angiogenic noninvasive therapy is very important for future therapeutic strategies in cardiovascular diseases, we examined in vitro, the effects of SW treatment on adult resident cardiac primitive cells isolated from bioptic fragments of normal human hearts and from explanted pathologic hearts with postischemic cardiomyopathy. This study demonstrates that SW have positive influence on both the proliferation and the differentiation of cardiomyocytes, smooth muscle and endothelial cells precursors, with a more obvious effect being evident in the cells from normal heart than in those taken from pathologic hearts. Our results suggest that SW treatment could inhibit or retard the pathologic remodeling and functional degradation of the heart if applied during the early stages of heart failure.

6. Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production.

Mariotto S, Cavalieri E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, Russo S, Suzuki H.

Department of Neuroscience and Vision, Section of Biochemistry, University of Verona, Strada Le Grazie 8, 37134 Verona, Italy. Nitric Oxide. 2005 Mar;12(2):89-96.

At low energy density (0.03mJ/mm(2)), extracorporeal shock waves (ESW), originally developed for clinical lithotripsy, have successfully been used for anti-inflammatory treatment of soft tissues. Since nitric oxide plays a critical role in inflammation, we hypothesized for ESW to increase NO production in cells. Using human umbilical vein endothelial cells as a model system, we observed that ESW, at low energy density, rapidly induced an enhancement of eNOS activity. In these cells, eNOS activity is modulated by tyrosine- and serine-phosphorylation. ESW shifted eNOS to a less-tyrosine-phosphorylated form, without affecting its serine-phosphorylation, thus accounting for its rapid enzyme activation. LPS/IFN-gamma treatment of human umbilical vein endothelial cells induced a rapid inhibition of eNOS activity and concomitant NF-kappaB activation which were efficiently counteracted by ESW treatment. Therefore, the present results indicate that the molecular mechanism of clinically observed anti-inflammatory action of ESW should include tyrosine-dephosphorylation of eNOS, a successive increase in NO production and suppression of NF-kappaB activation.



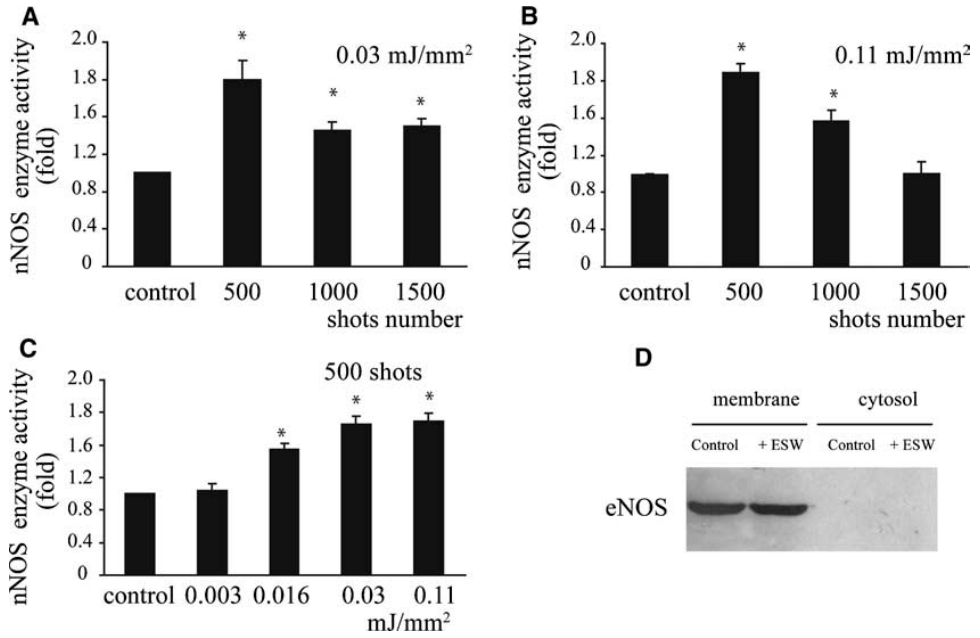
General view on the molecular pathway involved in ESW-elicited anti-inflammatory effect. Experimental data described in the present study indicate the following pathway, leading to the down-regulation of inflammatory process elicited by ESW. ESW quickly induce tyrosine-dephosphorylation of eNOS (A), enhancing the enzyme catalytic activity. Successive increase in the amounts of NO (B) keep suppressed NF-κB activation despite the presence of LPS/IFN-γ (C). Lack of NF-κB activation inhibits LPS/IFN-γ elicited expression of genes involved in the inflammatory process, down-modulating whole inflammatory process (D). Possible effect of ESW on association between eNOS and other proteins, such as caveolin and Hsp90, remains to be elucidated (E).

7. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves.

Ciampa AR, de Prati AC, Amelio E, Cavalieri E, Persichini T, Colasanti M, Musci G, Marlinghaus E, Suzuki H, Mariotto S.

Dipartimento di Scienze Neurologiche e della Visione, Sezione di Chimica Biologica, Universita degli Studi di Verona, Strada Le Grazie, 8, 37134 Verona, Italy. FEBS Lett. 2005 Dec 19;579(30):6839-45. Epub 2005 Nov 28

Here, we show that extracorporeal shock waves (ESW), at a low energy density value, quickly increase neuronal nitric oxide synthase (nNOS) activity and basal nitric oxide (NO) production in the rat glioma cell line C6. In addition, the treatment of C6 cells with ESW reverts the decrease of nNOS activity and NO production induced by a mixture of lipopolysaccharides (LPS), interferon-gamma (IFN-gamma) plus tumour necrosis factor-alpha (TNF-alpha). Finally, ESW treatment efficiently downregulates NF-kappaB activation and NF-kappaB-dependent gene expression, including inducible NOS and TNF-alpha. The present report suggests a possible molecular mechanism of the anti-inflammatory action of ESW treatment.



(A) Modulation of nNOS activity by different ESW shots at 0.03 mJ/mm2 energy level. C6 cells were treated at energy level 0.03 mJ/mm2 with a range of 500–1500 ESW shots, and nNOS activity was measured. (B) Modulation of nNOS activity by different ESW shots at 0.11 mJ/mm2 energy level. C6 cells were treated at energy level 0.11 mJ/mm2 with a range of 500–1500 ESW shots, and nNOS activity was measured. (C) Modulation ofnNOS activity by different energy levels of ESW treatment. C6 cells were treated at energy levels between 0.003 and 0.11 mJ/mm2 with 500 shots, and nNOS activity was measured. (D) Localization of eNOS after ESW treatment. C6 cells were treated at the energy level of 0.03 mJ/mm2 with 500 shots. Then, proteins in the membrane and cytosolic fractions were analyzed by Western blot, using an anti-eNOS antibody. For A, B and C, data are shown as a fold increase (means ± S.D., n = 6); *P < 0.005 versus non-treated cells.

8. Low-Energy Shock Wave for Enhancing Recruitment of Endothelial Progenitor Cells

A New Modality to Increase Efficacy of Cell Therapy in Chronic Hind Limb Ischemia

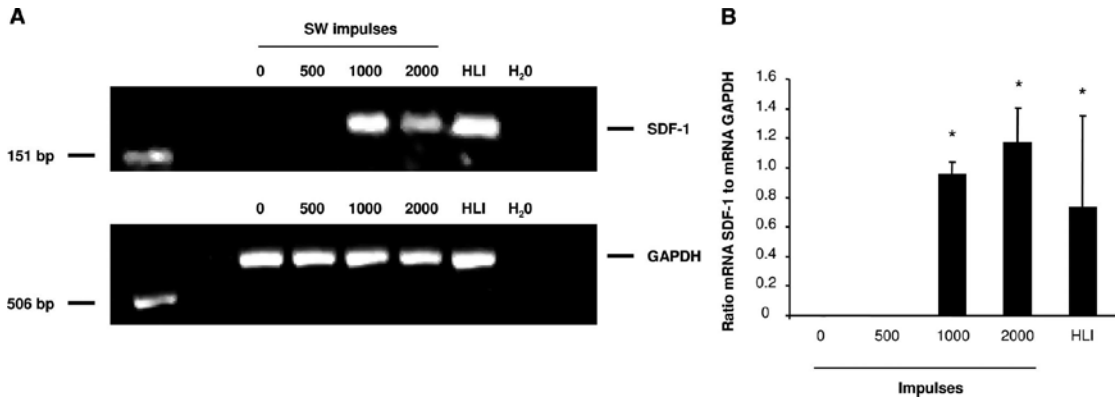
Alexandra Aicher, MD*; Christopher Heeschen, MD*; Ken-ichiro Sasaki, MD; Carmen Urbich, PhD; Andreas M. Zeiher, MD; Stefanie Dimmeler, PhD

Department of Medicine III, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany.
Circulation. 2006 Dec 19;114(25):2823-30.

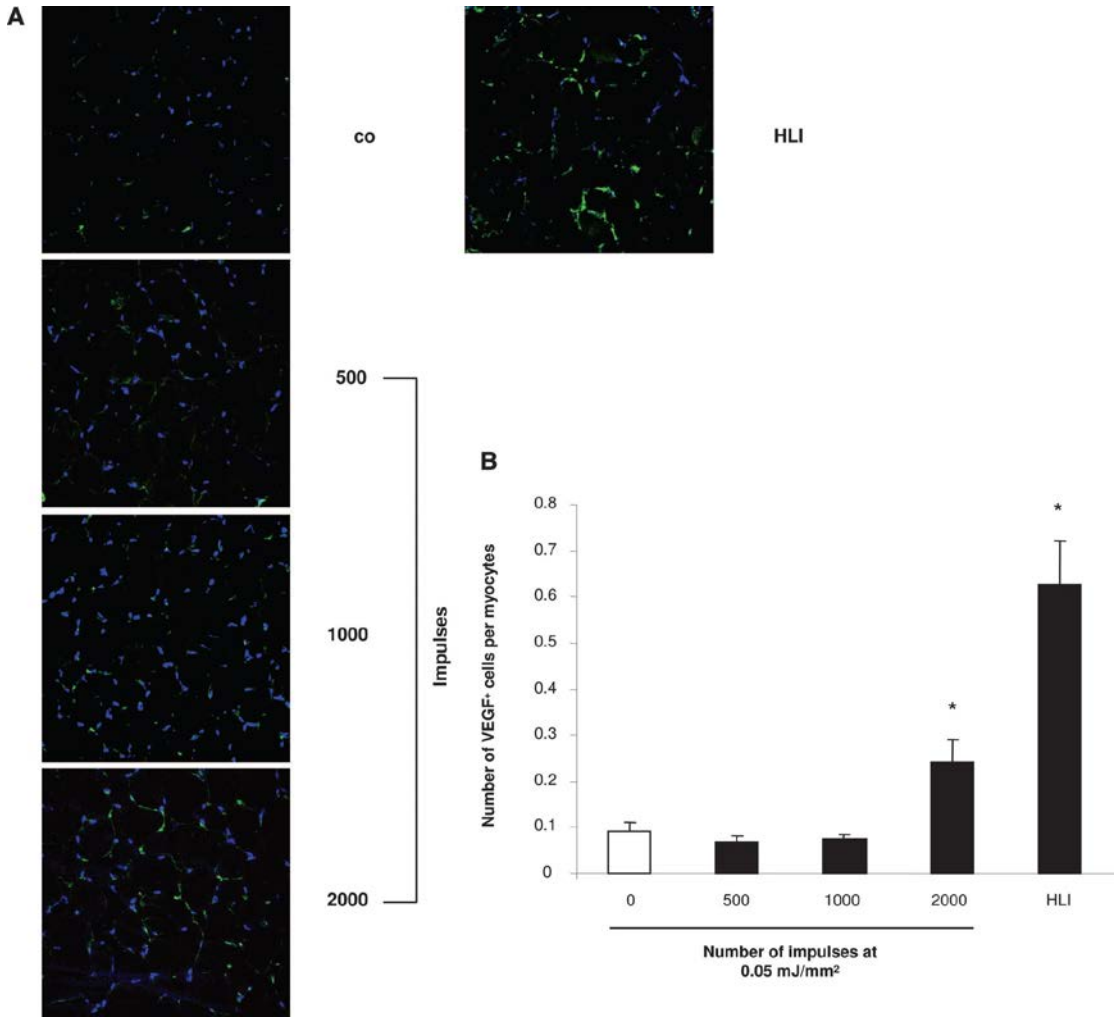
Background:
Stem and progenitor cell therapy is a novel approach to improve neovascularization and function of ischemic tissue. Enhanced tissue expression of chemoattractant factors such as stromal cell– derived factor 1 and vascular endothelial growth factor is crucial for the recruitment of circulating endothelial progenitor cells (EPCs) during acute ischemia. In chronic ischemia, however, expression of these chemoattractants is less pronounced which results in insufficient EPC recruitment into the target tissue. Therefore, we investigated the effect of targeted extracorporeal shock wave (SW) application in order to facilitate EPC recruitment into nonischemic and chronic ischemic tissue.

Methods and Results:
Hind limb adductor muscles of nude rats were treated with 500, 1000, and 2000 impulses of focused low-energy SW (flux density level: 0.05 mJ/mm2). Twenty-four hours later, mRNA expression of the chemoattractant stromal cell– derived factor 1 was significantly increased with 1000 impulses (stromal cell– derived factor 1/GAPDH: 0.95±0.09) and 2000 impulses (stromal cell– derived factor 1/GAPDH: 1.17±0.24; both $P<0.05$ versus untreated). Histologically, the number of vascular endothelial growth factor–positive endothelial cells per myocyte was significantly increased with 2000 impulses (0.24±0.05 versus 0.09±0.02; $P<0.01$). This preconditioning effect resulted in significantly enhanced recruitment and homing of EPCs that were intravenously infused 24 hours after SW treatment ($P<0.05$). In a rat model of chronic hind limb ischemia, SW-facilitated EPC treatment resulted in a significant increase in relative blood flow recovery as assessed by laser Doppler imaging ($P<0.05$).

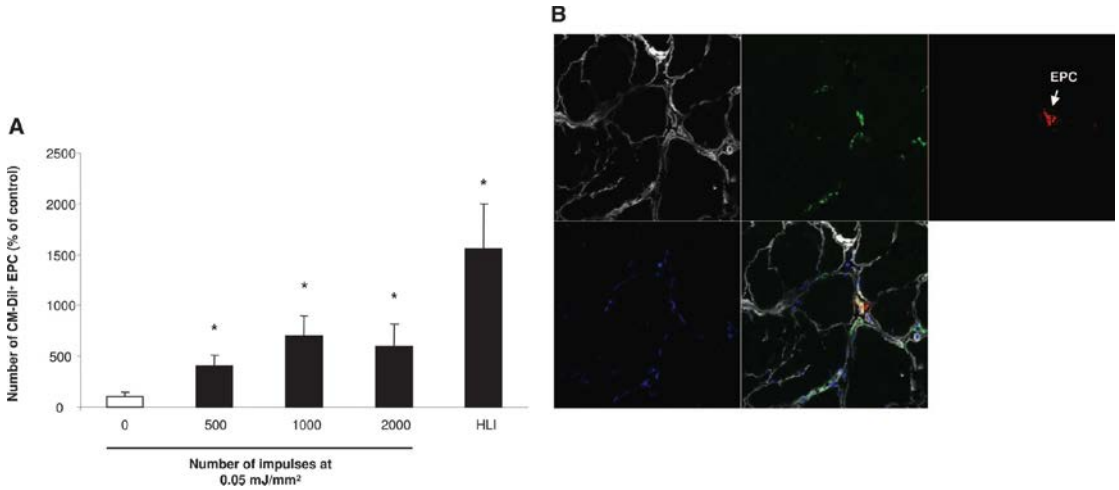
Conclusions:
Preconditioning of both nonischemic and chronic ischemic tissue with low-energy SW improves recruitment of circulating EPCs via enhanced expression of chemoattractant factors. Thus, SW facilitated cell therapy may improve the efficacy of EPC treatment in patients with chronic ischemia.



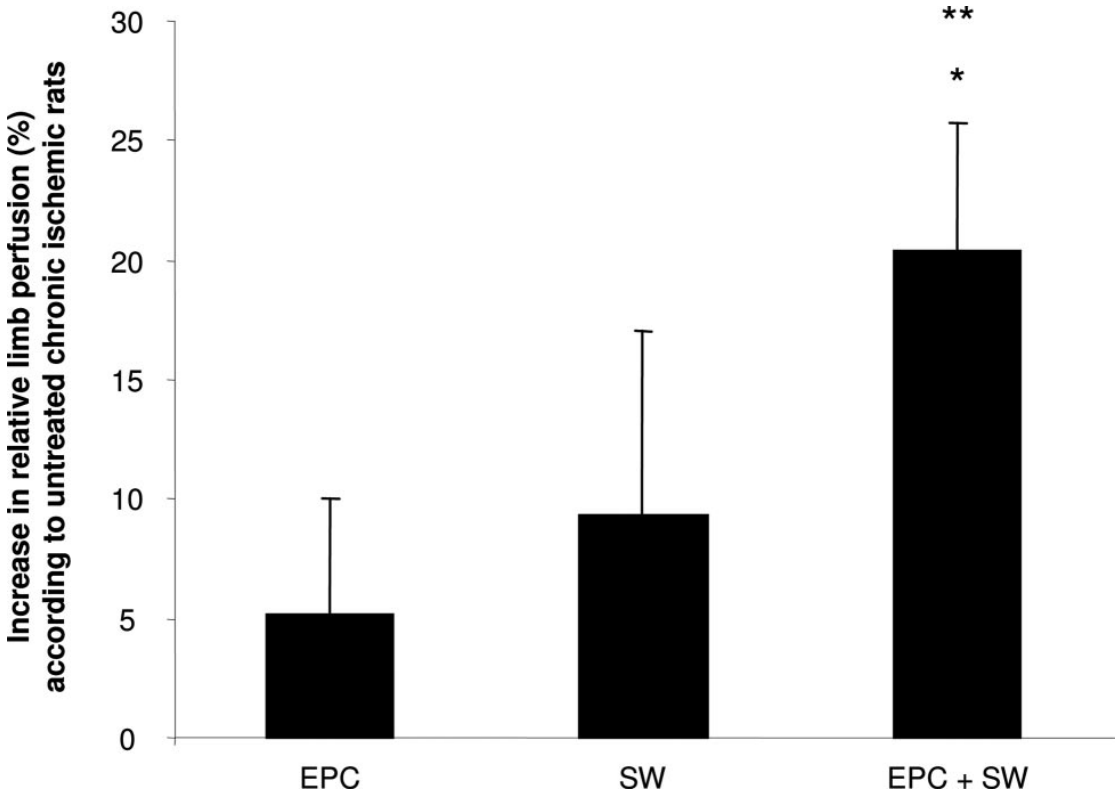
Expression of SDF-1 mRNA after SW treatment. (A) Expression of SDF-1 mRNA is determined in nonischemic hind limb adductor muscles after SW therapy with an energy density level of 0.05 mJ/mm2 and increasing numbers of impulses. GAPDH is used as a loading control. Hind limb ischemia (HLI) served as a positive control. (B) Quantification is given as a ratio of SDF-1 expression versus GAPDH for 3 animals (*P_0.05 versus no impulses). SDF-1 expression was below detection levels at 0 and 500 impulses.



A, Effect of SW treatment on the number of VEGF_cells per myocyte. VEGF_cells (green) and nuclear staining (blue) are shown after SW therapy with an energy density level of 0.05 mJ/mm2 and increasing numbers of impulses (co: control, untreated hind limb). B, Quantification for up to 9 sections per animal with at least 5 animals per group is shown (*P_0.01 versus no impulses). HLI indicates hind limb ischemia.



Recruitment of circulating EPCs to nonischemic tissue is augmented after SW preconditioning. A, Effect of SW pretreatment with energy flux density levels of 0.05 mJ/mm2 and 500 to 2000 impulses, (co: control, untreated hind limb). SWs were applied 24 hours prior to intravenous injection of human EPCs. Then, numbers of recruited EPCs in the adductor muscles were determined. *P_0.05 versus no impulses (up to 11 sections per animal checked for mice in control [n_7], 500 [n_7], 1000 [n_8], 2000 [n_7], and hind limb ischemia [HLI] [n_3] groups, respectively). B, Recruited CM-DiI_EPCs exhibit red fluorescence, von Willebrand factor is used as endothelial marker (green), membrane staining is performed by laminin (white), and nuclei (Sytox blue) are blue.



Effect of SW preconditioning on perfusion in unilateral chronic ischemic tissue. Effect of SW pretreatment 24 hours prior to intravenous injection of human EPCs assessed by laser Doppler imaging. The increase in perfusion is calculated compared with chronically ischemic rats without treatment (control, 7 rats; EPC, 10 rats; SW, 7 rats; combined, 9 rats). *P_0.01 versus untreated; **P_0.053 versus EPC treatment.

9. The effect of single shock waves on the vascular system of artificially perfused rabbit kidneys.

Seemann O, Rassweiler J, Chvapil M, Alken P, Drach GW.

Department of Urology, Klinikum Mannheim, Clinical Faculty of the University of Heidelberg, Germany. kidneys. J Stone Dis. 1993 Jul;5(3):172-8

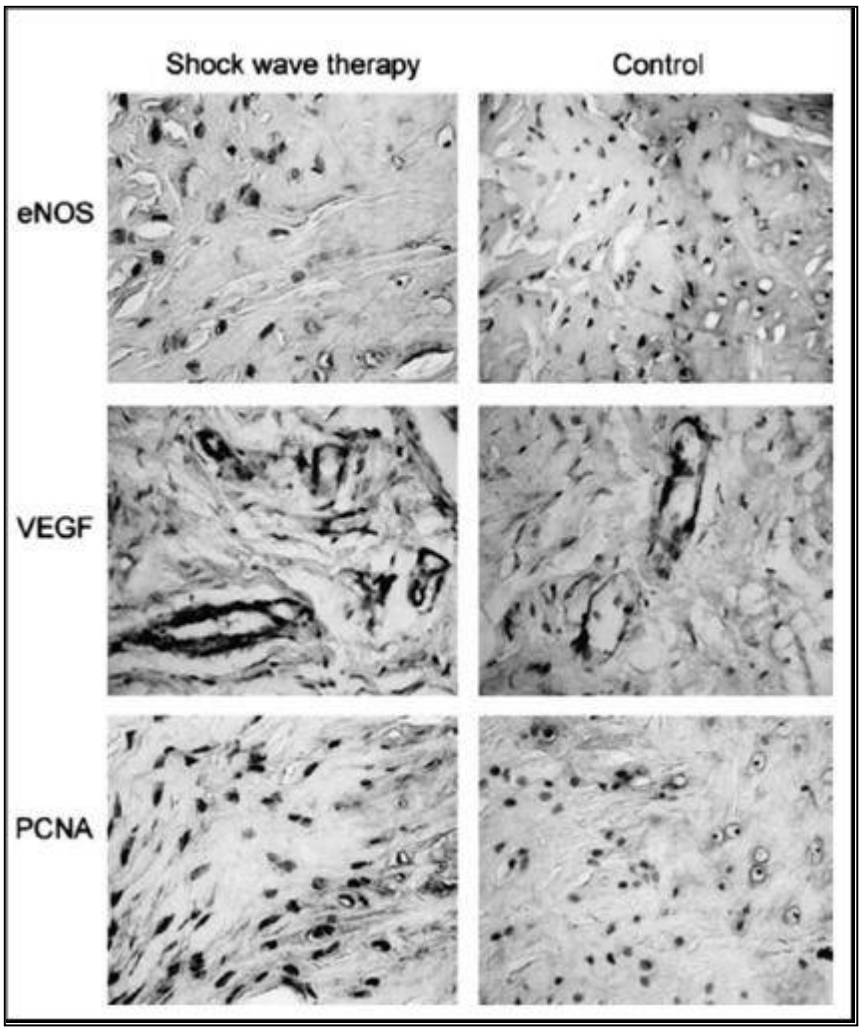
Extracorporeally-perfused rabbit kidneys were exposed to five shock waves at 14 kV on the XL1 Dornier experimental lithotripter (Dornier Medical Systems, Inc., Germering, Germany). While the perfusion flow rate was kept constant, the arterial perfusion pressure was recorded to assess changes in vascular resistance. Immediately after shock wave application, perfusion pressure decreased by 20%-30%, followed by a short, relative pressure rise that did not reach pretreatment values. Fifteen-twenty minutes later, arterial perfusion pressure reattained pretreatment values. Subsequent to treatment, urine flow decreased by greater than 50%. The observed pressure rise was also induced in nontreated kidneys by perfusion with the effluent of treated kidneys indicating that this is based on a humoral mechanism. On the other hand, shock wave application to formalin fixed kidneys only caused a marked decrease in arterial perfusion pressure, suggesting that this effect is due to a pure mechanical interaction of the shock wave also found with denaturated kidneys. The observed decrease of urine flow is probably caused by a decreased filtration rate. Since this was not the case in nontreated kidneys being perfused with the effluent of treated kidneys, the reduction of urine flow after extracorporeal shock wave lithotripsy does not appear to be mediated by a humoral factor, but is more likely a result of the mechanically-induced vasodilation with consecutive decline of the glomerular filtration rate.

10. An overview of shock wave therapy in musculoskeletal disorders.

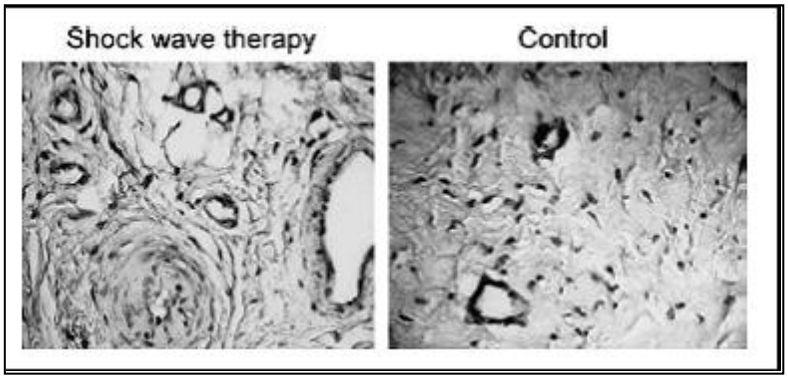
Wang CJ.

Department of Orthopedic Surgery, Chang Gung Memorial Hospital, 123, Dabi Road, Niaosung Shiang, Kaohsiung, Taiwan 833, ROC. Chang Gung Med J. 2003 Apr;26(4):220-32.

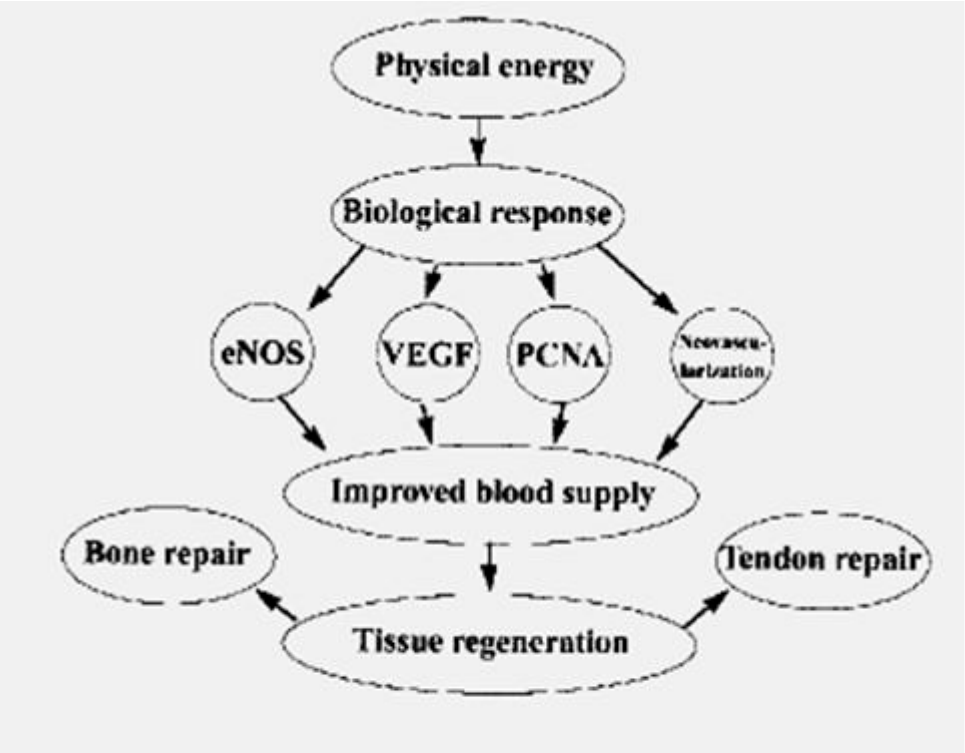
Shock waves are high-energy acoustic waves generated under water with high voltage explosion and vaporization. Shock wave in urology (lithotripsy) is primarily used to disintegrate urolithiasis, whereas shock wave in orthopedics (orthotripsy) is not used to disintegrate tissues, rather to induce neovascularization, improve blood supply and tissue regeneration. The application of shock wave therapy in certain musculoskeletal disorders has been around for approximately 15 years, and the success rate in non-union of long bone fracture, calcifying tendonitis of the shoulder, lateral epicondylitis of the elbow and proximal plantar fasciitis ranged from 65% to 91%. The complications are low and negligible. Recently, shock wave therapy was extended to treat other conditions including avascular necrosis of femoral head, patellar tendonitis (jumper's knee), osteochondritis dessicans and non-calcifying tendonitis of the shoulder. Shock wave therapy is a novel therapeutic modality without the need of surgery and surgical risks as well as surgical pain. It is convenient and cost-effective. The exact mechanism of shock wave therapy remains unknown. Based on the results of animal studies in our laboratory, it appears that the mechanism of shock waves first stimulates the early expression of angiogenesis-related growth factors including eNOS (endothelial nitric oxide synthase), VEGF (vessel endothelial growth factor) and PCNA (proliferating cell nuclear antigen), then induces the ingrowth of neovascularization that improves blood supply and increases cell proliferation and eventual tissue regeneration to repair tendon or bone tissues. The rise of angiogenic markers occurred in as early as one week and only lasted for approximately 8 weeks, whereas the neovascularization was first noted in 4 weeks and persisted for 12 weeks or longer along with cell proliferation. These findings support the clinical observation that the effect of shock wave therapy appears to be dose-dependent and symptom improvement with time. Additional information including the cellular and molecular changes after shock wave therapy are needed for further clarification on the mechanism of shock wave therapy in musculoskeletal system.



Tissue biopsies from the tendon–bone junction were stained with mouse anti-human eNOS, VEGF and PCNA antibodies respectively, and followed by HRP-conjugated goat anti-mouse antibody staining. The results were examined under microscopy with 40_ magnification with the study on the left, and the control on the right.



Tissue biopsies taken from the tendon–bone junction were subject to histomorphological staining after decalcification. The neovessels on microscopy were examined with 40_ magnification with the study side on the left, and the control side on the right.



The mechanism of shock waves appears to involve a cascade of interaction between physical shocks wave energy and biological responses

11. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits.

Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, Yang LC.

Department of Orthopedic Surgery, Chang Gung Memorial Hospital at Kaohsiung, 123 Ta-Pei Road, Niao-Sung Hsiang, 833 Kaohsiung, Taiwan. J Orthop Res. 2003 Nov;21(6):984-9.

Despite the success in clinical application, the exact mechanism of shock wave therapy remains unknown. We hypothesized that shock wave therapy induces the ingrowth of neovascularization and improves blood supply to the tissues. The purpose of this study was to investigate the effect of shock wave therapy on neovascularization at the tendon-bone junction. Fifty New Zealand white rabbits with body weight ranging from 2.5 to 3.5 kg were used in this study. The right limb (the study side) received shock wave therapy to the Achilles tendon near the insertion to bone. The left limb (the control side) received no shock wave therapy. Biopsies of the tendon-bone junction were performed in 0, 1, 4, 8 and 12 weeks. The number of neo-vessels was examined microscopically with hematoxylin-eosin stain. Neovascularization was confirmed by the angiogenic markers including vessel endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) expressions and endothelial cell proliferation determined by proliferating cell nuclear antigen (PCNA) expression examined microscopically with immunohistochemical stains. The results showed that shock wave therapy produced a significantly higher number of neo-vessels and angiogenesis-related markers including eNOS, VEGF and PCNA than the control without shock wave treatment. The eNOS and VEGF began to rise in as early as one week and remained high for 8 weeks, then declined at 12 weeks; whereas the increases of PCNA and neo-vessels began at 4 weeks and persisted for 12 weeks. In conclusion, shock wave therapy induces the ingrowth of neovascularization associated with early release of angiogenesis-related markers at the Achilles tendon-bone junction in rabbits. The neovascularization may play a role to improve blood supply and tissue regeneration at the tendon-bone junction.

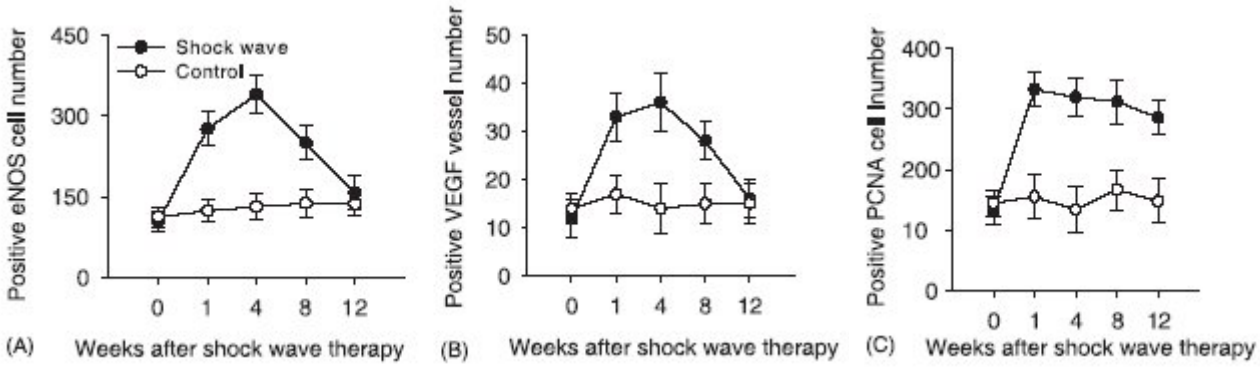


Fig. 3. The changes of eNOS, VEGF, and PCNA at different time intervals after shock wave therapy are shown graphically.

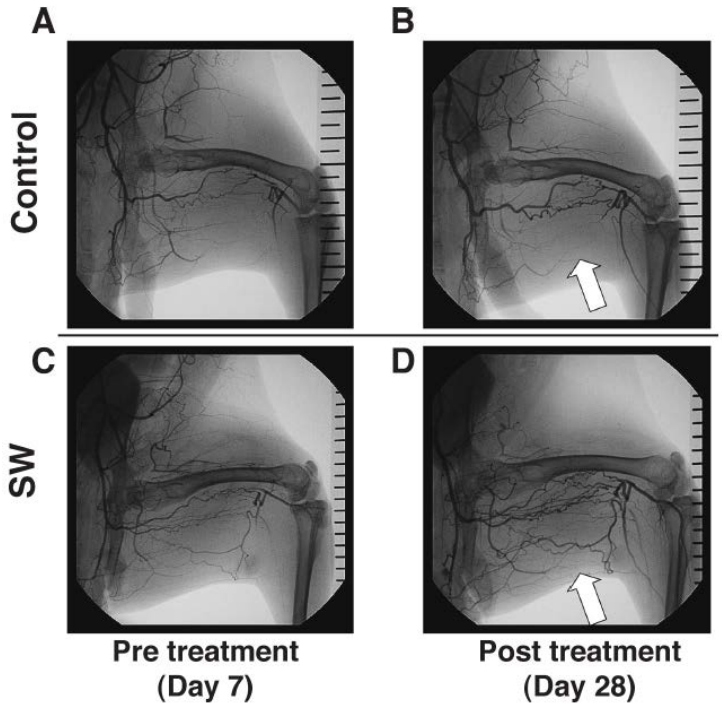
12. Extracorporeal shock wave therapy ameliorates hind limb ischemia in rabbits.

Keiji Oi, Yoshihiro Fukumoto, Kenta Ito, Toyokazu Uwatoku, Kohtaro Abe, Takatoshi Hizume, Hiroaki Shimokawa

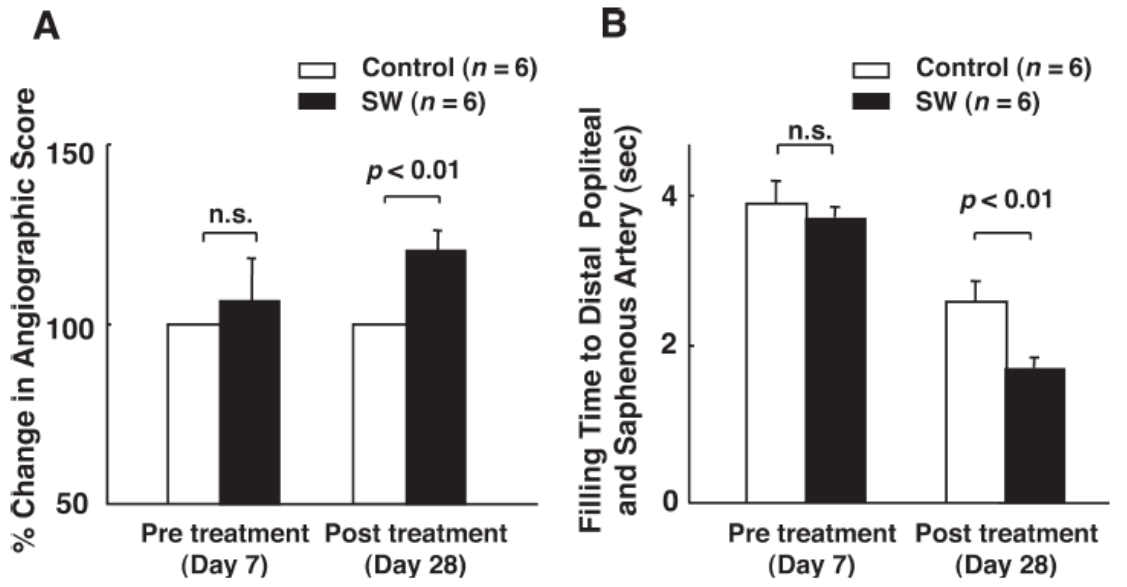
Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences.

Tohoku J Exp Med. 2008 Feb ;214 (2):151-8

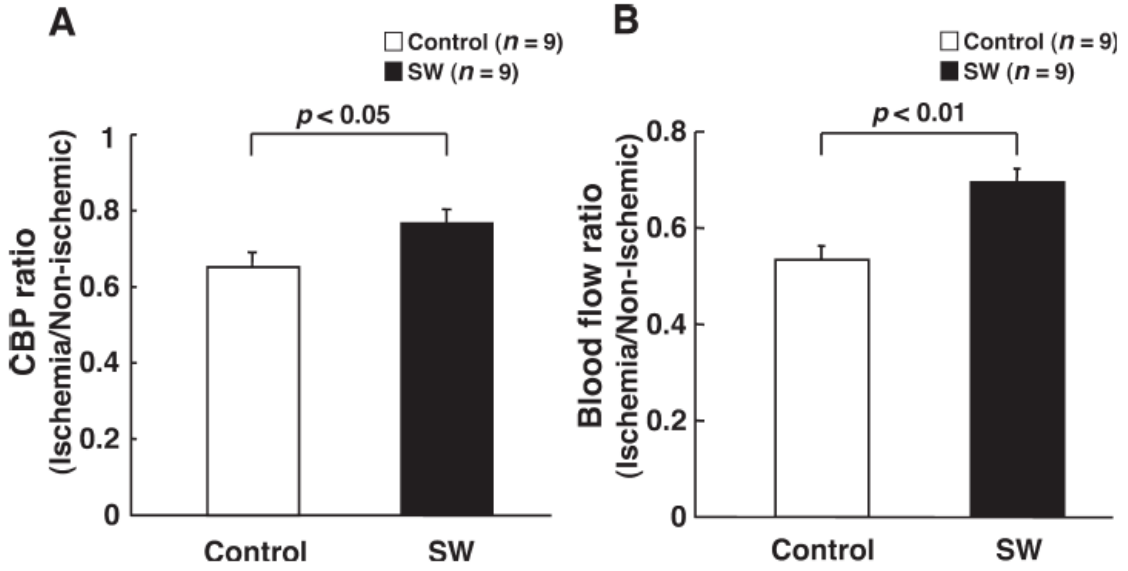
We have recently demonstrated that the low-energy extracorporeal cardiac shock wave (SW) therapy improves myocardial perfusion and cardiac function in a porcine model of chronic myocardial ischemia and also ameliorates myocardial ischemia in patients with severe coronary artery disease. The present study was designed to examine whether our SW therapy also is effective to ameliorate hindlimb ischemia in rabbits. Hindlimb ischemia was made by surgical excision of the entire unilateral rabbit femoral artery. One week after the operation, we performed the SW (n = 9) or sham-therapy (n = 9) to the ischemic region 3 times a week for 3 weeks. Three weeks after the SW therapy, the development of collateral arteries, the flow ratio of the ischemic/non-ischemic common iliac arteries, the blood pressure ratio of the ischemic/non-ischemic hindlimb, and the capillary density in the ischemic muscles were all significantly increased in the SW group compared with the control group, indicating that the SW therapy induced therapeutic angiogenesis. Importantly, no adverse effect, such as muscle damage, hemorrhage, or thrombosis, was noted with the therapy. Finally, we examined the role of endothelial nitric oxide synthesis (eNOS) and vascular endothelial growth factor (VEGF) in the mechanisms of SW-induced angiogenesis on day 28. The expression levels of eNOS and VEGF proteins in ischemic hindlimb muscles tended to be increased in the SW group compared with the control group. These results suggest that our low-energy SW therapy also is effective and safe for the treatment of peripheral artery disease.



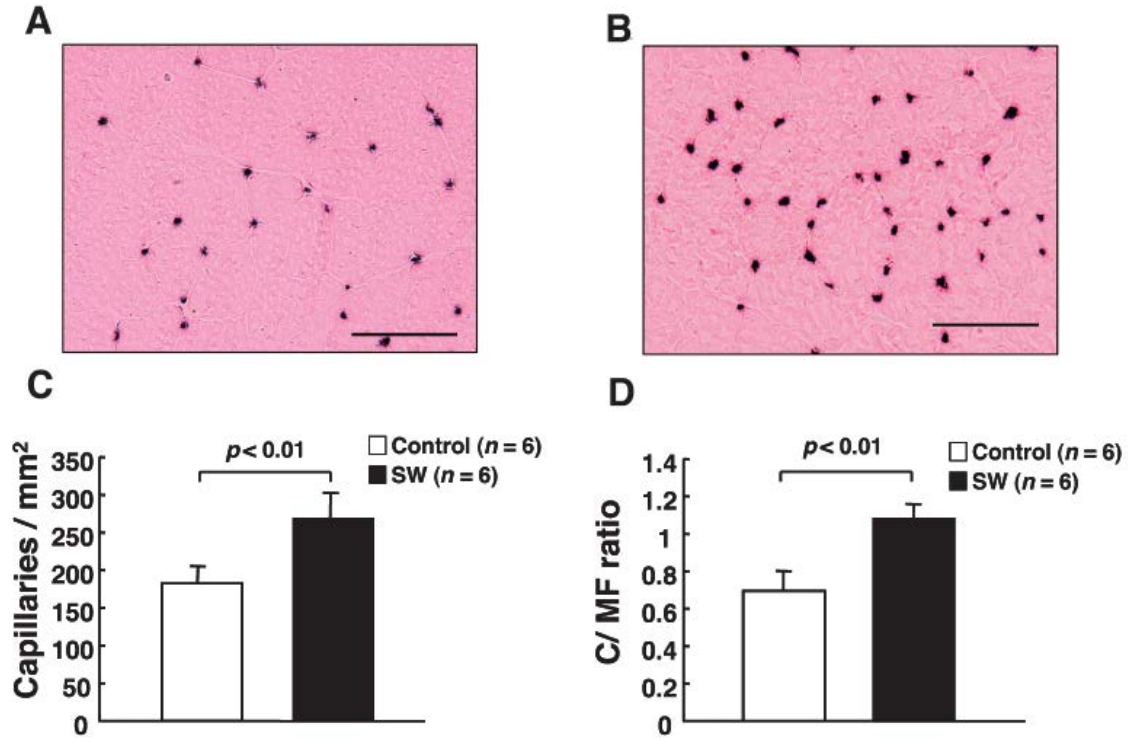
1. Representative selective internal iliac angiography of control rabbit at day 7 (A) and day 28 (B), and shock wave (SW)-treated rabbit at day 7 (C, before SW therapy) and day 28 (D, 3 weeks after SW therapy). Note that increased collateral arteries were noticed in the SW-treated animal at day 28 (D).



2. Effects of the SW therapy in the ischemic limbs on collateral vessel growth and collateral blood flow by angiography. (A) The SW therapy significantly increased the angiographic score expressed as percent change compared with control group at day 28. (B) Filling time to distal popliteal and saphenous artery was significantly decreased in the SW group compared with the control group at day 28. Results are expressed as means ± S.E.M.



3. Effects of the SW therapy in the ischemic limb on hindlimb blood pressure and common iliac arterial blood flow. The SW therapy significantly improved the calf blood pressure (CBP) ratio (ischemic/non-ischemic hindlimb) (A) and the common iliac flow ratio (ischemic/normal hindlimb) (B) at day 28. Results are expressed as means ± S.E.M.



5. Effects of the SW therapy on capillary density in the ischemic skeletal muscle. Capillary density in the ischemic muscle was increased in the SW group (B) compared with the control group (A) at day 28. Dark blue dots indicate capillaries that are positive for alkaline phosphatase staining. Bars indicate 100 μm. Quantitative analysis of capillary density indicates that capillaries/mm^2 (C) and capillaries/muscle fiber ratio (D) in the ischemic muscle were both significantly greater in the SW group than in the control group. Results are expressed as means ± S.E.M.

13. Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs.

Wang CJ, Huang HY, Pai CH.

Department of Orthopedic Surgery, Chang Gung Memorial Hospital/Kaohsiung Medical Center, Niao Sung Hsiang, Taiwan.

J Foot Ankle Surg. 2002 Jan-Feb;41(1):16-22.

The purpose of the research was to study the phenomenon of neovascularization at the Achilles tendon-bone junction after low-energy shock wave application. The study was performed on eight mongrel dogs. The control specimens were obtained from the medial one-third of the right Achilles tendon-bone unit before shock wave application. Low-energy shock waves of 1000 impulses at 14 kV (equivalent to 0.18 mJ/mm2 energy flux density) were applied to the right Achilles bone-tendon junction. Biopsies were taken from the middle one-third of the Achilles tendon-bone junction at 4 weeks and from the lateral one-third at 8 weeks, respectively, after shock wave application. The features of microscopic examination included the number of new capillaries and muscularized vessels, the presence and arrangements of myofibroblasts, and the changes in bone. New capillary and muscularized vessels were seen in the study specimens which were obtained in 4 weeks and in 8 weeks after shock wave application, but none were seen in the control specimens before shock wave application. There was a considerable geographic variation in the number of new vessels within the same specimen. Myofibroblasts were not seen in the control specimens. Myofibroblasts with haphazard appearance and intermediate orientation fibers were seen in all study specimens obtained at 4 weeks and predominantly intermediate orientation myofibroblast fibers at 8 weeks. There were no changes in bone matrix, osteocyte activity, and vascularization within the bone. Two pathologists reviewed each specimen and concurrence was achieved in all cases. The results of the study suggested that low-energy shock wave enhanced the phenomenon of neovascularization at the bone-tendon junction in dogs.

TABLE 1 New capillary formation after shock wave application

Specimens	Number of capillaries[a]	Average (range)
Control	0, 0, 0, 0, 0, 0, 0, 0	0
Study (4 wks)	17.7, 6.7, 7.7, 37.3, 24.3, 10.3, 20.3, 14.3	17.33 (6.7–37.3)
Study (8 wks)	33, 19.3, 10, 31, 6.7, 10.3, 5, 13.7	16.13 (5–33)

[a]200× high power field.

TABLE 2 Muscularized vessels after shock wave application

Specimens	Number of vessels[a]	Average (range)
Control	0, 0, 0, 0, 0, 0,0, 0	0
Study (4 wks)	2, 6, 1, 2, 4, 2, 1, 4.	2.75 (1–6)
Study (8 wks)	4, 5, 0, 8, 3, 4, 0, 5.	4.63 (0–8)

[a]200× high power field.

14. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo.

Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, Matsumoto Y, Kajihara N, Eto M, Matsuda T, Yasui H, Takeshita A, Sunagawa K.

Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan. Circulation 2004; 110: 3055-3061

Background:

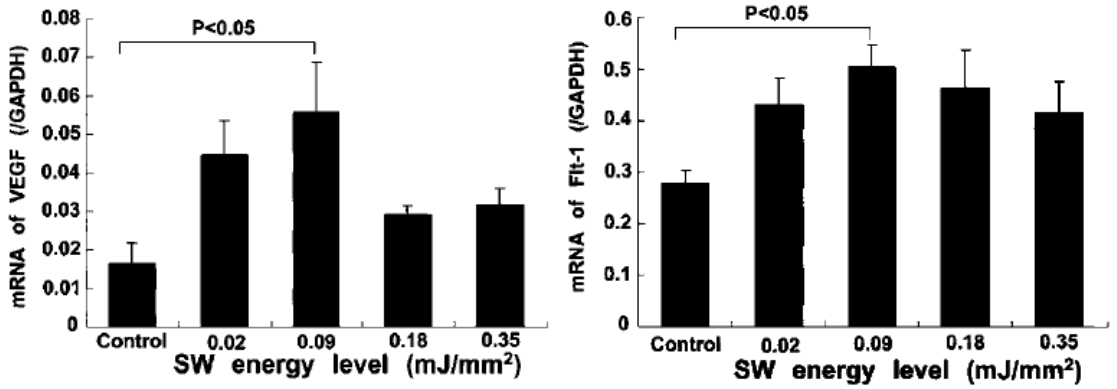
Prognosis of ischemic cardiomyopathy still remains poor because of the lack of effective treatments. To develop a noninvasive therapy for the disorder, we examined the in vitro and vivo effects of extracorporeal shock wave (SW) that could enhance angiogenesis.

Methods and Results:

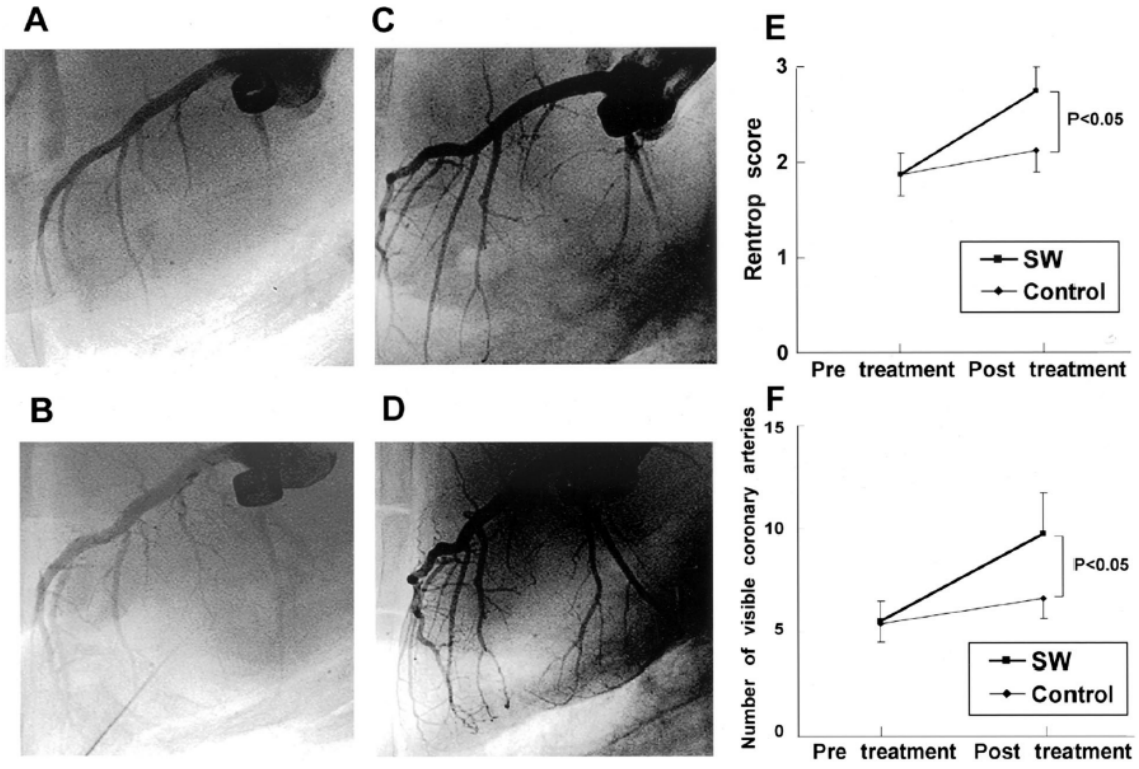
SW treatment applied to cultured human umbilical vein endothelial cells significantly upregulated mRNA expression of vascular endothelial growth factor and its receptor Flt-1 in vitro. A porcine model of chronic myocardial ischemia was made by placing an ameroid constrictor at the proximal segment of the left circumflex coronary artery, which gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction in 4 weeks. Thereafter, extracorporeal SW therapy to the ischemic myocardial region (200 shots/spot for 9 spots at 0.09 mJ/mm2) was performed (n=8), which induced a complete recovery of left ventricular ejection fraction (51+/-2% to 62+/-2%), wall thickening fraction (13+/-3% to 30+/-3%), and regional myocardial blood flow (1.0+/-0.2 to 1.4+/-0.3 mL x min(-1) x g(-1)) of the ischemic region in 4 weeks (all $P<0.01$). By contrast, animals that did not receive the therapy (n=8) had sustained myocardial dysfunction (left ventricular ejection fraction, 48+/-3% to 48+/-1%; wall thickening fraction, 13+/-2% to 9+/-2%) and regional myocardial blood flow (1.0+/-0.3 to 0.6+/-0.1 mL x min(-1) x g(-1)). Neither arrhythmias nor other complications were observed during or after the treatment. SW treatment of the ischemic myocardium significantly upregulated vascular endothelial growth factor expression in vivo.

Conclusions:

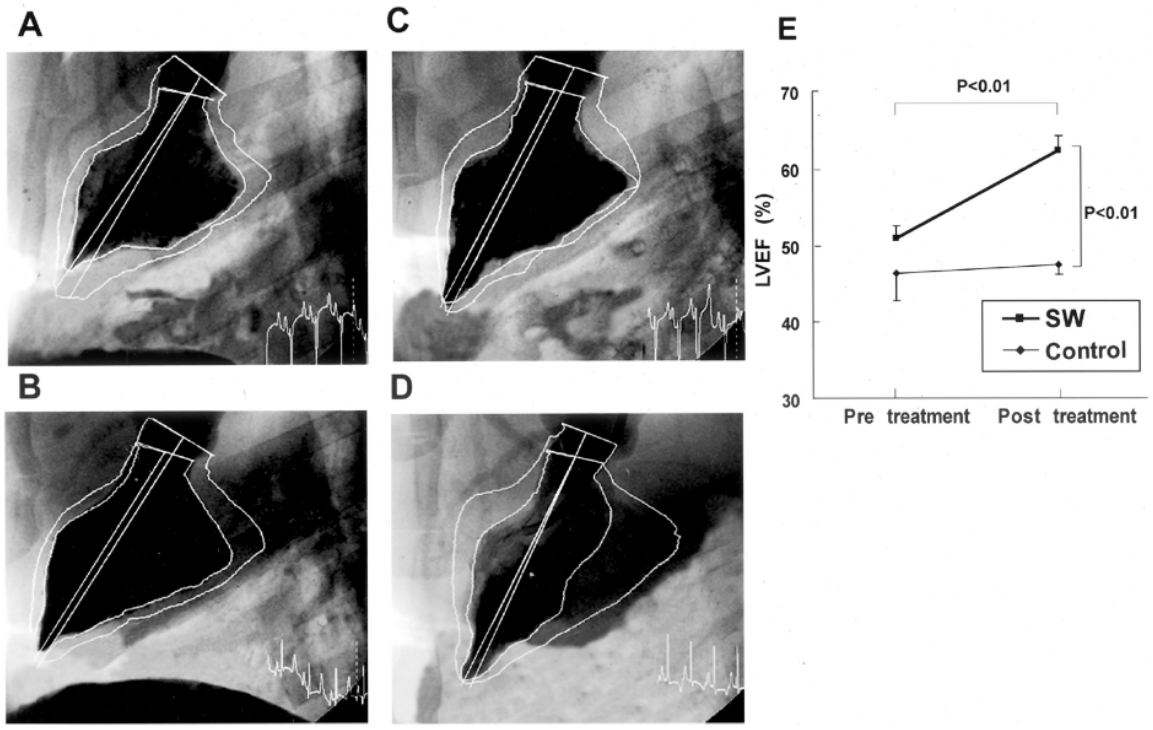
These results suggest that extracorporeal cardiac SW therapy is an effective and noninvasive therapeutic strategy for ischemic heart disease.



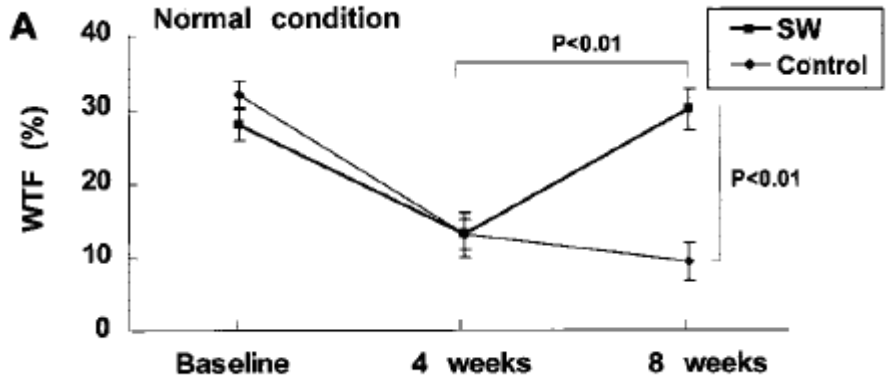
SW treatment upregulated mRNA expression of VEGF (A) and Flt-1 (B) in HUVECs in vitro with a maximum effect noted at 0.09 mJ/mm2. Results are expressed as mean_SEM (n_10 each).

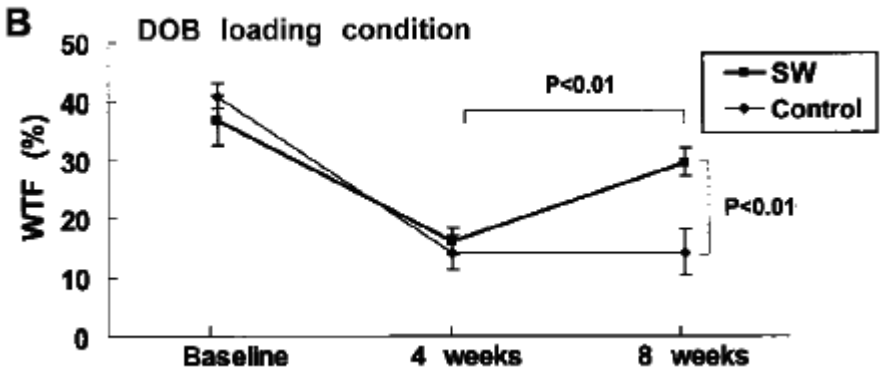


Extracorporeal cardiac SW therapy enhances coronary angiogenesis in vivo. A and C, Four weeks after the implantation of an ameroid constrictor, LCx was totally occluded and was perfused via collateral vessels with severe delay in both the control group (A) and the SW group (before SW therapy) (C). B and D, Four weeks after the first coronary angiography, no significant change in coronary vessels was noted in the control group (B), whereas a marked development of visible coronary vessels was noted in the SW group (D). E and F, Four weeks after the first coronary angiography, no significant increase in the Rentrop score (E) or visible coronary arteries from LCx (F) was noted in the control group, whereas increased Rentrop score and a marked development of visible coronary vessels were noted in the SW group. Results are expressed as mean_SEM (n_8 each).

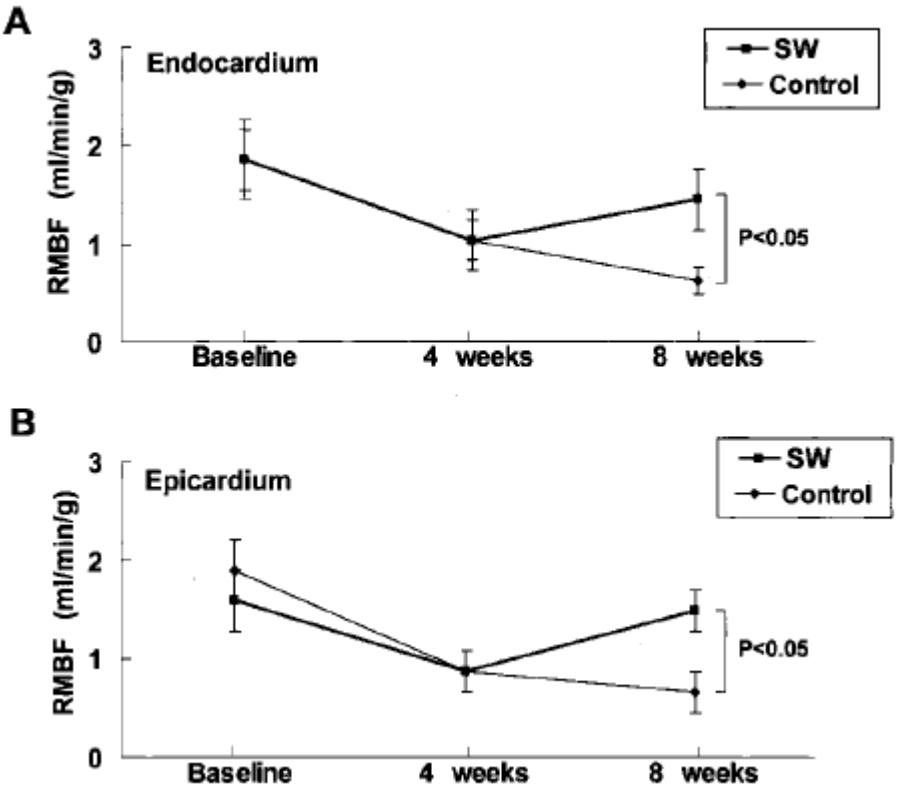


Extracorporeal cardiac SW therapy improves ischemia-induced myocardial dysfunction in vivo. A and C, Four weeks after the implantation of an ameroid constrictor, LV wall motion of the LCx (posterolateral) region was reduced in both the control (A) and the SW group (before the SW therapy) (C). B and D, Four weeks after the first left ventriculography, no significant change in LV wall motion was noted in the control group (B), whereas marked recovery was noted in the SW group (D). E, The SW therapy normalized left ventricular ejection fraction in the SW group but not in the control group. Results are expressed as mean_SEM (n_8 each).

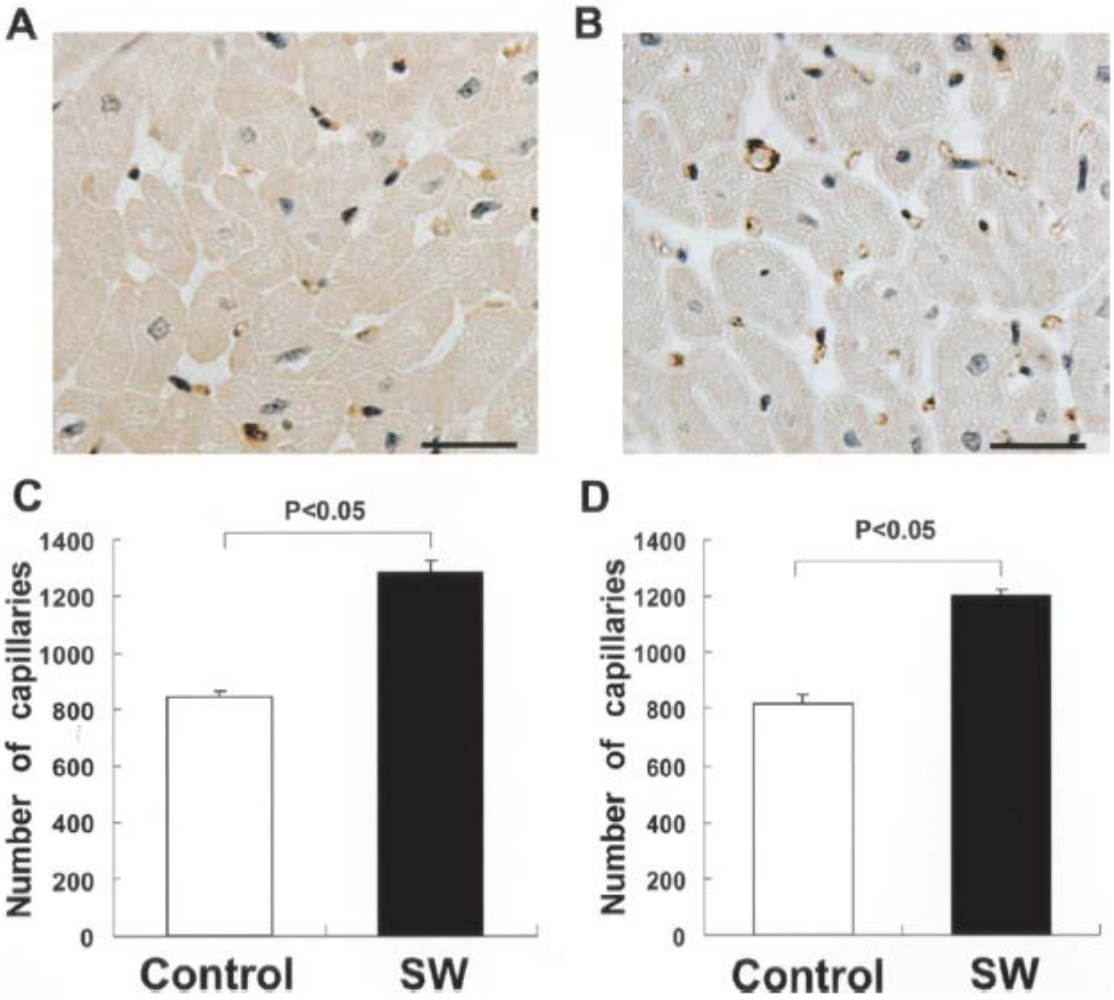




Extracorporeal cardiac SW therapy improves regional myocardial function in vivo. SW therapy induced a complete. recovery of WTF of the ischemic lateral wall under control conditions (A) and under dobutamine (DOB) loading conditions (B). Results are expressed as mean_SEM (n_8 each).



Extracorporeal cardiac SW therapy improves RMBF in vivo. SW therapy significantly increased RMBF, assessed by colored microspheres in both the endocardium (A) and the epicardium (B). Results are expressed as mean_SEM (n_8 each).



Extracorporeal cardiac SW therapy increases the density of factor VIII–positive capillaries in the ischemic myocardium. A and B, Factor VIII staining of the LCx region from the control (A) and the SW group (B). Scale bar represents 20 _m. C and D, Capillary density was significantly greater in the SW group (SW) than in the control group (Control) in both the endocardium (C) and the epicardium (D). Results are expressed as mean_SEM (n_6 each).

15. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs.

T Uwatoku, K Ito, K Abe, K Oi, T Hizume, K Sunagawa, H Shimokawa. Department of Cardiovascular Medicine, Kyushu

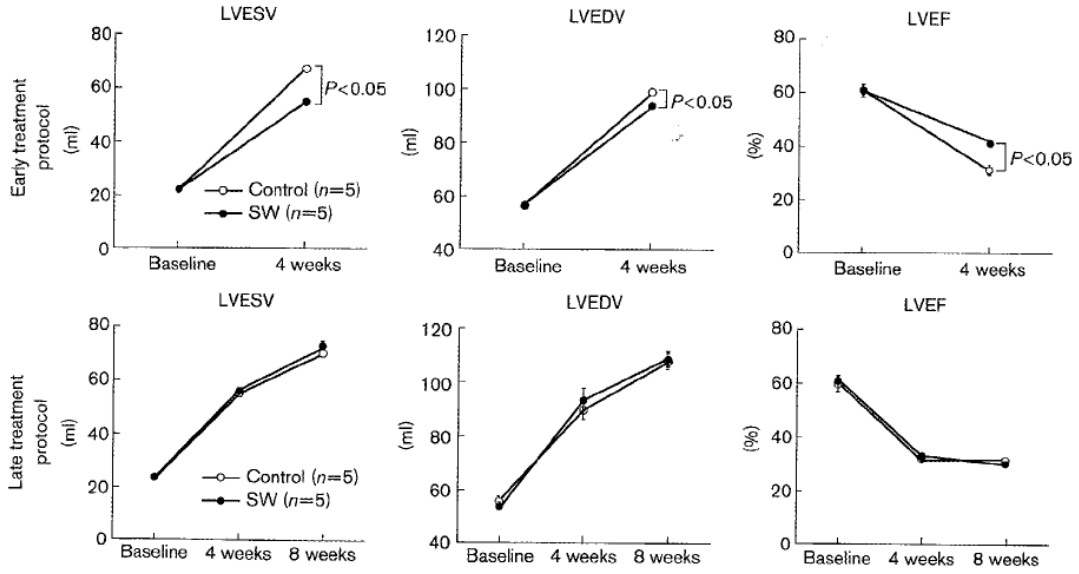
University Graduate School of Medical Sciences, Fukuoka, Japan. Coronary artery Disease, 2007: 18:397-404

Objective:
We have recently demonstrated that low-energy extracorporeal shock wave therapy improves chronic myocardial ischemia in pigs and humans. In this study, we examined whether our shock wave therapy is also effective at improving left ventricular remodeling after acute myocardial infarction in pigs.

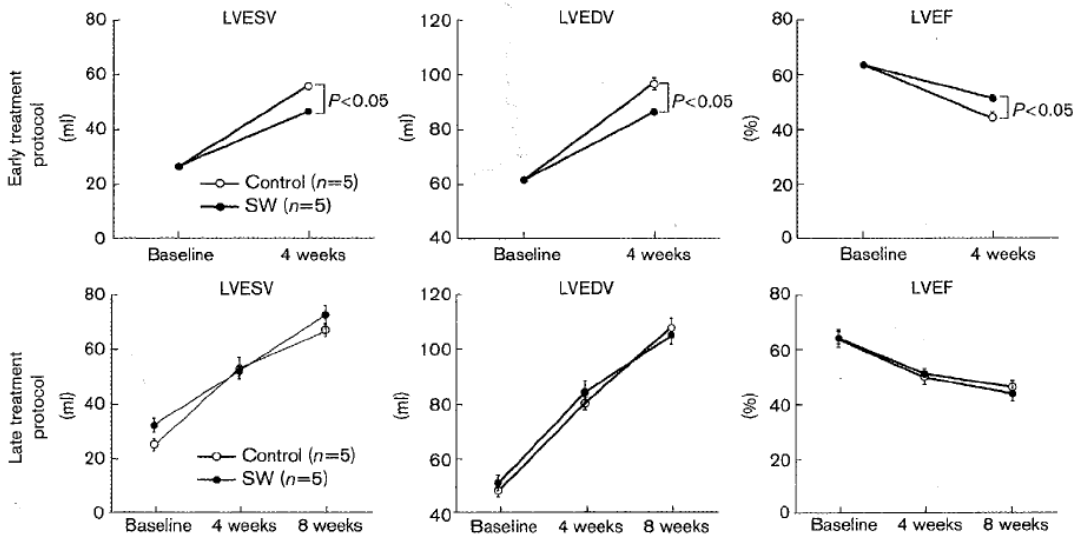
Methods:
Acute MI was created by surgically excising the proximal segment of the left circumflex coronary artery (n=20). In the early treatment protocol, the shock wave therapy was started 3 days after acute MI, whereas in the late treatment protocol, the therapy was started 4 weeks after acute MI (n=5 each). The remaining animals were treated in the same manner, but without the shock wave treatment in each protocol (n=5 each).

Results:
In the early treatment protocol, left ventricular ejection fraction was higher (42 1 vs. 32 1 %) , p<0.001) and left ventricular end-diastolic volume was smaller (95 1 vs. 99 2 ml, P<0.05) in the shock wave group compared with the control group. Furthermore, wall thickening fraction (32 1 vs. 28 1%, P<0.01), regional myocardial blood flow (1.7 0.2 vs. 1.0 0.1 ml/min/g, P<0.01), and number of capillaries in the border zone (1348 15 vs. 938 34 mm2, p<0.0001) were all significantly improved in the shock wave group compared with the control group. By contrast, in the late treatment group, no such beneficial effects of the shock wave therapy were noted.

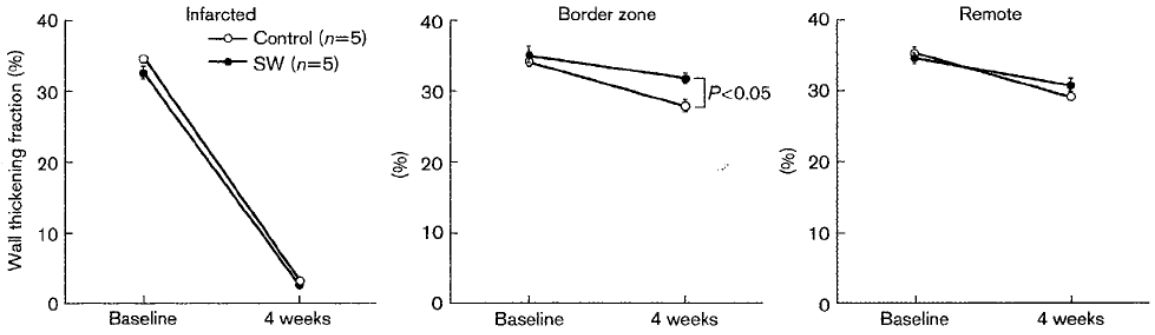
Conclusions:
These results suggest that our extracorporeal cardiac shock wave therapy is also an effective and noninvasive therapy for improving left ventricular remodeling after acute myocardial infarction when started in the early phase of the disorder.



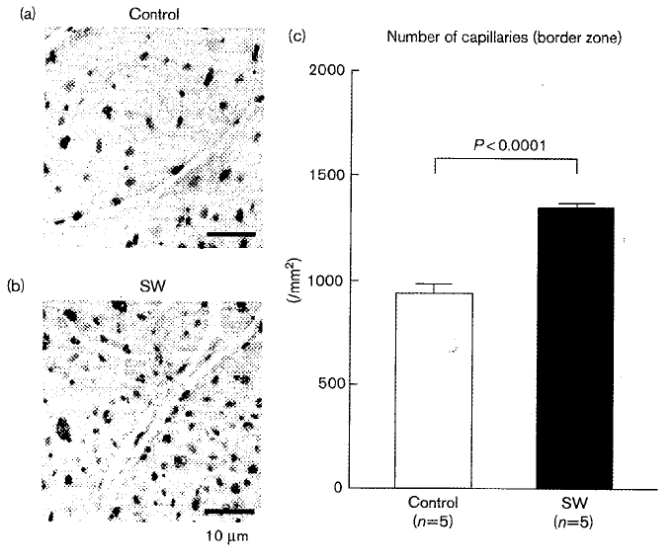
Results of left ventriculography for the inhibitory effects of the cardiac shock wave (SW) therapy on the development of left ventricular (LV) remodeling after AMI. The inhibitory effects of the SW therapy were noted in the early treatment protocol (upper panel) but not in the late treatment protocol (lower panel). Results are expressed as mean ± SEM (n=5 each). AMI, acute myocardial infarction; Control, control group without the SW therapy; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; SW, SW group.



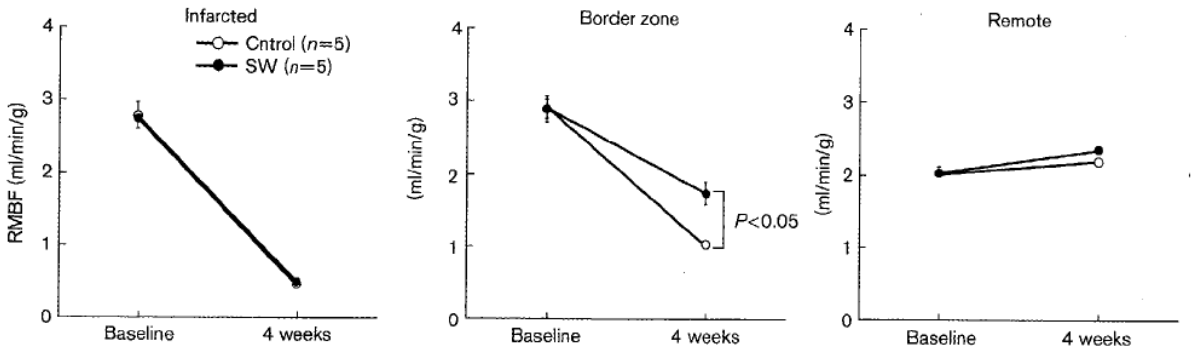
Results of echocardiography for the inhibitory effects of the cardiac shock wave (SW) therapy on the development of left ventricular (LV) remodeling after AMI. The inhibitory effects of the SW therapy were noted in the early treatment protocol (upper panel) but not in the late treatment protocol (lower panel). Results are expressed as mean ± SEM (n=5 each). AMI, acute myocardial infarction; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume.



Wall thickening fraction (WTF) in the early treatment protocol. Extracorporeal cardiac shock wave (SW) therapy improved regional myocardial function in the border zone. Results are expressed as mean ± SEM (n=5 each). Border zone, myocardium in the border zone; infarcted, infarcted myocardium; remote, myocardium in the remote, normal area.



Capillary density in the early treatment protocol. Representative factor VIII staining of the border zone myocardium in the control group (a) and in the shock wave (SW) group (b), and quantitative analysis of the number of capillaries in the border zone (c). Extracorporeal cardiac SW therapy significantly increased the density of factor VIII-positive capillaries in the border zone. Scale bar, 10 μm. Results are expressed as mean ± SEM (n=5 each).



Regional myocardial blood flow (RMBF) in the early treatment protocol. Results are expressed as mean ± SEM (n=5 each). Border zone, myocardium in the border zone; infarcted, infarcted myocardium; remote, myocardium in the remote, normal area. Extracorporeal cardiac shock wave (SW) therapy improved RMBF in the border zone.

ESMR Therapy

Clinical Trials
On Ischemic Heart Disease

1. Safety and efficacy of extracorporeal low energy shockwave application for the treatment of refractory angina pectoris and myocardial Ischemia in patients with end-stage coronary artery disease

Christoph K Naber[1], Sara Lammers[1], Tinatin Lind[1], Norbert Müller[2], Gil Hakim[3], Raimund Erbel[1].

Department of Cardiology, West German Heart Center Essen, University of Duisburg-Essen, Germany[1] , Department of Nuclear Medicine, University of Duisburg-Essen, Germany[2] , Medispec, USA[3]

Background:
The number of patients with end stage coronary artery disease increases rapidly due to improved techniques in bypass surgery and interventional cardiology. Myocardial ischemia in these patients often leads to refractory angina, a status of disease which can be treated clinically only with limited success so far. Experimental data indicate, that the application of low energy shockwaves may stimulate the release of nitric oxide and induce angionegensis. The following study was conducted to investigate the effects of percutanous myocardial, low-energy shockwave application in a prospective cohort of patients with end-stage CAD and refractory angina pectoris.

Methods:
24 patients with end stage coronary artery disease, SPECT documented reversible ischemia, and refractory angina were treated using a shock wave generator system (Cardiospec, Medispec, USA) designed to address the clinical-anatomical requirements of the chest cavity under transthoracic echo guidance. About 300 impulses were applied to the ischemic areas using energy level of 0.09 mJ/mm2. This treatment was repeated three times a week on the first week of each month, for three months.

Results:
Clinical results showed a significant symptomatic improvement regarding CCS class (3.2 ± 0.8 t baseline vs. 2.2 ± 0.1 at 6-months follow up; $p<0.0001$), Seattle Angina Questionnaire (mean improvement by 32.6%; $p=0.002$) and exercise capacity (66.6 ± 6.8 watt at baseline vs. 95.8 ± 5 watt at 6-months follow up; $p<0.025$). Blinded SPECT analysis demonstrated that myocardial perfusion at stress and at rest was improved significantly at 6-months follow up versus baseline ($p<0.001$). Therapy was well tolerated by all patients. No side effects and no rise of cardiac enzymes were observed.
Conclusions: The present study shows that the extracorporeal application of low intensity shockwaves to the ischemic myocardium in patients with advanced CAD is safe and feasible. In our cohort, low energy shockwaves improved symptoms, delayed ischemic threshold, and increased myocardial perfusion in these end stage patients.

Introduction

The number of patients with end stage coronary artery disease (CAD) increases rapidly due to constant improvement in the fields of bypass surgery and interventional cardiology. In many cases the disease becomes too diffuse and extensive to be treated by conventional revascularization techniques. Refractory angina is frequently observed in these patients, and can then be treated only by conservative medical means which have demonstrated limited success thus far.

The COURAGE study (1) compared optimal medical therapy with or without PCI for patients with stable coronary disease. Freedom from angina was observed only in 66% of patients in the PCI group, and 58% of patients in the medical therapy group after 1 year.

Alternative methods to reduce patients' symptoms and to enhance myocardial perfusion, include: sympathectomy(2), external counterpulsation(3), epidural spinal electrical stimulation(4), intermittent urokinase-therapy(5). While these approaches to a major extent are aimed at improving the patients symptoms, other concepts try to induce neoangiogenesis such as transmyocardial laser-revascularization(6), the myocardial or intracoronary application of proteins(7) or genetic vectors(8) encoding proteins with angiogenesis potential, and cell based therapies(9). Recent studies demonstrate that also the application of low intensity shockwaves (SW) may induce the release of angiogenesis-mediating growth and proliferating factors such as endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and proliferating cell antinuclear antigen (PCNA). (10-15)

Nishida et al., using a porcine model of chronic myocardial ischemia, showed that low intensity SW treatment is able to induce neo-angiogenesis in ischemic myocardium. This mechanism was followed by a significant improvement of myocardial perfusion and a restored left ventricular function. (16) In another porcine model, low intensity shockwaves displayed a beneficial effect on the remodeling process following acute myocardial infarction (MI).(17)

Preliminary experience in a small, non-controlled series of 9 patients (18) indicate that the myocardial application of low intensity shockwaves appears to be safe and may improve clinical symptoms. These data and the data from the porcine models make it tempting to hypothesize that low-energy SW treatment can induce myocardial angiogenesis, improve myocardial perfusion, and reduce symptoms in patients with endstage CAD.

The aim of the following study was to test this hypothesis in a prospective, and consecutive cohort of patients with end-stage CAD with a standardized safety and treatment protocol of low intensity cardiac shock wave application using SPECT analysis for an objective investigation of myocardial perfusion.

Methods

Patient selection:

Consecutive patients with coronary artery disease and stable angina class III or IV were included into the study when they were on stable medication for no less than 6 weeks. Patients were found eligible if there was no technical possibility or expected clinical benefit from further percutaneous coronary intervention or surgical revascularization as determined independently by a cardiologist and a cardiac surgeon. Written informed consent was obligatory, the study was approved by the local ethics committee. Drug therapy remained unchanged for a period of 3 months after SW therapy.

Patients who experienced unstable angina or myocardial infarction, within three months prior to the shock wave therapy, heart failure, NYHA-stage III or IV, intraventricular thrombus, or severe lung or valvular disease were excluded from the study.

Ischemia detection using myocardial scintigraphy

Using identical stress protocols based on standard procedures, myocardial perfusion was assessed by Dobutamine SPECT with Technetium 99m-(Tc-99m) within 4 weeks prior to treatment and 6 months post baseline. (19,20).

Tomographic images were taken using a gamma camera with a computer interface where acquisitions were performed over a 180° semicircular orbit. Data were acquired in a 64x64 matrix for 32 and 64 projections in a step-and-shoot format. Each image set was normalized to maximal myocardial activity (horizontal and vertical long axis, and short axis planes). Using a 17-segment myocardial model (21), a semi-quantitative model interpretation was performed by an experienced investigator blinded to the patient's clinical history, shockwave therapy date, and stress and rest SPECT scan study dates. Segments were graded using a 6-point scoring system ranging from 0 (normal) to 5 (no perfusion). The SPECT protocol utilized was performed on patients during rest and stress in accordance with standard operating procedures of our institution.

Scores were analyzed as follows: first, a segmental analysis was performed to observe the change in the perfusion score of each segment under stress or under rest conditions, pre and 6 months post baseline. The second analysis looked at the total distribution of the scored segments from all patients under stress and under rest conditions at pre and at 6 months post baseline.

Shock wave application and therapy:

Shockwaves were applicated with a commercially available cardiac shock wave generator system (CardiospecTM, Medispec, Germantown, USA) under echocardiographic guidance. With this generator, as a modification from lithotripsy to cardiac therapy, the energy flux density is adjustable between 0.03 and 0.2 mj/mm2, with a focus size of 6 x 6 X 40 mm. The system includes a shock wave generator system with a therapeutic Shock Wave Applicator head (SWA), an external ultrasound system with adjustable transducer holder mounted on the shockwave device, and an ECG-trigger monitor. Patients were positioned on the patient table and ECG electrodes were placed on the thorax for R-wave triggering.

Treatment schedule:

The treatment schedule was divided into three blocks with three sessions per week. The three treatment blocks were scheduled every 4 weeks. Ths nine single 20 minute treatment sessions concluded a treatment course for each patient. The procedure did not require anesthesia or sedation, and did not require hospitalization, however patients were monitored post treatment for 1 hour for potential side-effects and cardiac enzymes (CK, CKMB, Troponin I) were measured at bseline and after each treatment cycle.

Treatment design strategy

A SPECT bulls-eye view was used to identify a myocardial area with reversible ischemia. To facilitate treatment, the area was then identified on a 16-segment echocardiography (22) bulls-eye view which is tilted 45° degrees clockwise to the SPECT bulls-eye view (Figure 1a and 1b). The area of interest was divided into 3 zones, corresponding to the 3 weeks of treatments. SW application started at the border zone and than continued to the inward zones. For optimal therapy, the treatment zones were divided into target spots corresponding to the size of the focal zone of the shockwave applicator (Ø1 cm circles ; Figure 1c and 1d). The distance to these target spots circles was measured and marked on the ultrasound screen enabling the operator to see the treated zone in real time (figure 2). The SWA was fixed at the measured distance. An inflatable silicon cushion and

ultrasound gel were used for optimal delivery of the shockwaves into the body. Each treatment for each target spot consisted of 100 pulses gated by R wave trigger. The energy level applied was 0.09 mJ/mm2 (16-18).
A three-lead ECG, continuous oxygen saturation and blood pressure monitoring were performed during the procedure. To test for myocardial tissue damage, Troponin I, CK, and Myoglobin levels, were measured before and after each treatment (1 and 6 hours). Additionally, a 12-lead ECG was recorded before and after the procedure for 1 hour. All patients were classified according to their symptoms using the Canadian Cardiac Society – classification of angina pectoris and to the Seattle angina questionnaire (SAQ) before and after the procedure(23). Exercise tolerance of the patients was performed by bicycle exercise testing with steps of 25 Watts increasing every 2 min prior to the initiation of treatments and at 6 months post baseline. The diagnosis of ischemia and the criteria for interruption of exercise were established according to the AHA/ACC guidelines. (24)

Statistics:

The following statistical tests were used in the analysis of the data presented in this study: The data parameters were characterized and presented by the calculated estimators: sample size (N), mean, standard error, median, minimum, maximum and 95% Confidence Interval (CI) The paired T-test and Non-parametric Sign Rank Test were applied for testing differences between the different time points (pre and post, baseline and post baseline measurements) within each study group.
The McNermar's Test was applied for dichotomous variables, for testing differences between the various time points (pre-treatment and post-treatment, baseline and post baseline measurements) within each study group.
Survival analysis using Kaplan-Mayer method was applied for comparing survival curves. Statistical significances were calculated using log-rank test. Signed rank test on the differences was applied for testing differences in perfusion grade of the segments (pre-treatment and post-treatment, baseline and post baseline measurements)

All tests applied were two-tailed, and p value of 5% or less was considered statistically significant. The data was analyzed using the SAS® system.

Results

Safety and tolerability:

Patient characteristics are displayed in Table 1. Mean age was 63.8± 8.2 years. 18 male and 6 female patients were included. All patients tolerated the treatment well and no adverse events were reported. Shock wave application was well tolerated without any pain or discomfort. No local hematoma was be observed. In addition patients did not complain about coughing or respiratory disorders during and after the therapy. During the treatment there were no changes of heart rate, blood pressure or oxygen saturation. Standard cardiac enzymes (Troponin I, CK, and Myoglobin) did not increase significantly during the procedure or within 6 hours following the last treatment performed at each week of treatment. (Figure 3 showes Troponin I levels). No relevant arrhythmias where reported during or after treatment. All patients completed therapy and could be reevaluated after a follow-up period of 6 months. No subjective or objective major adverse events occurred in the follow up phase.

CCS class:

Mean CCS angina score declined significantly from 3.2±0.08 before treatment to 2.2±0.1 after 6 months ($p<0.0001$) (Figure 4a). None of the patients that were classified as CCS class IV remained at that stage 6 months post baseline (21% vs. 0%). The percentage of patients that were classified at CCS class III was reduced from 79% to 35%. The rest of the patients reported angina pectoris CCS class II and I (figure 4b). 60% of patients showed at least one CCS class decrease, 20% of patients showed a decrease of two CCS classes, and 11% of patients reported no change (not shown; $p<0.0001$)

Seattle Angina Questionnaire:

Physical limitation according to the Seattle Angina Questionnaire (Q1-9) improved by 41.6% after 6 months ($p<0.015$), anginal stability and frequency (Q10-12) improved by 64.2% ($p<0.006$), and treatment satisfaction and disease perception (Q13-19) improved by 24.3% ($p<0.0015$). Overall patients reported 32.6% improvements in their SAQ score 6 months post baseline ($p=0.0015$).

Bicycle Exercise Capacity:

Maximum exercise capacity at baseline was 66.6±6.8 Watt at baseline and 95.8±5.0 Watt at 6 months follow up ($P<0.025$). (Figure 5a).

In addition, analysis of the reasons for exercise stress test termination (figure 5b) (exertion, significant ST segment changes, angina pectoris, and dyspnea) showed that at baseline 92% had terminated the stress test due to cardiac reasons while only 39% terminated the test due to cardiac reasons at 6 months post baseline ($p<0.035$).

Myocardial Perfusion by SPECT:

Distribution of segments by perfusion class at 6 months follow-up is presented in table 2. Changes were calculated on each of the classes 0 to 6, and were found statistically significant. ($p<0.05$).

A segment by segment analysis of the perfusion class of the whole heart showed a significant improvement of the myocardial perfusion at 6 months in 52.2% at stress and in 56.5% under resting conditions ($P<0.001$; Figure 6). In 27.5% (stress) and 23.2% (rest) the perfusion did not change, and in 20.3% of segments, the perfusion worsened at stress and at rest.

Discussion

Shock waves consist of acoustic energy that can be transmitted in a liquid medium. They can be artificially generated by discharge of a high voltage spark under water, and can be focused with great precision to any intended treatment area inside the body .The focused shock waves generate, thus, an energy flux in the treatment zone measured in milijoules per millimeter square. These forces can be controlled by regulating the voltage of the spark generator.

Extracorporeal shock waves have been successfully applied for treatment pourposes to human tissue for more than 20 years. Developed in Germany and first used in human patients in 1980, extracorporeal shock wave therapy (ESWT) has meanwhile become the primary source of treatment for kidney stone lithotripsy. ESWT was also introduced and explored for the clinical use in the treatment of slow healing fractures in 1989 (25) and has been since expanded to other chronic orthopedic indications (26,27,28). The observed immediate increase in blood flow due to local vasodilatation and the formation of new capillaries and even muscularized vessels in the treated tissue indicated the potential of ESWT for cardio-vascular indications (10-12).

Belcaro et al. were the first to use ESWT to treat critical limb ischemia and succeeded to show that low energy shockwaves increase local perfusion. (29, 30)
Using HUVEC (human umbilical vein endothelial) cells it could be shown that low energy shockwaves, are able to rapidly increase eNOS (endothelial nitric oxide synthase) activity and intracellular NO production (14). A dose finding study in a similar setting demonstrated a maximum level of eNOS activation at an energy level of 0.03 to 0.11 mJ/mm2 (15). Animal models suggest that these effects can be observed for up to 4 weeks after treatment (10,11).
The first study to demonstrate that also neovascularization may be a beneficial effect of shockwaves was performed by Wang et al. (10) They demonstrated that shock wave therapy induces neovascularization at the tendon-bone junctions associated with the early release of angiogenesis-mediating growth and proliferation factors including eNOS, VEGF (vessel endothelial growth factor) and PCNA (proliferating cell antinuclear antigen) leading to an improved blood supply and tissue regeneration (10). In a further study they showed that not only the growth of capillaries is induced but also the growth of muscularized vessels. (11) Oi et al. demonstrated in a controlled study of hind limb ischemia in rabbits that shockwaves induce the development of collateral arteries, increase the capillary density which corresponds to the increase of blood flow and blood pressure in the treated areas. (31)
In myocardial tissue, these mechanisms were first demonstrated in a porcine model of chronic myocardial ischemia by Takahiro Nishida et al. (16). They placed an ameroid constrictor at the proximal segment of the left circumflex coronary artery, which gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction for over four weeks. Thereafter ESWT to the ischemic myocardial region was performed, using an energy level of 0.09 mJ/mm2 which corresponds to the energy level used in our study. They found a complete recovery of the left ventricular ejection fraction, the wall thickening fraction and regional myocardial blood flow. In addition, they also found a significant increase of markers of neovascularization such as VEGF, the VEGF receptor Flt-1, and a significant growth of capillaries in the ischemic myocardium of the treatment group when compared to the non-treated hearts. The same group showed in another porcine model that early ESWT can improve left ventricular remodeling after acute Myocardial infarction and increase the density of Factor VIII-positive capillaries in the border zone of the ischemic area. (17)
In the present study we proved that these findings from the animal model can be transferred into the clinical us e.g. for patients with end-stage coronary artery disease. The treatment was well tolerated by all patients, and no adverse events were observed. This included no signs of clinically significant myocardial damage, no relevant arrhythmias, and no bleeding episodes, even in patients receiving Coumadine or anti-platelet agents. Our findings indicate, that low energy shockwaves have a beneficial effect when applied to the ischemic myocardium of these patients. After treatment, exercise tolerance increased, the ischemic threshold was delayed, and SPECT analysis showed a significant improvement of myocardial perfusion. Although the underlying mechanism are not rigorously proven yet, the findings from pre-clinical studies indicate that two major effects may contribute to our observations: immediate vasodilatation(32) which is equivalent to the clinical reports of an immediate improvement of symptoms from treated patients, and the induction of neo-vascularization in the treated tissue, which most likely accounts for the observed long term effects.

Limitations:

Although our findings demonstrate that extracorporeal application of low energy shockwaves to the myocardium of end stage coronary artery disease patiets appears safe, feasible, and effective regarding an improbment of myocardial perfusion, a prospective, randomized trial will have to prove the true relevance of this new therapeutic approach.

Conclusions

The present study shows that the extracorporal application of low energy shockwaves to the ischemic myocardium of patients with end-stage CAD and refractory angina pectoris is safe, feasible, and appears to be effective. Our data demonstrate that the treatment can improve symptoms, delay the ischemic threshold, and increase the myocardial perfusion in these patients. No adverse events were reported and no myocardial damage was observed. If proven in blinded randomized trials, myocardial low energy shockwave treatment holds a valid alternative for patients who no longer benefit from current revascularization therapies.

Table 1: patient demographics, medical history, symptoms, and current medication at baseline

All = 24	N or mean	SE or %
Male	18	75
Age (years)	63.8	±8.2
BMI (kg/m²)	30	±4.6
Medical History		
3-vessel disease	21	87.5
Previous CABG	19	79.1
Previous MI	11	45.8
Diabetes*	9	37.5
Smoking*	7	29.1
Hyperlipoproteinemia*	24	100.0
Hypertension*	24	100.0
Previous PCI		
Stenting	20	83.3
PTCA	19	79.1
Current medication		
Beta Blockers	24	100.0
Statins	24	100.0
ACE Inhibitors	17	70.8
Calcium antagonists	11	45.8
Coumadine	4	16.6
Clopidogrel	20	83.3
ASS	23	95.8
Nitrates	18	75.0
Clinical symptoms		
CCS III	18	75.0
CCS IV	6	25.0

* history of; MI=myocardial infarction; PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft; PTCA= percutaneous transluminal coronary angioplasty; ACE= angiotensin converting enzyme; ASS= acetylsalicylic acid; CCS= Canadian Cardiovascular Society Functional Classification of Angina Pectoris

Table 2: Distribution of segments by perfusion class* at rest and at stress.

Class	Rest		p-value	Stress		p-value
	Baseline	6 Months		Baseline	6 Months	
0	22%	45%	p < 0.05	16%	33%	p < 0.05
1	16%	20%		14%	25%	
2	28%	20%		29%	17%	
3	16%	6%		13%	13%	
4	13%	4%		17%	4%	
5	6%	4%		10%	7%	

*0 – normal perfusion, 1 – minimal perfusion defect, 2 – mild perfusion defect, 3 – moderate perfusion defect, 4 - severe perfusion defect, 5 – no perfusion

Figure 1: (a): SPECT bulls-eye view (LV segmentation), the red line surrounds the ischemic zone to be treated (b): Echocardiography segmentation, same patient, the red line surrounds the ischemic zone to be treated. (c):Treatment road mapping by dividing the ischemic zone into three similar portions corresponding to the three treatment-weeks. (d): Treatment road mapping for the first week with the respective focal zones.

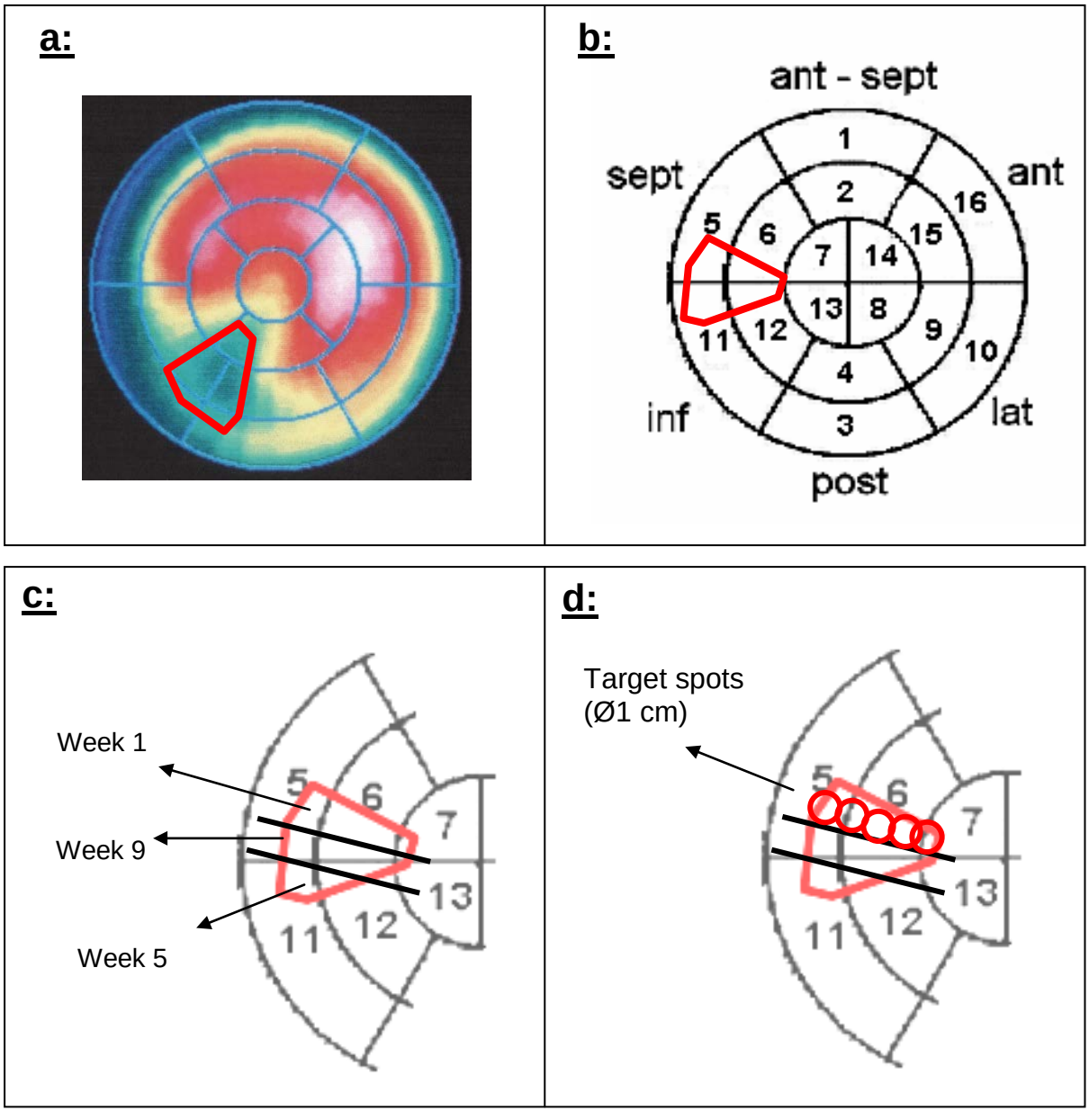


Figure 2: Shockwave focal zone alignment

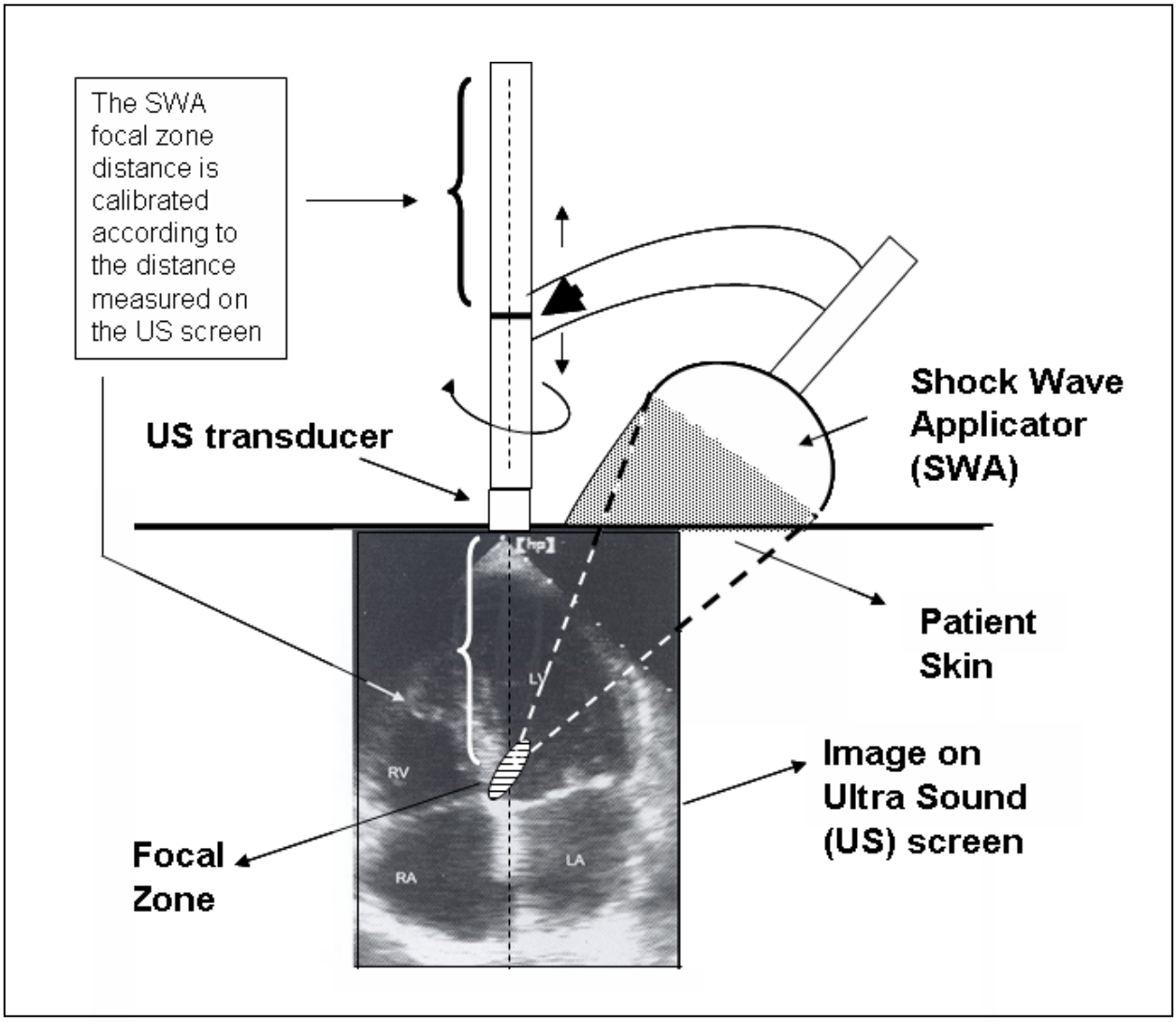


Figure 3: Troponin I levels at baseline and 6 hours post the last treatment day at each treatment week. (p=NS)

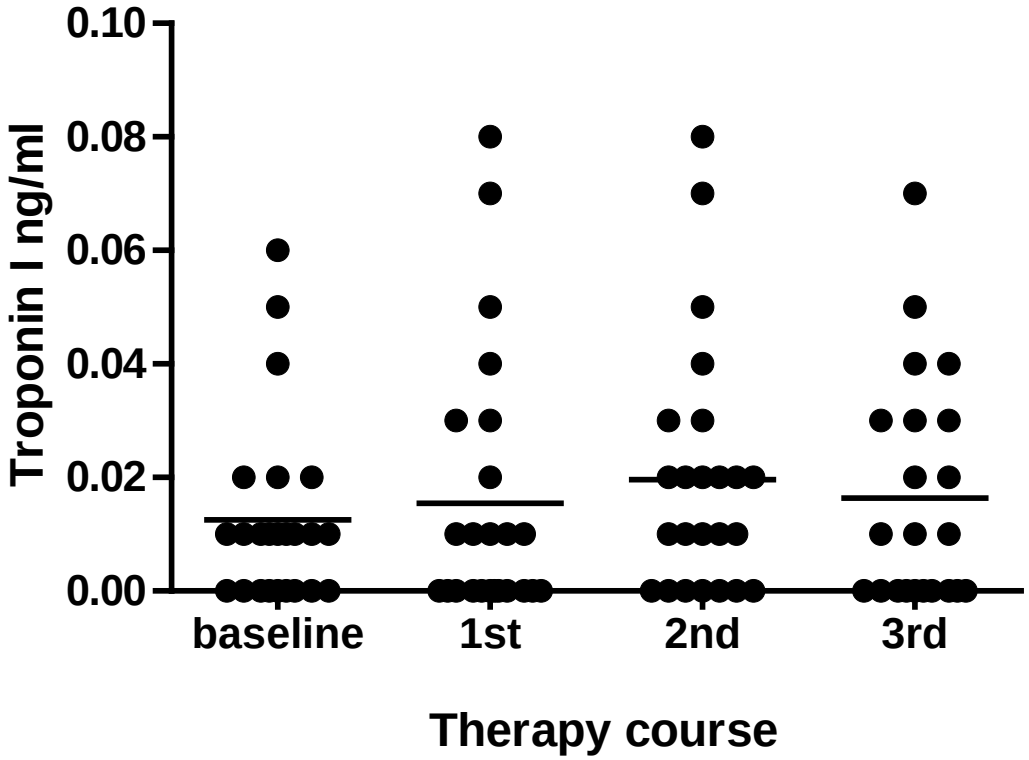
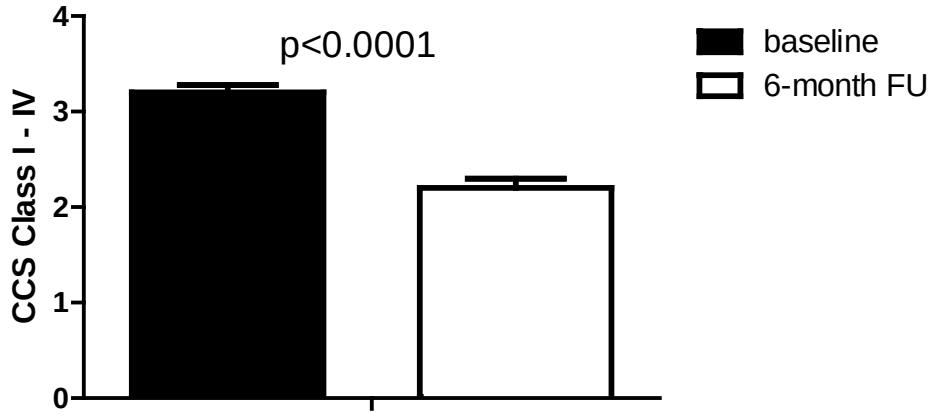


Figure 4:

(a): Mean CCS class change at 6 months post baseline (p<0.0001)



(b): Change of CCS class distribution prior to treatment and 6 months post baseline

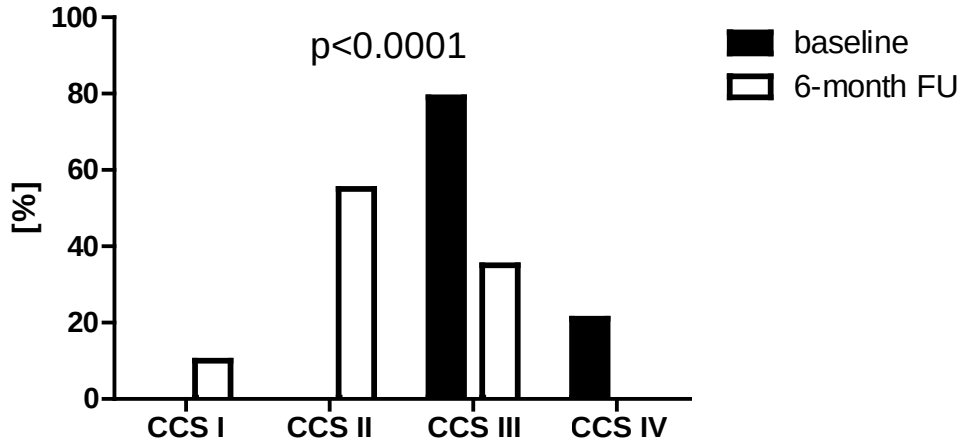
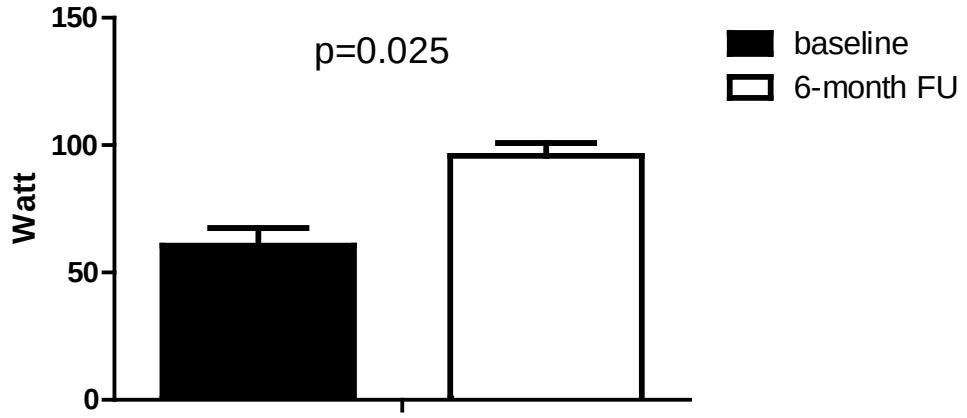


Figure 5:

(a): Mean change in exercise capacity at 6 months post baseline (p<0.025);



b) Change in cardiac reasons for terminating exercise test at 6 months post baseline.

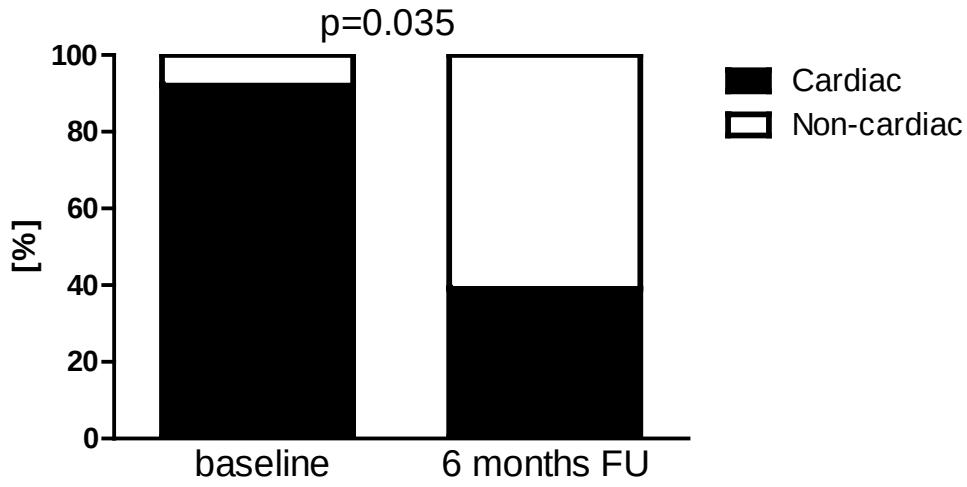
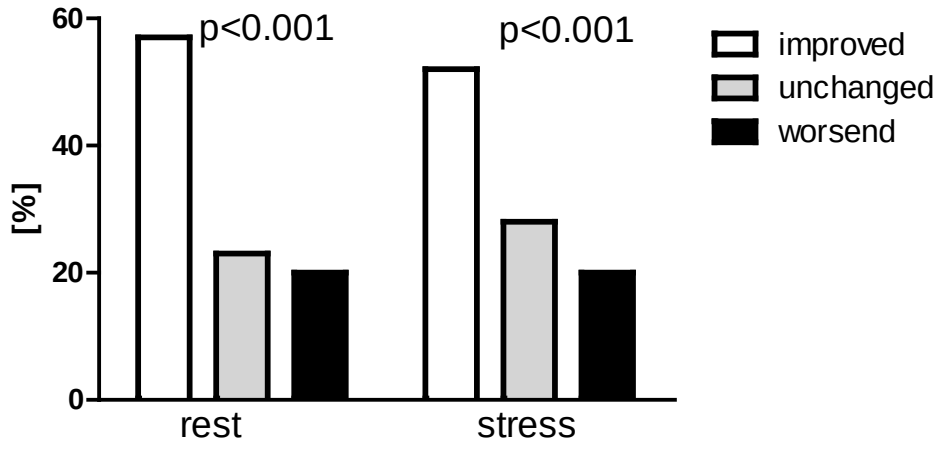
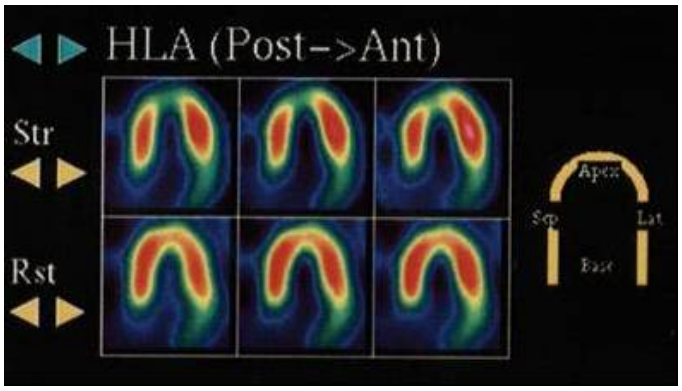


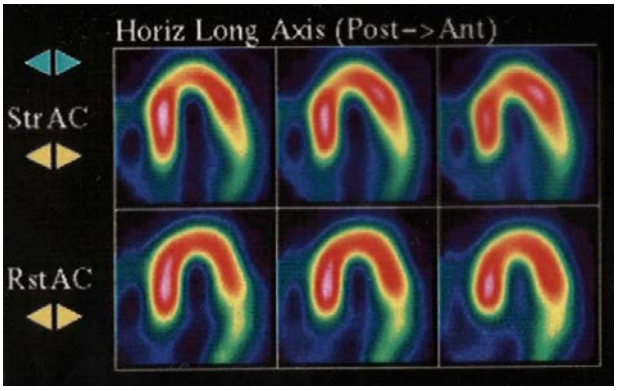
Figure 6: Analysis of total heart - change in SPECT segment perfusion grade, a segment by segment analysis from baseline to 6 months (p< 0.001)



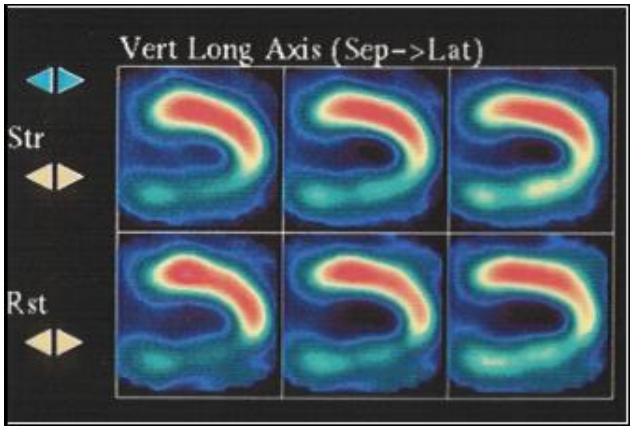
Baseline:

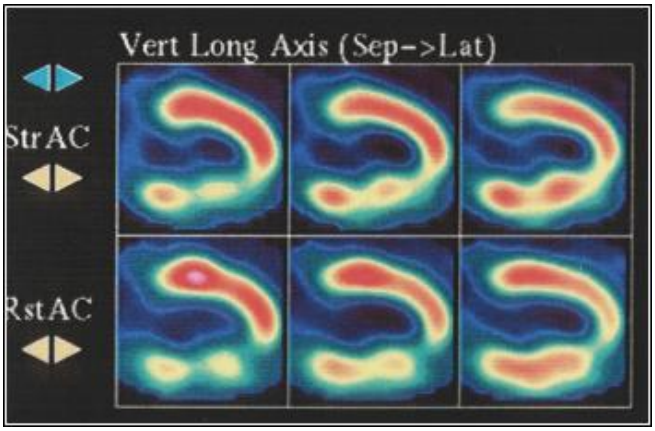


6 months post treatment:

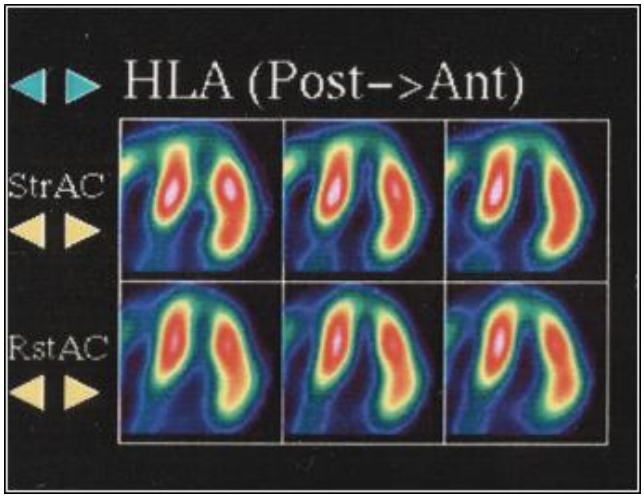


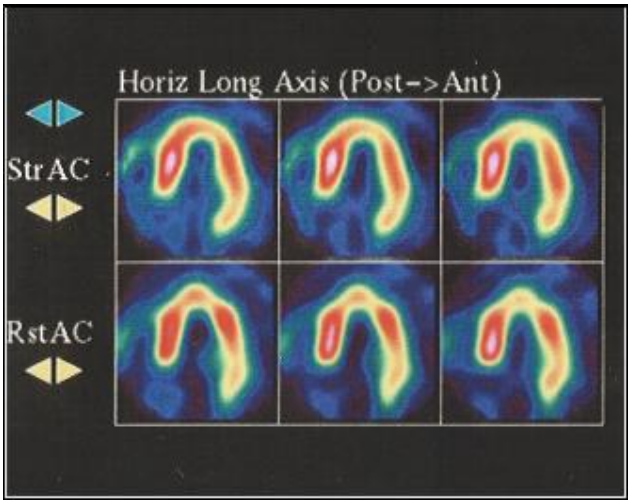
62, male, 3 vessels Disease, Hypertension, CABG X 2, Post MI, PTCA & Stent.
Pre: CCS class IV; Post: CCS class III





50, male, 3 vessels Disease, Hypertension, CABG, PTCA.
Pre: CCS class III, 100 w. Post: CCS class III, 125 w





67, male, 3 vessels Disease, Hypertension, CABG X 2, PTCA & Stent.
Pre: CCS class IV 75 w; Post: CCS class III 75 w

2. Initial clinical experience with extracorporeal shock wave therapy in treatment of ischemic heart failure

Yury A. Vasyuk1, Alla B. Hadzegova1, Evgeny L. Shkolnik1, Maya V. Kopeleva1, Olga V. Krikunova1, Elena N. Iouchtchouk, Elena M. Aronova2

(1) Moscow State University of Medicine & Dentistry, Department of functional methods in internal medicine, Moscow, Russian Federation

(2) Prof. A.A. Ostroumov city hospital 33, Nuclear medicine department, Moscow, Russian Federation

Abstract:

Background: Previous experimental studies suggested beneficial effect of ESWT in patients with ischemic heart failure.

Methods: 24 patients with ischemic heart failure and LVEF<40% received ESWT in addition to their stable treatment. ESWT was performed with 9 sessions with 100 shocks per spot in hibernated or ischemic segments detected by low dose dobutamine stress-echocardiography. Troponin I level was tested after every treatment week. Patients were evaluated at baseline, 3 and 6 months after ESWT with clinical examination, MLHF, echocardiography. Tc99m MIBI SPECT was performed on inclusion and 6 months.

Results: ESWT significantly decreased NYHA class from 2.2+/-0.8 to 1.7+/-0.7 at 3 months p<0.01 without any worsening to 6 months after ESWT (1.7+/-0.7). 6-minute walk test improved from 414+/-141 to 509+/-141 and 538+/-116 p<0.01 at 3 and 6 months, respectively. Steady decrease of CCS angina class from 2.6+/-0.7 to 2.1+/-0.8 and 1.9+/-0.7 p<0.01 at 3 and 6 months, respectively was observed. MLHF improved from 35.4+/-15.7 to 27.8+/-15.1 and 28.2+/-17.0, p=0.04. Significant increase in left ventricular ejection fraction (LVEF) at rest (from 31.4+/-7.5 to 38.2+/-9.4 p<0.01) as early as one month after ESWT. LVEF improvement was stable and persisted on 3 and 6 months after ESWT (37.3+/-9.5 and 39.4+/-11.4, respectively). Summed rest score (from 23.9+/-8.1 to 21.4+/-7.1, p=0.03) and stress score improvement (from 28.2+/-8.4 to 24.6+/-6.4, p=0.04) by SPECT was registered.
Troponin I level was always negative.

Conclusions: Significant clinical improvement, accompanied by beneficial changes of LVEF and rest/stress perfusion was found after ESWT.

Key words: ischemic heart failure, shock wave, non-invasive angiogenesis, ejection fraction, hibernation

Abbreviations list:
ESWT = extracorporeal shock wave therapy
LVEF = left ventricular ejection fraction
SPECT = single photon emission computed tomography
MLHF = Minnesota Living with Heart Failure questionnaire
SSS = summed stress score
SRS = summed rest score

Background: About 5.8 million people in the United States have heart failure with 670,000 people diagnosed with it each year. Heart failure is associated with both high level of mortality and cost burden on health care system [1]. The left ventricular ejection fraction (LVEF) is one of the most important predictors of prognosis with substantial mortality increase below 40% [2].
S. Rahimtoola was first to show that many patients with left ventricular dysfunction exhibit improvement of ventricular function after revascularization [3]. To explain the improvement in function, the concept of dysfunctional but viable myocardium with potential to recover function after revascularization was introduced. Viable myocardium has different characteristics and these form the basis for the different imaging modalities that are most frequently used for the assessment of myocardial viability [4]. Cell membrane integrity and mitochondrial function is evaluated by ^{201}Tl and ^{99m}Tc-labeled tracer SPECT respectively, preserved glucose metabolism with ^{18}F-FDG PET, contractile reserve with dobutamine stress-echocardiography. To date there is no agreement for indication of surgical revascularization in patients with viable myocardium and heart failure [5]. Despite possible symptomatic relief and cardiac function improvement surgical treatment is limited in heart failure patients due to high incidence of major adverse events [6]. Extracorporeal shock wave therapy (ESWT) is a new noninvasive angiogenesis-based option in patients with refractory angina pectoris. Previous experimental study suggested beneficial effect of ESWT in patients with ischemic heart failure [7].

Methods: The Ethical committee of Moscow State University of Medicine & Dentistry approved the study protocol and informed consent form was signed by the patients.
24 stable patients (20 men; mean age 63.3±6.1) with ischemic heart failure due to documented acute myocardial infarction (at least 6 months before inclusion) and systolic dysfunction (left ventricular ejection fraction < 40%) with evidence of hibernated myocardium detected by low dose dobutamine stress-echo were included in the study. 12 patients (50,0%) had recurrent myocardial infarction in history. Two patients had previously undergone PCI. The mean duration of heart failure was 6,0 years (3,0; 12,0). All patients received optimal stable treatment for heart failure including ACE-inhibitors 24 (100%), beta-blockers 23 (95,8%), aspirin 22 (91,7%), statins 13 (54,2%), prolonged nitrates 15 (62,5%), diuretics 14 (58,3%) for at least 3 months.
The patients were evaluated at baseline, 3 and 6 months with a clinical examination, quality of life assessment (Minnesota living with heart failure -

MLHF), 6 minute walk test, echocardiography.
To assess myocardial perfusion ^{99m}Tc-MIBI single photon emission computed tomography (SPECT) was performed at baseline and 6 months after the last ESWT treatment. The same camera («Entegra», General Electric, USA) was used. Two day rest-stress protocol was used with modified Bruce treadmill protocol with tracer injection on peak exercise (370 mBq). Summed stress score (SSS) and summed rest score (SRS) were calculated semi-quantitatively using a 20-segment model by a blind observer.
ESWT was performed with Cardiospec, Medispec, USA in a standardized protocol of 9 sessions (with 3 sessions every other day in 1, 5, and 9 week) with 100 shocks per spot at 0.09 mJ/mm^2 energy level in hibernated or ischemic segments detected by low dose dobutamine stress-echocardiography (Fig. 1). Troponin I level was tested after every treatment week.
When non parametrical distribution was found the data was presented as median (25%;75%) and Wilcoxon matched pairs test was used for significance of changes before and after ESWT, otherwise mean +/-SD and t-test for dependant samples were used. Shapiro-Wilk's test was test to determine normality. All statistical tests were performed using Statistica 7.0 (Statsoft, USA). All tests were two-tailed with an alpha level of P =0.05. Due to the exploratory nature of the study, no correction for multiple testing was applied.

Results:
Four patients (16,6%) died during follow-up (2 from recurrent myocardial infarction, 2 from sudden death). One patient withdrew the study after the first treatment week due to long distance to the hospital. Finally 19 patients were examined 6 months after the last treatment.
Treatment with ESWT significantly decreased NYHA class from 2.2+/-0.8 to 1.7+/-0.7 at 3 months $p<0.01$ without any worsening to 6 months after ESWT (1.7+/-0.7) (Fig. 2a). Clinical improvement was associated with significant improvement in 6-minute walk test from 414+/-141 to 509+/-141 and 538+/-116 ($p<0.01$) at 3 and 6 months after ESWT, respectively (Fig. 2b).
ESWT resulted in steady decrease of CCS angina class from 2.6+/-0.7 to 2.1+/-0.8 and 1.9+/-0.7 $p<0.01$ at 3 and 6 months after ESWT, respectively. Significant decrease of nitroglycerin use per week was observed from 2.0 (1,0;5,0) to 1.0 (0.0; 3.0) at 3 months after ESWT ($p<0,01$). Antianginal effect lasted up to 6 months after ESWT 1.0 (0.0; 2.0).
Significant improvement of MLHF from 35.4+/-15.7 to 27.8+/-15.1 and 28.2+/-17.0, $p=0.04$ was observed. Improvement in quality of life was mainly due to physical subscore: from 16,9+/-8,1 to 12.2+/-6.8 and 12.9+/-7.3 ($p<0,01$), respectively.
The functional improvement of ESWT-treated patients was associated with significant increase in left ventricular ejection fraction (LVEF) at rest (from 31.4+/-7.5 to 38.2+/-9.4 $p<0.01$) as early as one month after ESWT (Fig. 3). LVEF improvement was stable and persisted on 3 and 6 months after ESWT (37.3+/-9.5 and 39.4+/-11.4, respectively). Small, but significant improvement of summed rest score by SPECT was observed (from 23.9+/-8.1 to 21.4+/-7.1 at 6 months after the

last treatment, p=0.03) (Fig. 4). In patients able to exercise (modified Bruce protocol, n=12) significant improvement of summed stress score was registered (from 28.2+/-8.4 to 24.6+/-6.4 at 6 months after the last treatment, p=0.04) despite increased exercise tolerance from 4,0+/-2,2 to 4,7+/-2,4 MET (p=0,05).
ESWT was safe in our patients with ischemic heart failure. No adverse events were registered. Troponin I level was negative in all of the patients.

Discussion

High prevalence of hibernated myocardium in patients with ischemic heart failure and limited revascularization options in this population lead to unfavorable prognosis [8-9]. The present study demonstrates that ESWT non-invasively improves left ventricular function and perfusion in patients with ischemic heart failure. Associated increase of LVEF and clinical improvement was observed early after the treatment and persisted for 6 months follow-up. To our knowledge this is the first clinical study of ESWT in heart failure population. Recently published experimental study of direct epicardial shock wave therapy showed marked improvement of LVEF and decline of NT-proBNP on rat model of chronic heart failure [7]. Authors were able to confirm upregulation of VEGF and ESWT induced
angiogenesis in heart failure similar to previous clinical and animal studies in stable angina [10, 11]. But direct epicardial shock wave therapy can be used only in combination with CABG due to invasive nature of procedure. Higher energies of shock waves used in this study require additional safety confirmation. Energy levels used in our study were safe and didn't produce any damage to myocardium (confirmed by negative troponin I). Similar to other studies in refractory angina our shock wave therapy produced marked improvement of 6-minute walk test and treadmill exercise tolerance [10]. Significant improvement of SPECT stress and rest perfusion confirms angiogenesis based mechanism of ESWT in chronic heart failure, as it was shown in several clinical studies before [10,12]. Opposite to previous studies we have tried to include in the study patients similar to usual clinical practice without too strict inclusion and exclusion criteria.

Limitations of the study

Study included limited number of patients. Due to exploratory nature and from ethical point of view this study didn’t have placebo arm. But early clinical and functional improvement confirmed objectively by echocardiography and SPECT was stable for 6 months after ESWT. However, properly powered randomized controlled trial is needed to confirm beneficial effects of ESWT in ischemic heart failure.

Conclusions: Significant clinical improvement, accompanied by beneficial changes of LVEF and rest/stress perfusion was found after ESWT. In this small trial ESWT was safe and effective in patients with ischemic heart failure and systolic dysfunction. If confirmed in randomized controlled trial ESWT may become effective addition to traditional treatment of ischemic heart failure.

The study was supported by research grant from Medispec, USA. No other relationship with industry and financial associations that might pose a conflict of interest in connection with the submitted article are present. The corresponding author: Evgeny L. Shkolnik, M.D. Moscow State University of Medicine & Dentistry, Department of functional methods in internal medicine, Moscow, Russian Federation.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.* Circulation. 2010;121:e1-e170.
2. Volpi A, DeVita C, Franzosi G, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: results of the GISSI-2 data base. Circulation 1993;88:416-29.
3. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985;72(Suppl V):V123-V135.
4. Underwood SR, Bax JJ, vom Dahl J, et al. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. Eur Heart J 2004; 25(10):815-36.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.
6. P. Buszman Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. Am J Cardiol 2007;99:36–41
7. D. Zimpfer et al. Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure. J Thorac Cardiovasc Surg 2009;137:963-70
8. Auerbach MA, Schoder H, Hoh C, et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. Circulation 1999;99:2921-6.
9. Cleland JG, Pennel D, Ray D, et al. Prevalence of hibernation and reversible ischemia in patients with heart failure due to ischemic heart disease: baseline data from the CHRISTMAS study. Eur J Heart Fail 2001; 3: S75
10. Y. Fukumoto et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis 17:63–70
11. Nishida T, Shimokawa H, Oi K et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation. 2004 Nov 9;110(19):3055-61.
12. Khattab AA, Brodersen B, Schuermann-Kuchenbrandt D, et al.

Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol. 2007 Sep 14;121(1):84-5.

Figure 1. Title – Study design.
Caption - 24 patients with ischemic heart failure and LVEF<40% received ESWT in addition to their stable treatment. ESWT was performed with 9 sessions with 100 shocks per spot in hibernated or ischemic segments detected by low dose dobutamine stress-echocardiography.

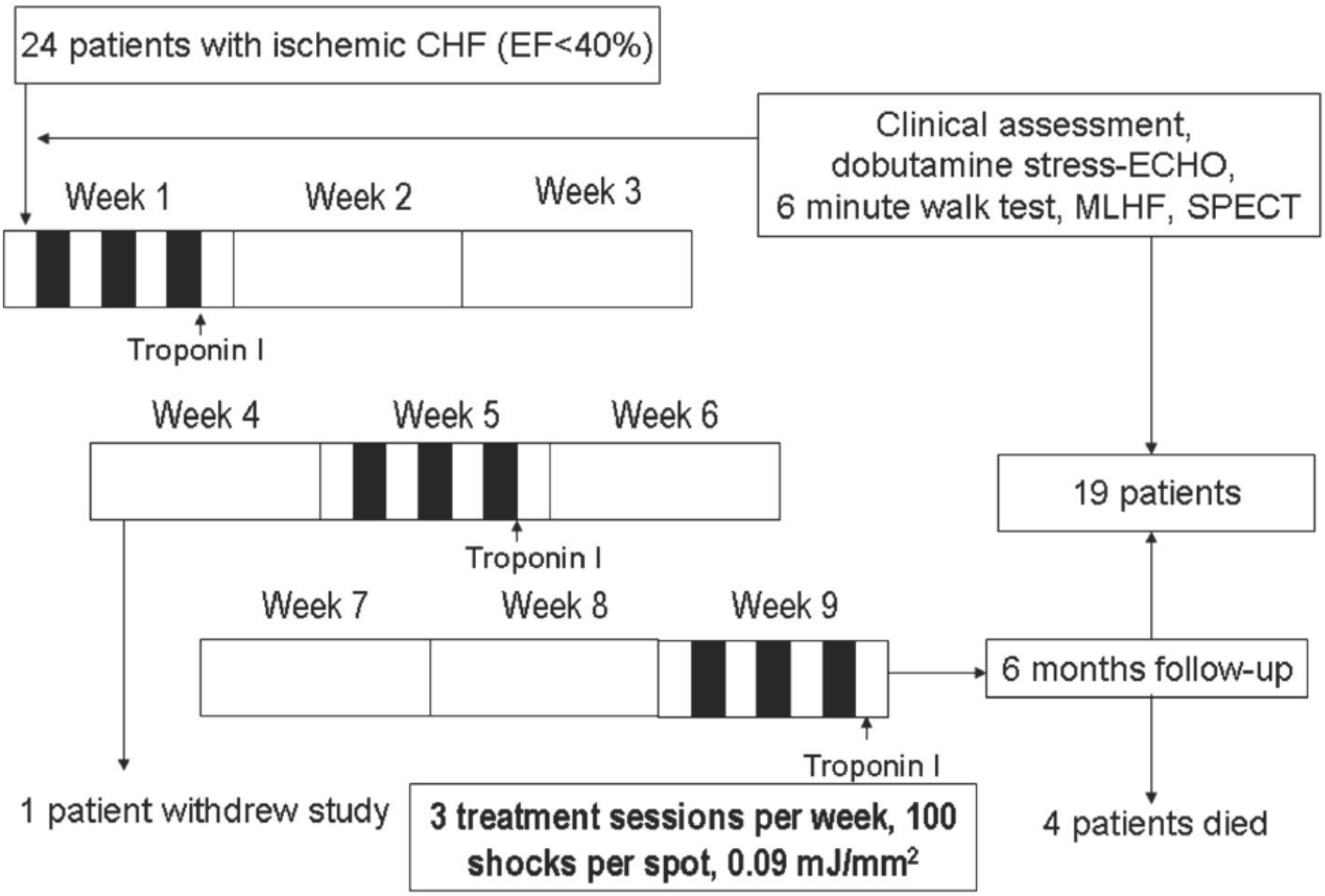


Figure 2. Title – Clinical improvement.
Caption - ESWT significantly improved NYHA class (a) and 6-minute walk test distance (b). * - P<0.01 vs baseline.

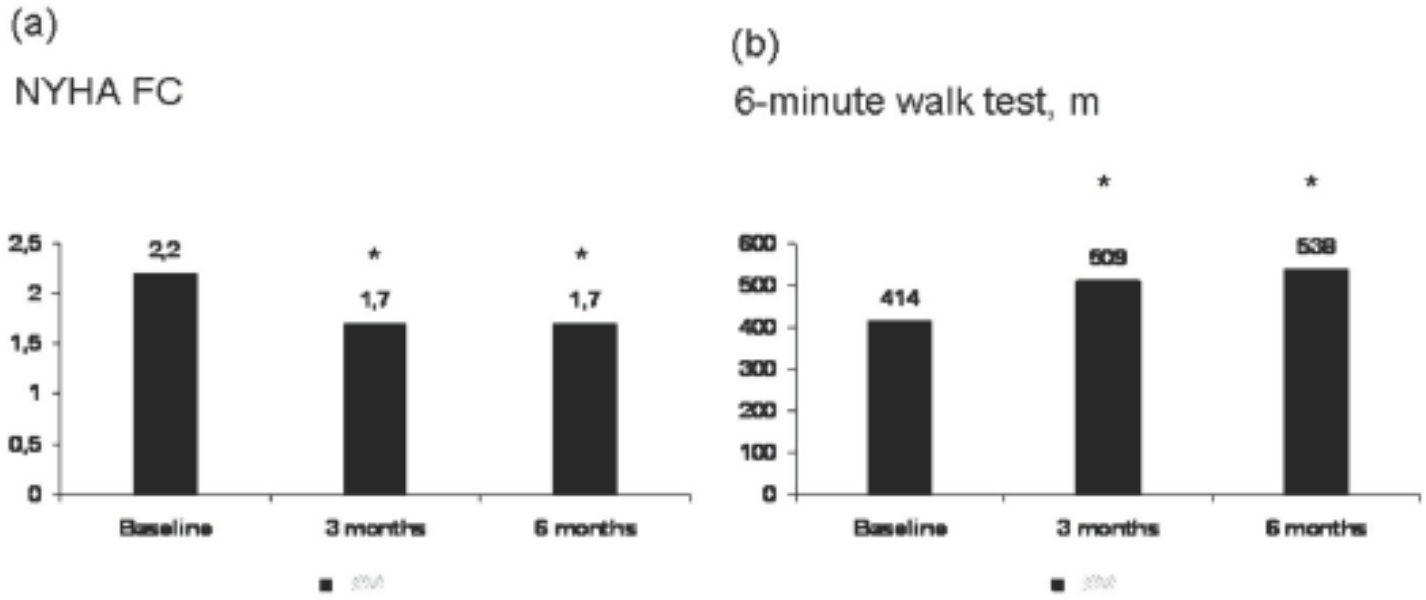


Figure 3. Title – LV function.
Caption - ESWT was associated with significant and stable increase in left ventricular ejection fraction. * - p<0.01 vs. baseline.

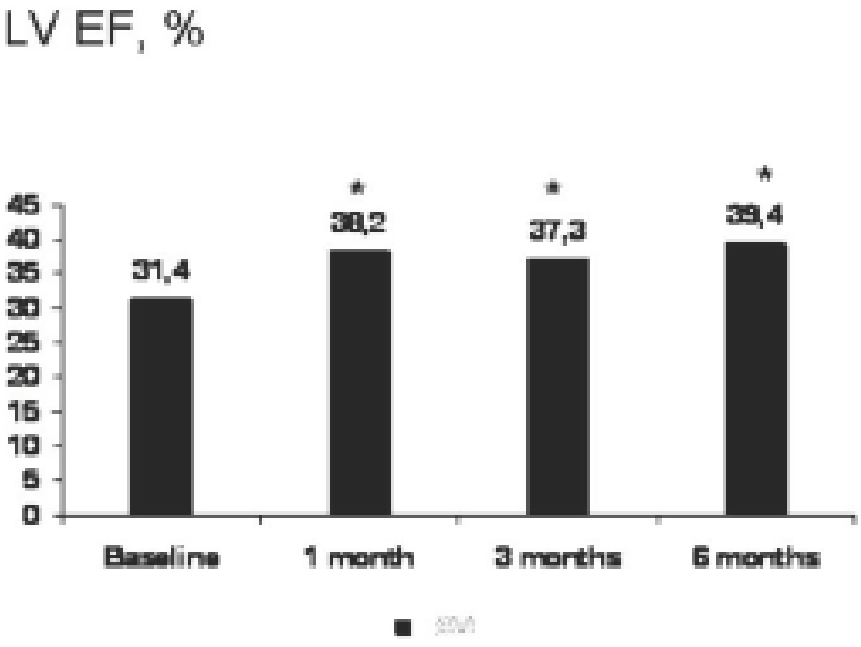
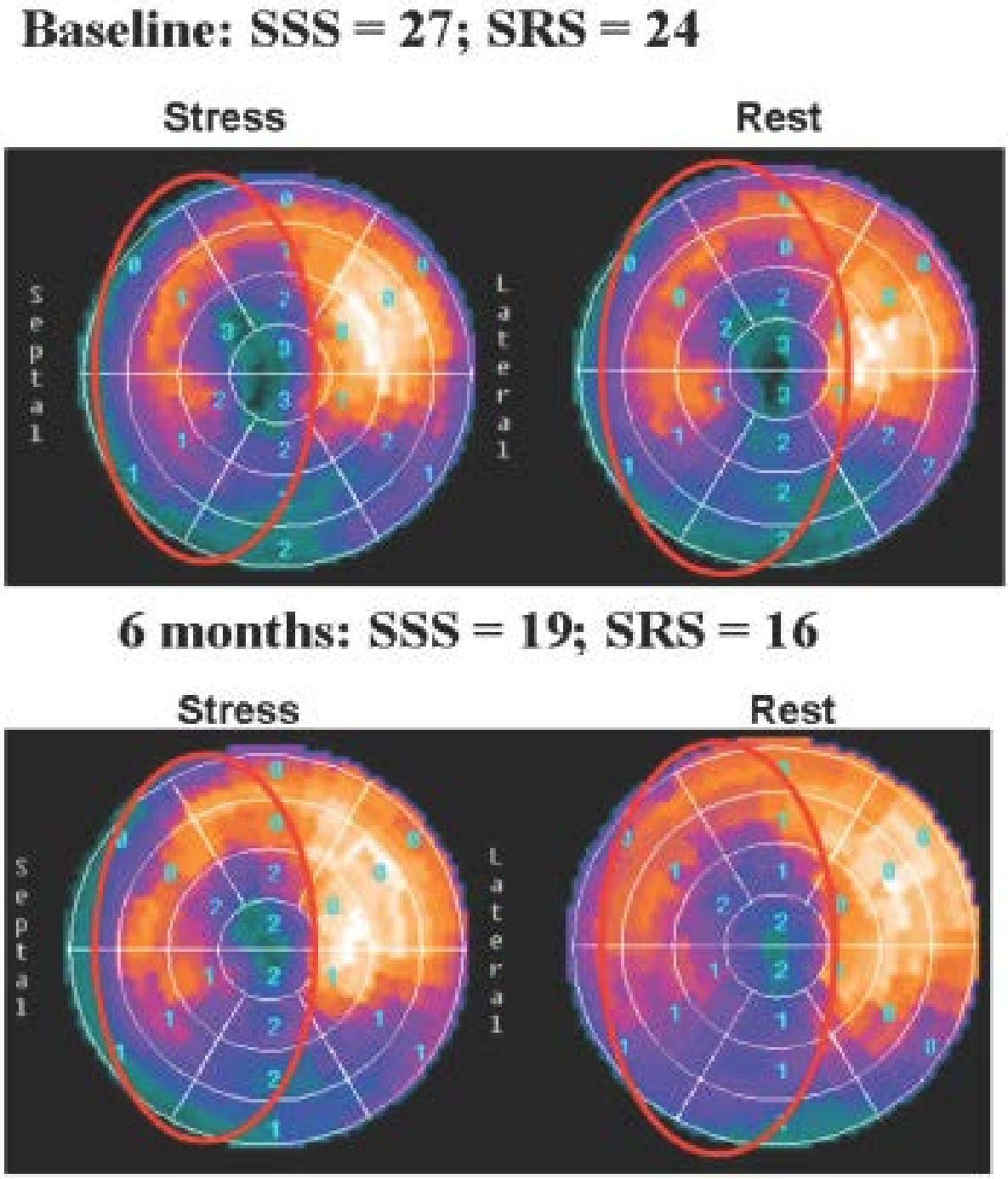


Figure 4. Title - Typical SPECT polar maps of the patient M.
Caption – Marked improvement of SSS and SRS scores was observed despite increase of exercise tolerance from 2.0 to 3.4 MET. Treated area is shown with red line.



3. Revascularization with Extracorporeal Shock Wave Therapy: First Clinical Results

Caspari GH, Erbel R.

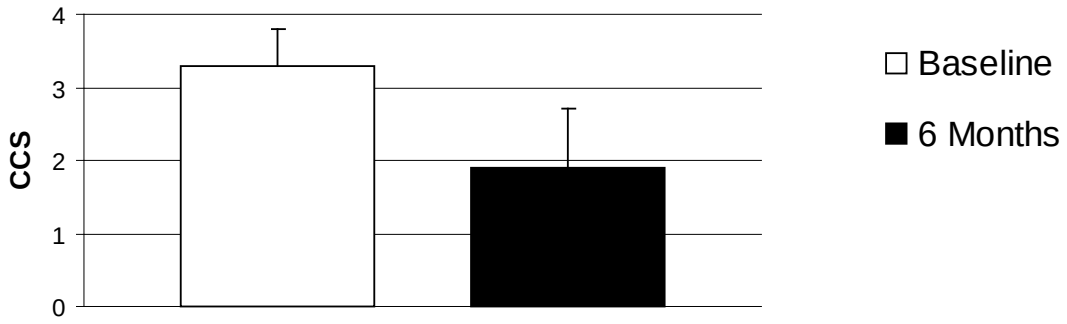
University of Essen, Germany. Circulation 100 (suppl 18):84, 1999

Revascularisation with Extracorporeal Cardiac Shock Wave Therapy: First Clinical Results

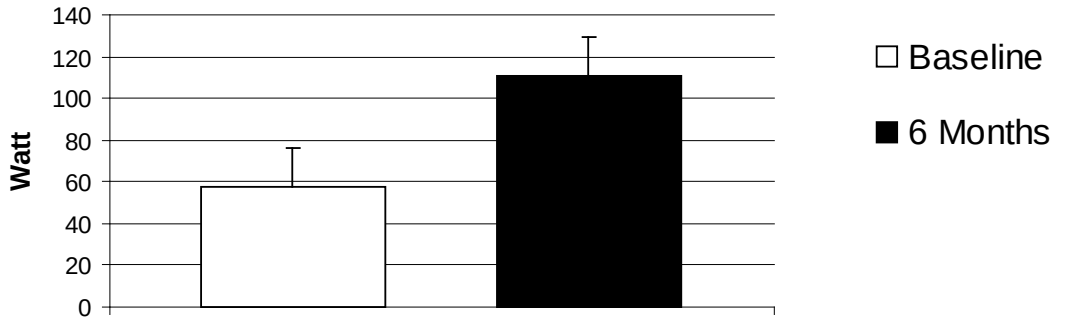
Guido H Caspari med., Raimund Erbel med., Univ of Essen, Essen Germany

Background: Due to the improvement of interventional cardiology and coronary artery bypass grafting techniques the survival rate of patients is increasing, therefore resulting in a need for end-stage coronary heart disease (CHD) therapy. The purpose of our study was to evaluate the safety and clinical effectiveness of an extracorporeal myocardial revascularisation by Cardiac Shock Wave Therapy (CSWT) in patients with CHD. **Methods:** We used a special R-wave triggered shock wave device (modified lithotripter) with in-line ultrasound localisation. This system allows accurate positioning of the therapy focus into the myocardium. The penetration depth can be selected. We have applied 3x1500 impulses with energy flux densities of 0,02 and 0,04 mJ/mm^2 in 9 patients (65±7 years) with CHD. During and in a period of 6 months after therapy the medication remained unchanged. **Results:** The application was painless. During CSWT and 12 hours later no changes in basic hemodynamics, cardiac enzymes, ECG or Echo were found. Also no arrhythmias were detected by Holter. The CCS-Angina class (AP) decreased from (3,3±0,5) before CSWT to (1,9±0,8) after 6 months ($P<0,01$), followed by a increase of the maximal exercise capacity (EC)(58±18 vs 111±18; $P<0,01$). Also physical limitation (24±12 vs 41±8; $P<0,01$) and anginal frequency (30±17 vs 51±16; $P<0,01$) decreased in the Seattle Angina Questionaire. Further all patients improved in myocardial perfusion. Global wash out (35,3±7,1 vs 41,4±5,5) increased and the mean number of ischemic segments (6,3±0,4 vs 3,9±0,1; $P<0,05$) decreased. **Conclusions:** The initial observations show, that CSWT is a safe and feasible technique and seems to relieve AP and increase EC. Also an improved myocardial perfusion could be documented. However, more experience is required before CSWT can be an alternative adjacent therapy.

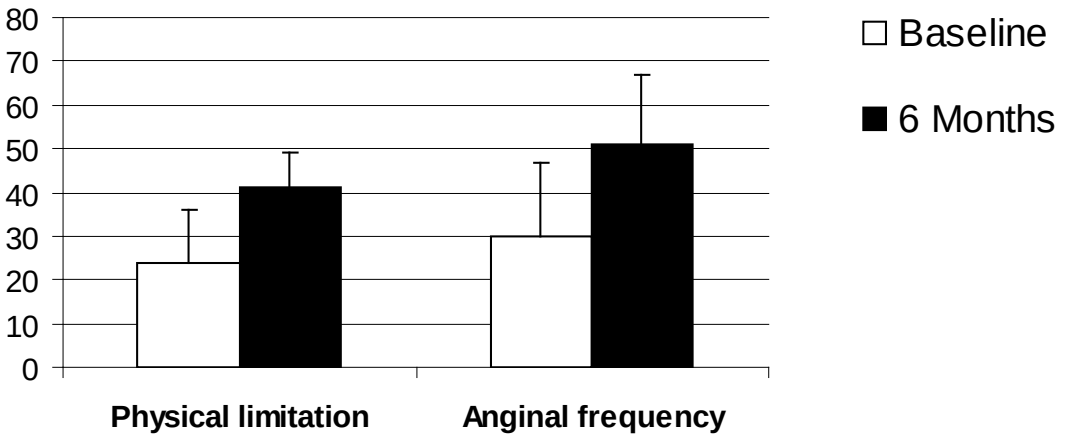
AP-CCS, p<0.01

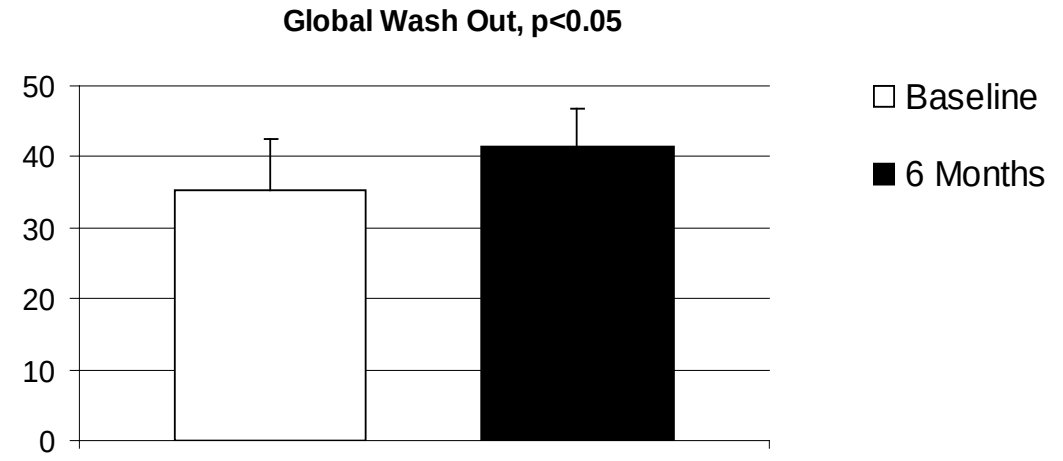


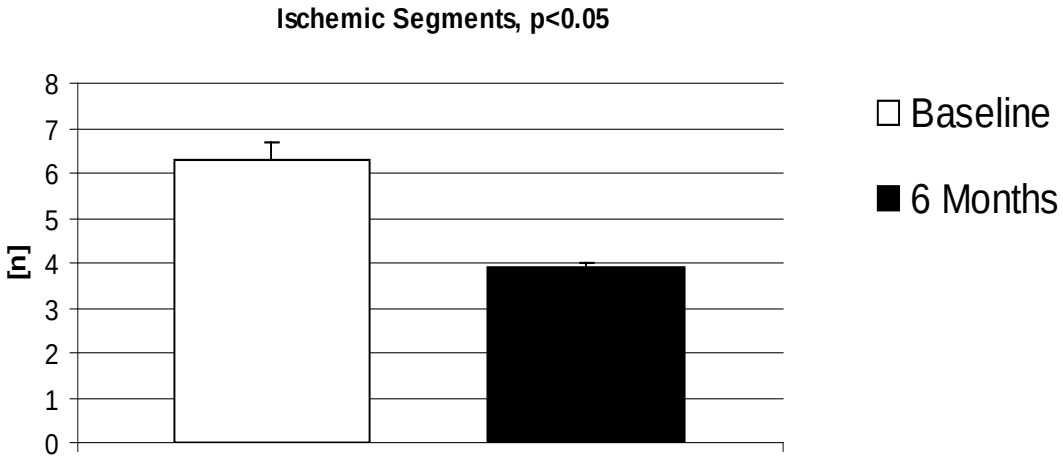
Exercise Capacity, p<0.01



Seattle Angina Questionnaire, p<0.01




Global Wash Out, p<0.05
50
40
30
20
10
0
Baseline
6 Months


Ischemic Segments, p<0.05
[n]
8
7
6
5
4
3
2
1
0
Baseline
6 Months

4. Autoangiogenesis induced by Cardiac shock wave therapy (CSWT) increases myocardial perfusion in endstage CAD patients.

A.Gutersohn, G.Caspari, E.Marlinghaus Uniklinikum, Essen;

Augusta Krankenhaus, Düsseldorf; Storz Medical, Kreuzlingen, CH. Z Kardiol 93: Suppl 3 (2004)

Background:

Improvement of interventional cardiology, cardiac surgery increases survival rate of CAD patients (pts.). This leads to a growing number of pts. with no interventional options. In this study CSWT were applied in pts. with endstage CAD. Also an in vitro study of HUVEC cells treated with CSWT was performed.

Methods:

R-Wave triggered shock waves were focused via in-line ultrasound on anterior and septal ischemic areas of 22 pts. with documented CAD and anterior ischemia proven by SPECT. Mean age 66 ± 7,3. About 3x150 impulses were applied to the pts. hearts using energy fluxes of 0,02 to 0,04 mJ/mm^2. SPECT was performed before and after 6 months follow up in addition pts. had to answer Seattle Angina Questionnaire. HUVEC cells were treated in a 2ml Cryo tube 5-1000000 cells/ml. Different energy flux densities 0.02, 0.05, 0.1, 0.3 mJ/mm2 were used. After shock wave treatment cells were grown for 24h. Cells were centrifuged and m-RNA was isolated using standard methods. PCR was performed using VEGF165 m-RNA primer. Cell death was measured using MTT-assay

.

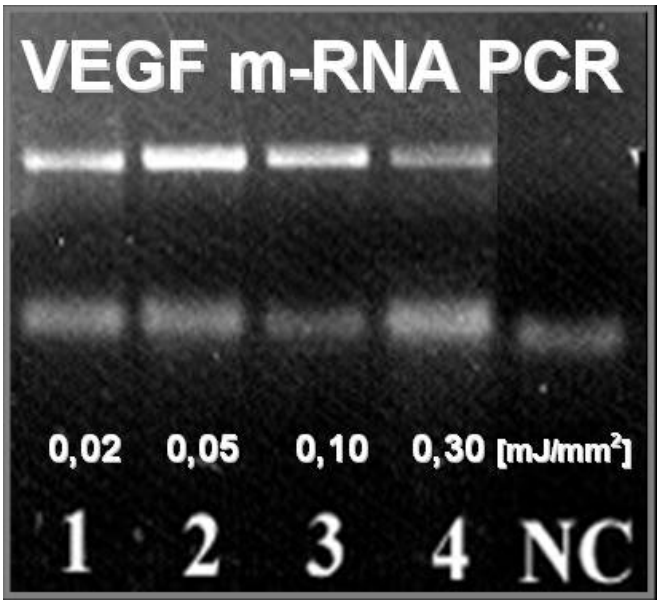
Results:

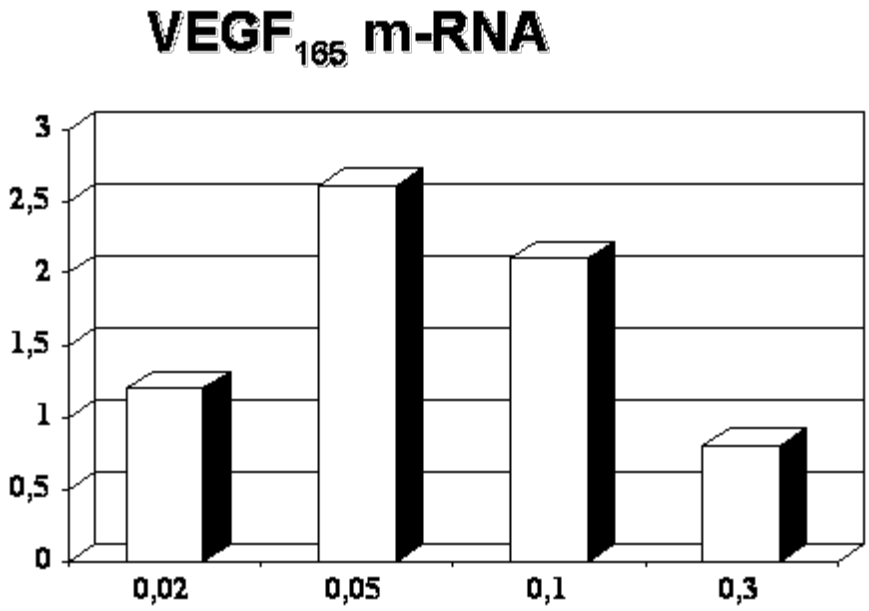
Pts. experienced no side effects during and after treatment. CCS class and exercise capacity showed a decrease in CCS class from 3,3 ± 0,5 to 1,9 ±0,8 after CSWT ($p<0.01$) and an increase in exercise capacity 58 watt ±18 vs. 111 watt ±18 ($p<0.01$). In addition SPECT revealed an increase in perfusion in treated myocardial areas whereas in non treated there was no perfusion increase.

Segments	n	no change	decrease	increase
untreated	144	105	23	16
treated	144	84	6	54

SPECT data before and after in treated and untreated regions n=12 pts. p<0.001 (Mann Whitney Rank)

This increase is due to angiogenesis induced by CSWT which was proven in HUVEC cells where an VEGF m-RNA increase is found after CSWT. Also animal data of a Japanese group prove that CSWT increases myocardial perfusion via neoangiogenesis.


VEGF m-RNA PCR
0,02
0,05
0,10
0,30 [mJ/mm²]
1
2
3
4
NC


VEGF165 m-RNA
3
2,5
2
1,5
1
0,5
0
0,02
0,05
0,1
0,3

5. Short and Long Term Clinical Improvement in Patients with Refractory Angina Using Cardiac Shock Wave Therapy (CSWT)

Achim Gutersohn, Guido Caspari, Raimund Erbel,

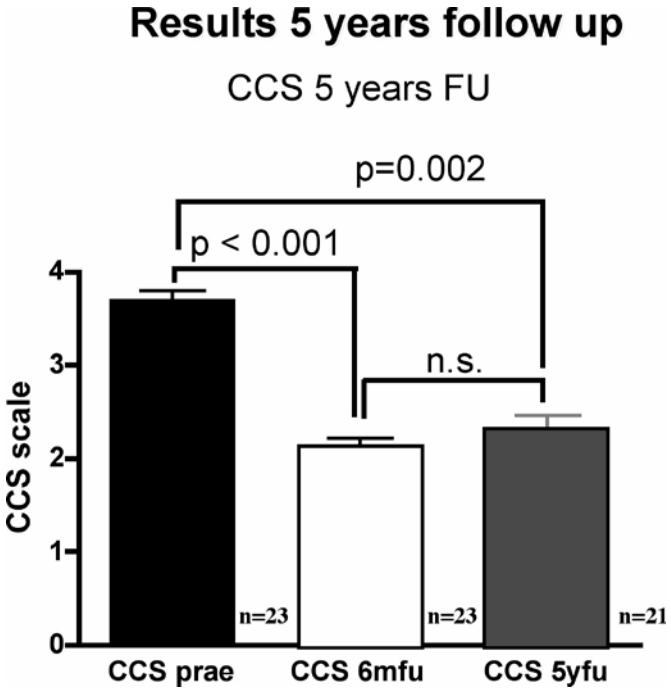
West German Heart Center University of Duisburg Essen, Essen, Germany, Augusta Hospital, Duesseldorf, Germany. Presented at the ACC, March, 2006.

More sophisticated invasive and operative techniques in cardiovascular disease lead to an increasing number of patients with endstage CAD with no therapeutic options and refractory angina. An initial pilot study has proven acute positive effects on clinical symptoms. Here we present five year follow up data after cardiac shock wave therapy (CSWT).

Methods:
CSWT was performed in 23 pts. with endstage CAD and proven ischemia using SPECT. R-Wave triggered shock waves were focused via in-line ultrasound on ischemic areas. About 3 x 150 impulses were applied three times per week repeating this after 3 and 6 weeks. Shock wave were administered to ischemic areas using increasing energy fluxes densities from 0.05 to 0,1 mJ/mm. Pts. were examined in SPECT before and after a 6 months. Also they were evaluated after 5 years.

Results:
Pts. experienced no side effects. SPECT revealed a significant increase in perfusion in treated myocardial areas in 60% of the patients whereas in non treated there was no perfusion increase. CCS class was reduced from initial 3.69 to 2.1 ; at 2.32 after 5 years. Survival after 5 Years was 91.6 %.

Conclusion:
We conclude that CSWT is a new, safe and efficient non-invasive therapy for treating myocardial ischemia in CAD pts. which are ineligible for other interventions. In vitro and animal data prove that the mechanism of action is an increase of angiogenic factors like VEGF resulting in angiogenesis.



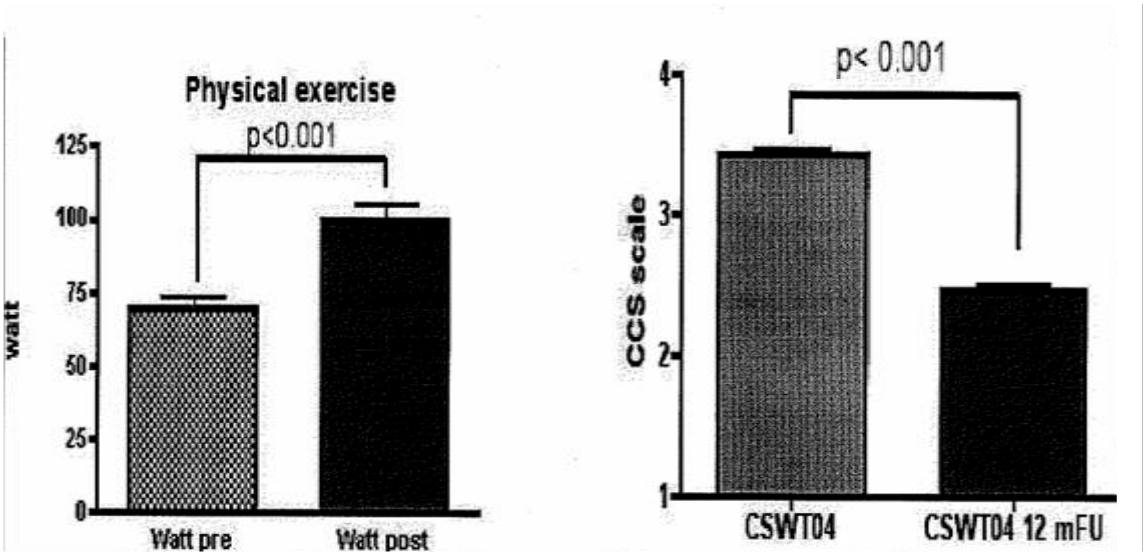
6. Autoangiogenesis Induced by Cardiac Shcok Wave Therapy (CSWT) Increases Perfusion and Exersice Tolerance in Endstage CAD Patients with Refractory Angina

Achim Gutersohn, Guido Caspari, Raimund Erbel.

University Hospital, Essen, Germany & Augusta Hospital, Düsseldorf, Germany.

Presented at the 69th Annual Scientific Meeting of the Japanese Circulation Society, 2005

CSWT provides a non invasive technique to induce angiogenesis. R-Wave triggered shock waves were applied to 14 pts. with proven ischemia in a meandershape like application, mean age 66. About 3 x 1800 impulses were applied using energy flux 0,05 mJ/mm. Perfusion was assessed using SPECT before and after 12 months. Results: No side effects during and after treatment were seen. SPECT revealed a significant increase in perfusion in treated myocardial areas in 80% of the patients. CCS class reduced from 3,42 to 2,41(p=0.001). Exercise tolerance increased from 70 to 100 Watts.CSWT is a save, non invasive therapy to treat ischemia. CSWT induces angiogenesis therefore myocardial perfusion is increased which leads to a better exercise tolerance and reduced angina pectoris .



7. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease.

Fukumoto Y, Ito A, Uwatoku T, Matoba T, Kishi T, Tanaka H, Takeshita A, Sunagawa K, Shimokawa H.

Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan. Coron Artery Dis. 2006 Feb; 17(1):63-70

Objective:

Prognosis of severe coronary artery disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting remains poor. We have recently demonstrated that shock wave therapy effectively induces neovascularization and improves myocardial ischemia in a porcine model in vivo.

Methods:

With permission from the Ethical Committee of our Institute, we treated nine patients with end-stage coronary artery disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting (55-82 years old, five men and four women) with our cardiac shock wave therapy (200 shots/spot at 0.09 mJ/mm for 20-40 spots, 3 times a week/series). We followed-up the patients at 1, 3, 6, and 12 months after the therapy to examine the amelioration of myocardial ischemia. When needed, shock wave therapy was performed up to three series at 0, and 1, 3 or 6 months.

Results:

The cardiac shock wave therapy improved symptoms (Canadian Cardiovascular Society functional class score, from 2.7+/-0.2 to 1.8+/-0.2, $P<0.01$) and reduced nitroglycerin use (from 5.4+/-2.5 to 0.3+/-0.3/week, $P<0.05$). The treatment also improved myocardial perfusion as assessed by dipyridamole stress thallium scintigraphy (severity score, 25.2+/-7.2% improvement, $P<0.05$; extent score, 23.3+/-9.0% improvement, $P=0.10$; washout rate, 20+/-3 to 34+/-3, $P<0.05$). Myocardial perfusion was improved only in the ischemic area treated with the therapy. These beneficial effects persisted for 12 months. No procedural complications or adverse effects were noted.

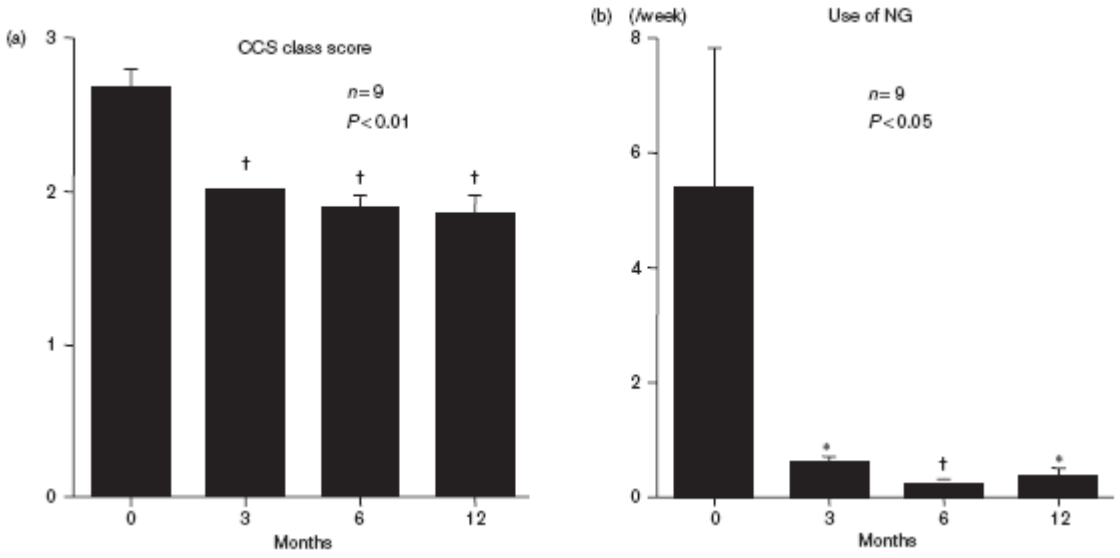
Conclusions:

These results indicate that our extracorporeal cardiac shock wave therapy is an effective and non-invasive treatment for end-stage coronary artery disease, although further careful evaluation is needed

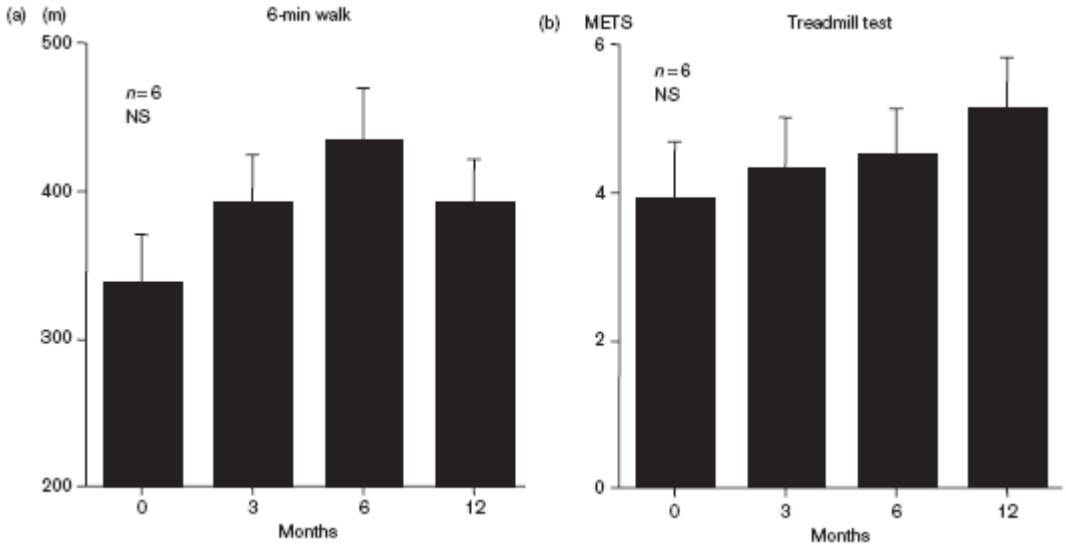
Table 2 **Clinical features and outcome of the shock wave therapy**

Patient	Target area	SW treatment				CCS class	
		0 month	1 month	3 months	6 months	0 month	12 months
1	Inf, Lat, Pos	+	−	−	−	3	2
2	Ant, Sep, Inf, Lat, Pos	+	+	+	−	3	2
3	Ant, Sep, Lat	+	+	−	+	3	2
4	Ant, Lat	+	−	+	−	2	2
5	Ant, Lat, Inf, Pos	+	+	+	−	2	2
6	Inf, Pos	+	+	−	−	3	1
7	Inf, Lat	+	+	+	−	3	2
8	Ant	+	+	−	−	3	2
9	Inf, Lat, Pos	+	+	+	−	2	2

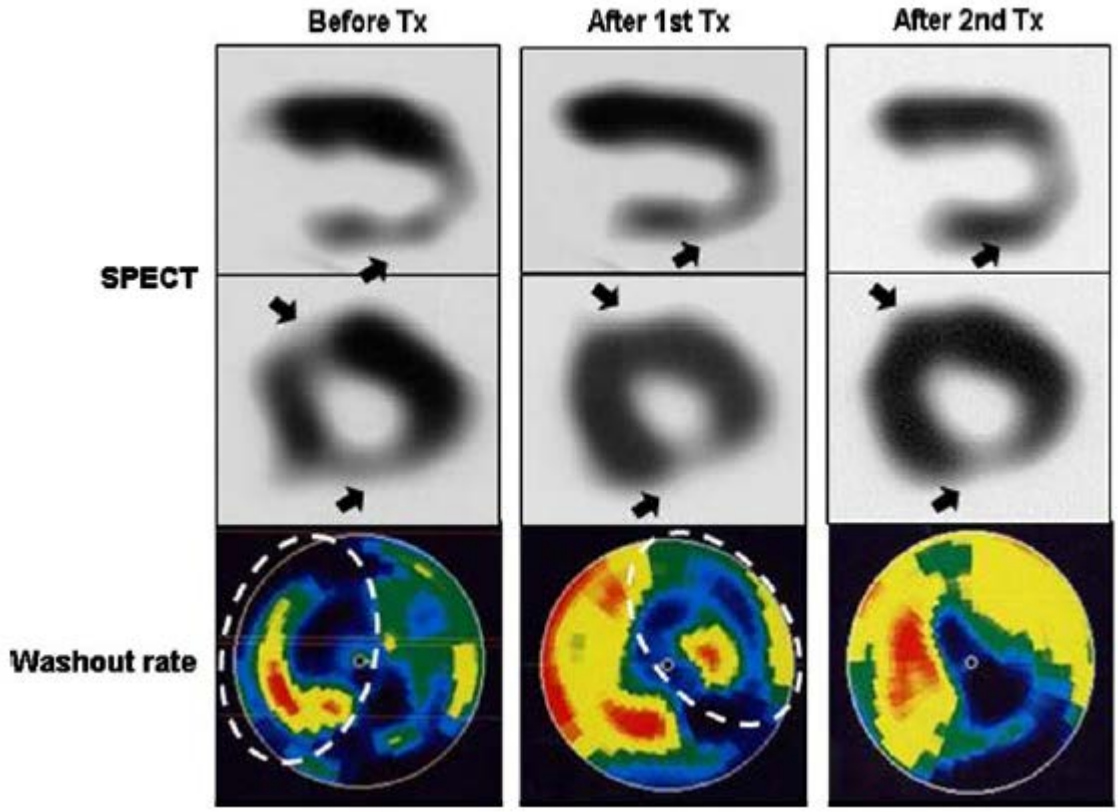
SW, shock wave; CCS, Canadian Cardiovascular Society; Inf, inferior; Lat, lateral; Pos, posterior; Ant, anterior; Sep, septal. The '+' and '−' refer to shock wave therapy performed and not performed, respectively.



Extracorporeal cardiac shock wave therapy significantly improved Canadian Cardiovascular Society (CCS) scores (a) and the use of nitroglycerin (NG) (b). Results are expressed as mean±SEM. *P<0.05 and wP<0.01 vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA).



Extracorporeal cardiac shock wave therapy tended to improve exercise tolerance; 6-min walk (a) and treadmill test (b). Results are expressed as mean±SEM.



Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map demonstrated that the shock wave (SW) treatment ameliorated myocardial perfusion only where SW was applied; in the anteroseptal wall after the first treatment (Tx) and in the lateral wall after the second treatment (arrows).

8. Extracorporeal Shock Wave for Therapy of Refractory Angina Pectoris: The Shock Trial

Jean-Paul Schmid, Mauro Capoferri, Tiziano Schepis, Patrick Siegrist, Verena Schroeder, Philippe A. Kaufmann, Otto M. Hess,

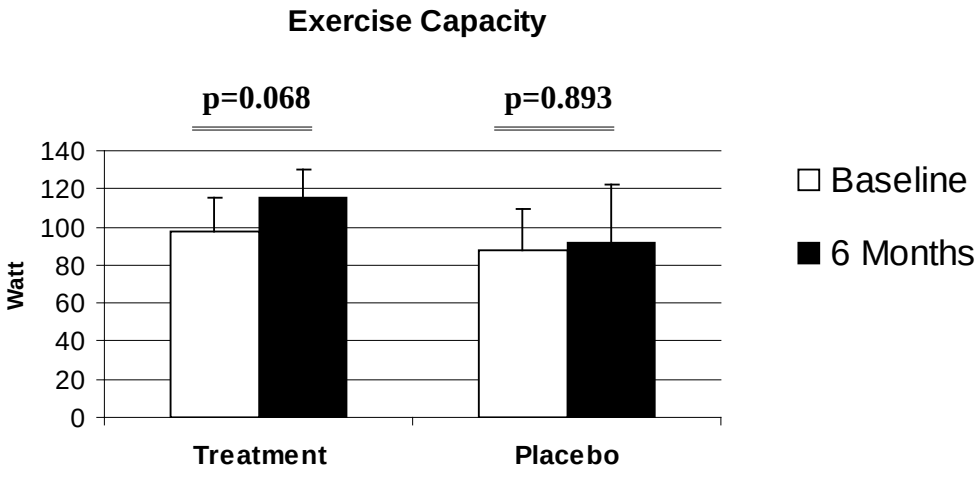
University Hospital, Bern, Switzerland, University Hospital, Zurich, Switzerland.
Presented at the ACC, March, 2006.

Background:
Extracorporeal shock wave therapy (ESWT) has been shown to increase capillary density and regional myocardial blood flow in animal experiments. In addition, non-enzymatic nitric oxide production and the up-regulation of vascular growth factor's mRNA have been described. We hypothesized that ESWT in patients with chronic stable angina pectoris would relieve symptoms and ameliorate the ischemic threshold.

Methods:
15 patients (mean age 68 ± 8 years, 14 male) with chronic stable angina pectoris and evidence of inducible myocardial ischemia during MIBI-SPECT imaging were randomized into a treatment (n=8) and a placebo arm (n=7). 9 treatment sessions (9 to 12 spots of the ischemic myocardium with echocardiographic guidance; 50 shots/spot at 0.09 mJ/mm^2 vs placebo) were applied during a 3 month's period. Medication was kept unchanged.

Results:
In the treatment group, the ischemic threshold, determined during a cardiopulmonary exercise stress test, increased from 98 ± 27 to 115 ± 15 W (p=0.068), whereas in the placebo arm, the threshold did not change (88 ± 21 to 92 ± 30 W; p=0.893). The item "physical functioning" of the quality of life questionnaire SF-36 showed an amelioration from 61 ± 17 to 71 ± 16 (p=0.180) in the treatment group, but no change occurred in the placebo group (63 ± 24 to 62 ± 23). Neither arrhythmias, troponin rise nor other complications were observed during or after the treatment.

Conclusions:
These preliminary data suggest that ESWT improves symptoms and delays the ischemic threshold in patients with chronic stable angina pectoris.



9. Comparison of cardiac shock wave therapy and percutanous myocardial laser revascularisation therapy in endstage CAD patients with refractory angina

A. Gutersohn, E. Marlinghaus.

University Clinic Duisburg Essen, Westgerman Heart Center, Dep. Cardiology, Essen, Germany; STORZ Medical, Kreuzlingen, Switzerland. Eur Heart J 2006, 27(Abstract Suppl), 351

Backgrounds:

Different therapies aim to increase myocardial perfusion in patients with endstage CAD and refractory angina. PMLR had the idea to nourish myocardium via intracardiac channels made by laser. Cardiac shock wave therapy (CSWT) provides a new non-invasive technique to induce angiogenesis in tissue.

Methods:

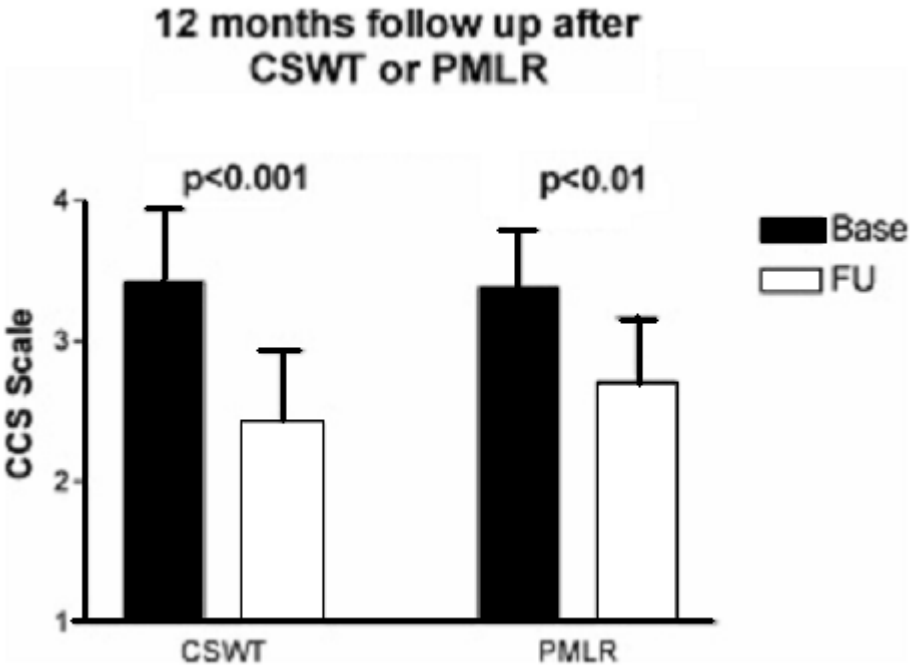
20 pts were treated with PMLR and 14 pts were treated by CSWT, all had proven reversible myocardial ischemia in SPECT. R-Wave triggered shock waves were focused via in-line ultrasound on ischemic areas. About 3 x 1800 impulses were applied to ischemic areas using energy fluxes 0,1 mJ/mm (SLC Storz Medical, Switzerland). Pts. were examined in SPECT after 12 months follow up.

Results:

3 pts (PMLR) could not be treated due to thin target wall (<6mm), there were intraprocedual ventricular extra beats. CSWT group experienced no side effects during and after treatment. SPECT revealed an increase in perfusion in treated myocardial areas in 70% of the patients whereas there was no perfusion increase in the PMLR group. CCS class reduction was significant in the CSWT group from 3,42 ± 0,51 to 2,41 ± 0,52 ($p<0.001$) and in the PMLR group 3,38 ± 0,41 to 2,71 ± 0,45 ($p<0.01$) after 12 months. Exercise tolerance improved in CSWT 69.64 ± 17.48 to 100 ± 22,82 watts ($p<0.01$) and PMLR 72.44 ± 20.32 to 96,54 ± 21,77 watts ($p<0.05$) after 12 months.

Conclusion:

CSWT could be performed in all patient whereas in 15% of pts PMLR could not be performed. In PMLR there were procedual side effects like arrhythmias and CK rise whereas in CSWT treatment no such side effects could be seen. In vitro and in vivo data prove an increase of angiogenic factors after CSWT. We conclude that CSWT is a new safe and feasible therapy. It increases myocardial perfusion and exercise tolerance and reduces angina pectoris.


12 months follow up after
CSWT or PMLR
p<0.001
p<0.01
Base
FU
CCS Scale
4
3
2
1
CSWT
PMLR

10. Extracorporeal cardiac shock wave therapy: First experience in the everyday practice for treatment of chronic refractory angina pectoris

Ahmed A. Khattab, Broder Brodersen, Daniela Schuermann-Kuchenbrandt, Hans Beurich, Ralph Tölg, Volker Geist, Torsten Schäfer, Gert Richardt.

Herz-Kreislauf-Zentrum Segeberger Kliniken GmbH, Am Kurpark 1, 23795 Bad Segeberg, Germany. Institute for Social Medicine, University of Lübeck, Lübeck, Germany

Int J Cardiol. 2007 Sep 14;121(1):84-5.

Several alternative therapies have emerged for treating patients with chronic refractory angina pectoris, yet only a few have given rise to sufficiently published data regarding safety and effectiveness. It is imperative to establish an effective and preferably non-invasive therapy for this expanding patient cohort. We report initial experience with cardiac shock wave therapy (CSWT) in the everyday practice for refractory angina. Ten patients with chronic refractory angina pectoris were enrolled for CSWT at our institution. All were symptomatic on minimal activity (CCS class III or IV) inspite of receiving maximally tolerated medical therapy. They showed evidence of myocardial ischemia on exercise Tc99 SPECT perfusion scans with no possibility for coronary percutaneous intervention or bypass grafting on a recent angiogram. The patients were subjected to 9 CSWT sessions (3 cycles) over
3 months. All patients gave written informed consents. The MODULITH SLC (Storz Medical AG, Kreuzlingen – Switzerland) was used throughout this treatment. The
physical principles, mechanism of action and technical details of shock waves and the above-mentioned generator have been described elsewhere [1]. Briefly, this device is
able to precisely focus shock waves transthoracically on the desired segment of the heart under the guidance of an in-line 2-D echocardiography. Shock waves are applied in an Rwave triggered manner to avoid ventricular arrhythmias. The
shock wave is a mechanical force that induces local shear stress without heat production at low energy levels [2]. The energy level and amount of shock waves applied have been derived from in vitro and animal experiments [3].
Semiquantitative visual interpretation by a blinded experienced physician was performed for both baseline and follow-up myocardial tomograms by assigning each of the 17 segments of the left ventricle 0 to 4 points both at rest and during stress according to its uptake [4]. At follow-up, a reduction of ≥2 points compared to baseline scores was considered a substantial reduction of ischemia in that segment.
Summed stress scores in the treated segments before and after therapy were compared and the mean values were tested for statistical significance. Successful CSWT was
defined as an improvement of anginal symptoms to become ≤CCS class II and a substantial reduction of ischemia in the treated myocardium. A non-parametric test for paired data was used to investigate differences before and after treatment
Eight patients completed the 9 sessions. One patient who was on psychotherapy because of chronic depression did not tolerate therapy and described it as painful and in another patient therapy was discontinued because of a slight Troponin T elevation after the 6th

session without further consequences. One death out of hospital occurred 4 weeks after the last session. Nine out of 10 patients had CCS angina class
≤2 at follow-up. The mean CCS class at baseline was 3.3±0.5 and at follow-up was 1.0±1.3 (p=0.007) (Fig. 1). Among the 8 patients a total of 22 ischemic segments were subjected to treatment. The mean summed stress score was
8.3±2.2 at baseline and fell to 3.0±3.1 at follow-up (p=0.02) (Fig. 2). Per definition CSWT was successful in 6 out of 8 patients (75%). Myocardial perfusion improved
only in the ischemic areas treated by CSWT. Extracorporeal shock wave therapy is a non-invasive, safe and easy-to-use application. In a randomised study, Nishida et
al. [3] have shown among a porcine model of chronic myocardial ischemia complete recovery of left ventricular ejection fraction, wall thickening fraction, and regional myocardial blood flow of the ischemic region in 4 weeks (all p<0.01) after receiving shock wave treatment (n=8) as compared to animals which did not receive the therapy (n=8). A clinical pilot study was able to reproduce these favourable preclinical
results among nine selected patients [5]. We report the first series from clinical routine. There was a significant improvement in anginal symptoms that was
associated by a substantial reduction of ischemic myocardium. It remains unclear, however why two patients did not show an objective improvement inspite of clinical benefit. One explanation could be the need for more shock waves and/or higher energy levels according to size and severity of the ischemic zone; or that the angina improvement is in part a placebo effect.
Drawing conclusions must be done carefully; nevertheless, we can report that CSWT for refractory angina pectoris is effective in ameliorating anginal symptoms by limiting the underlying ischemia burden of the myocardium.

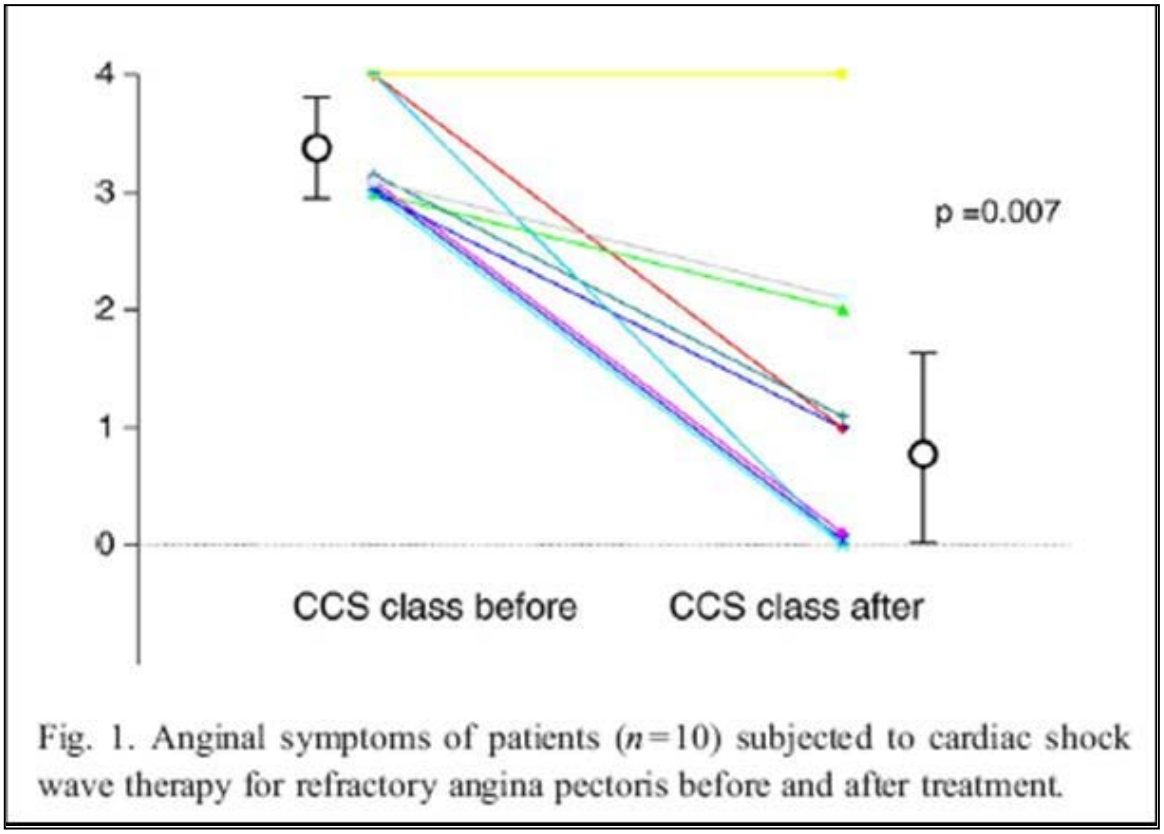


Fig. 1. Anginal symptoms of patients ($n=10$) subjected to cardiac shock wave therapy for refractory angina pectoris before and after treatment.

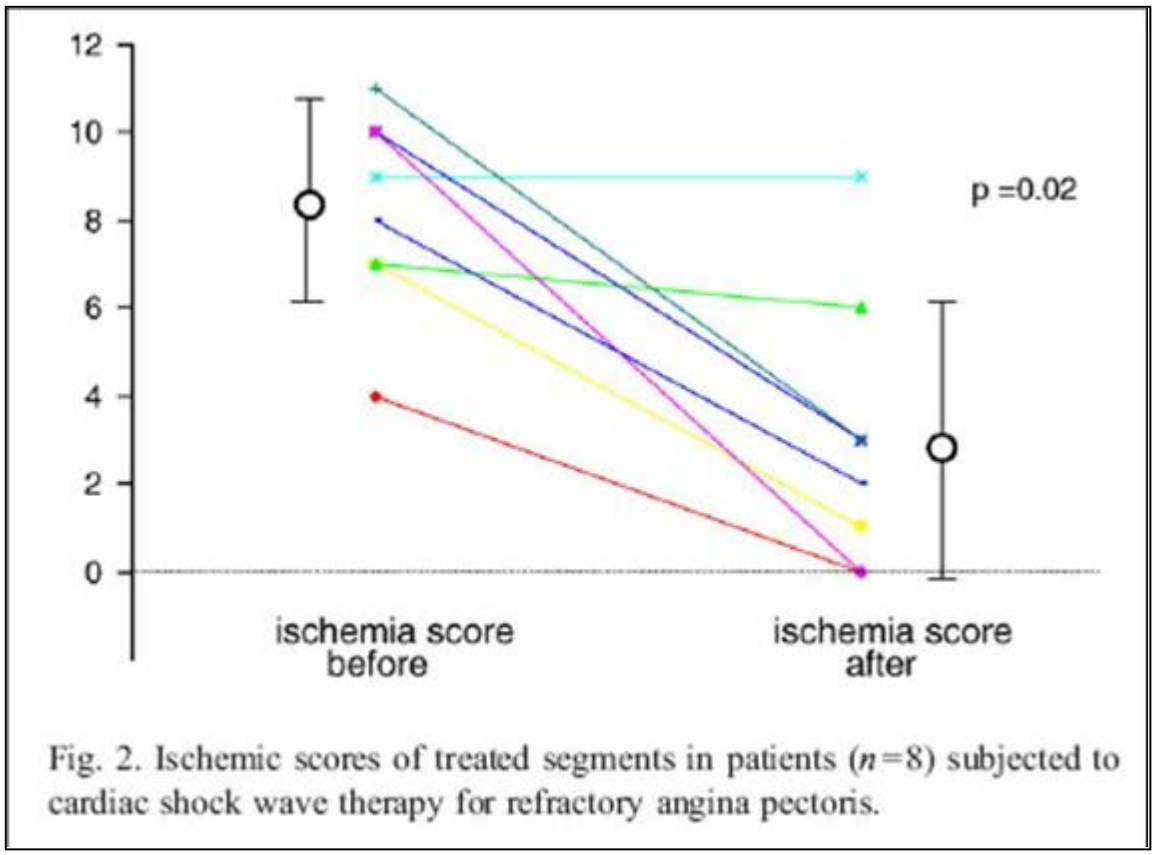


Fig. 2. Ischemic scores of treated segments in patients (n=8) subjected to cardiac shock wave therapy for refractory angina pectoris.

References

[1] Mariotto S, Cavalieri E, Amelio E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric
Oxide 2005;2:89–96.
[2] Ichioka S, Shibata M, Kosaki K, et al. Effects of shear stress on wound healing angiogenesis in the rabbit ear chamber. J Surg Res 1997;72: 29–35.
[3] Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004;110:3055–61.
[4] Berman DS, Hachamovitch R, Kiat H, et al. Incremental prognostic value and cost implications of normal exercise Tc-99m sestamibi myocardial perfusion SPECT. J Am Coll Cardiol 1995;26:639–47.
[5] Fukumoto Y, Ito A, Uwatoku T, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis 2006;17(1):63–70.

11. Extracorporeal Shock Wave Therapy improves symptoms in Refractory Angina Pectoris Patients with advanced Coronary Artery Disease not suitable for Revascularization

L. Faber, N. Bogunovic, O. Oldenburg, F. van Buuren, D. Horstkotte

Department of Cardiology, Heart Center North Rhine-Westphalia, Ruhr-University, Bad Oeynhausen, Germany. Interim analysis

Background:

High intensity extracorporeal shock waves (SW) are used for nephro- and cholelithotripsy. Low-intensity SW therapy (SWT) has been shown to increase capillary density and regional myocardial blood flow in animal experiments. We hypothesized that SWT might be beneficial in patients (pts.) not suitable for revascularization suffering from severe chronic angina pectoris (CCS class III or IV) refractory to individually optimized medical treatment.

Methods:

16 pts. (mean age: 66±10 years, 13 males, n=1 pt. with previous implantation of a spinal chord stimulator, # of previous CABG procedures / pt.: 1.2 [0-2]; # of previous PCI procedures / pt.: 1.7 [0-6]) with evidence of inducible myocardial ischemia during positron emission tomography (PET) underwent a series of 9 echocardiography-targeted SW applications (3 sessions per week, weeks 1, 5 and 9). ECG and cardiac markers were checked after each application; clinical status, echocardiography, and exercise tolerance were assessed at baseline and 4 weeks after completion of the program. Anti-anginal medication (combination of 3 drugs in 13 and 2 in 3 pts.) remained unchanged.

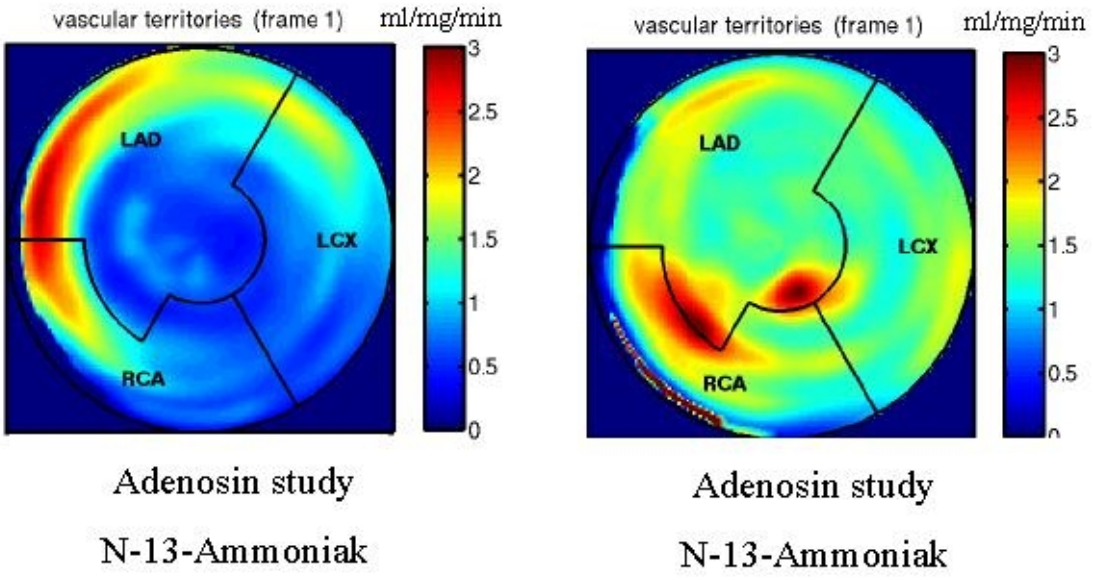
Results:

CCS angina class decreased from 3.1±0.7 to 2.4+0.6 (p=0.0004). Maximum ergometric workload slightly increased from 80±45 to 90±39 watts (p=0.04), the double product (heart rate x systolic blood pressure) from 14676±4400 to 16460±5006 (p=0.2). LV end diastolic diameter decreased from 54±7 to 51±6 mm (p=0.01), and LV ejection fraction slightly increased from 57±16 vs. 59±15% (p=0.2). Neither arrhythmias, troponin rise, nor other device related complications were observed during or after any of the treatment sessions.

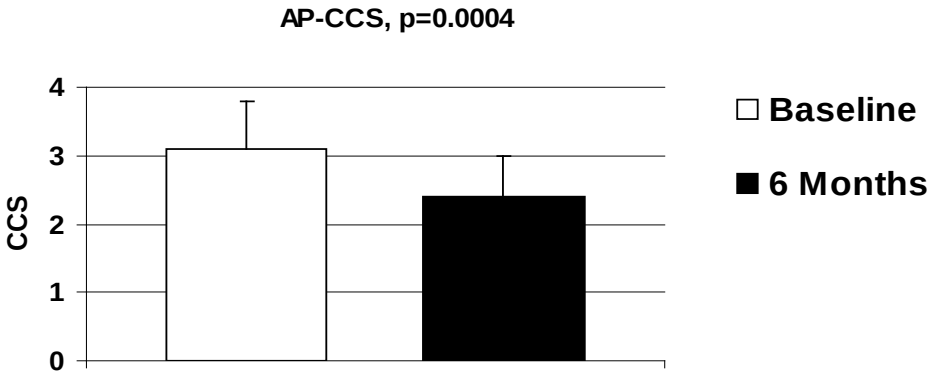
Conclusions:

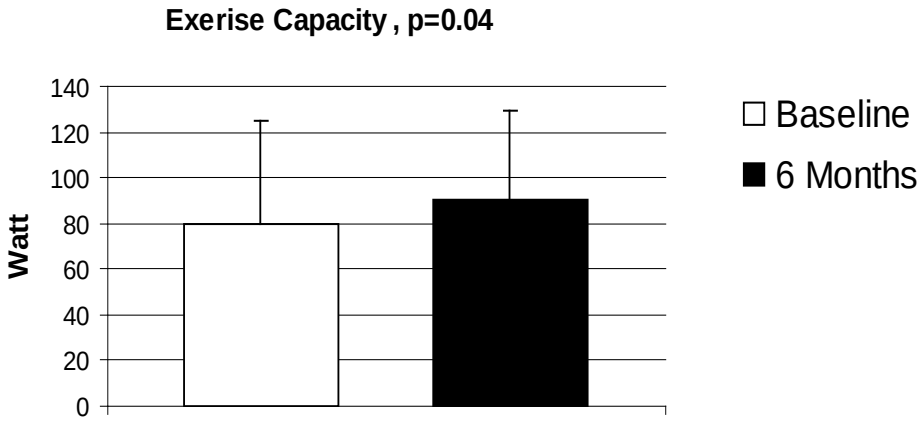
These preliminary data suggest that SWT safely improves symptoms in pts. with chronic refractory angina pectoris. The mechanism of action remains speculative from these data.

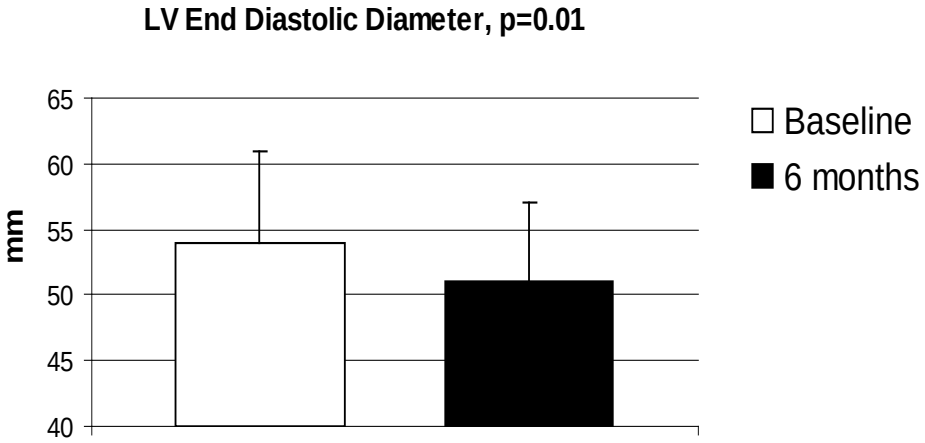
Pre: **Post:**



Courtesy of Prof. Dr. W. Burchert, study performed by Dr. O. Lindner
Dept. of Nuclear Medicine, Heart and Diabetes Ctr. NRW, Bad Oeynhausen,




Exerise Capacity , p=0.04
Watt
140
120
100
80
60
40
20
0
Baseline
6 Months


LV End Diastolic Diameter, p=0.01
mm
65
60
55
50
45
40
Baseline
6 months

12. Cardiac shockwave therapy ameliorates ischemia and symptoms in patients with end-stage coronary artery disease and chronic refractory angina pectoris

J. Vainer, J. Habets, A. Lousberg, J. Waltenberger.

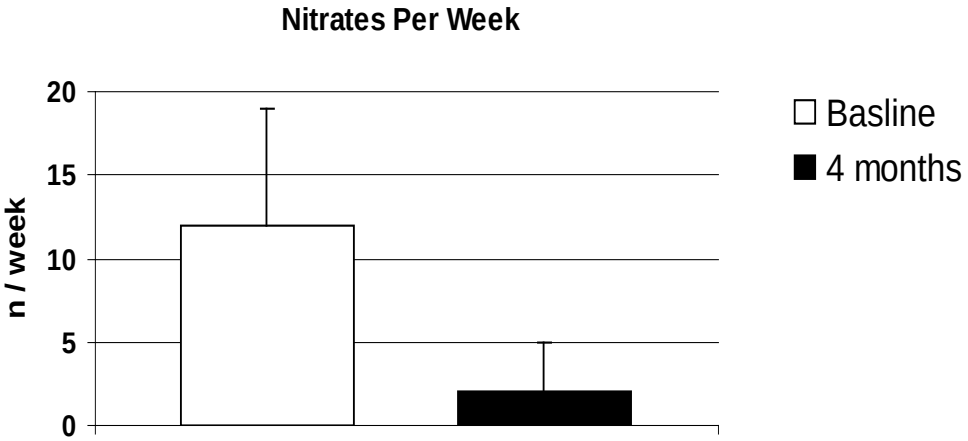
University Hospital, Maastricht, Netherlands
Interim analysis

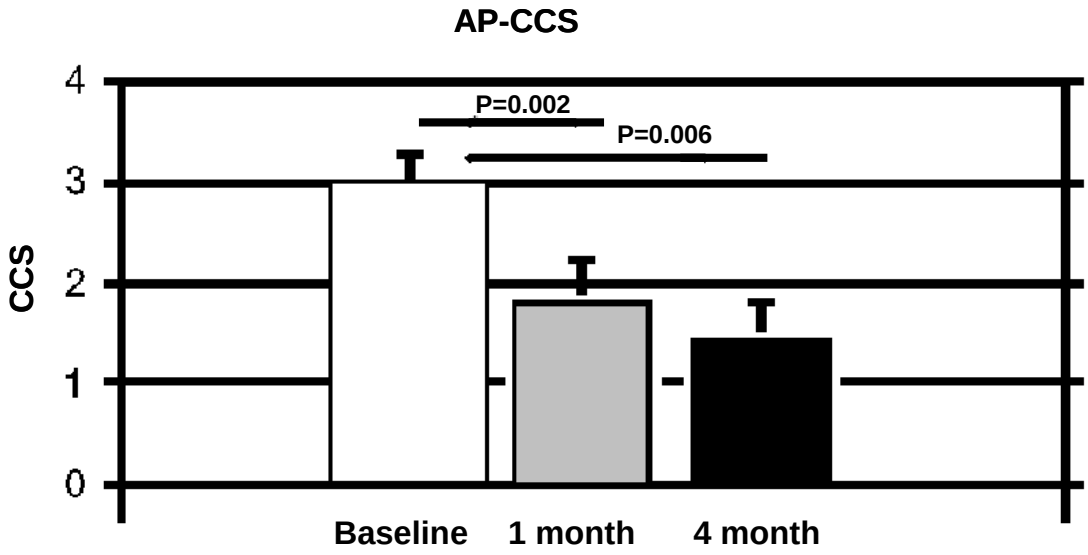
Purpose:
After exhausting all conventional invasive and non-invasive therapeutic options in patients (pts) with end-stage coronary artery disease and chronic refractory angina pectoris (CRAP), there is little to offer but neurostimulation and experimental therapies. Cardiac shockwave therapy (CSWT) might improve symptoms and decrease ischemia burden by stimulating collateral growth in the chronic ischemic myocardium. This prospective pilot study was performed to evaluate the feasibility and safety of cardiac shockwave therapy.

Methods:
A total of 8 male patients (mean age 72±6 years, mean left ventricular ejection fraction 56±14%) with end-stage coronary artery disease and reversible ischemia on thallium scintigraphy (TS) were included. All pts had a history of CABG, 2 pts underwent re-CABG and 3 pts PCI. CSWT was applied to ischemic zones (100 impulses/spot, 0.09 mJ/mm2) in an Echo-guided and ECG-triggered fashion. Per session, 3-5 different spots were treated. The protocol included 3 treatment sessions within one week, which were repeated after 1 and 2 months, resulting in a total of 9 treatment sessions. Clinical assessment was done using exercise test, angina score (NYHA class), quantification of nitrate use, TS and magnetic resonance imaging (MRI) at baseline as well as 1 and 4 months after the last treatment session.

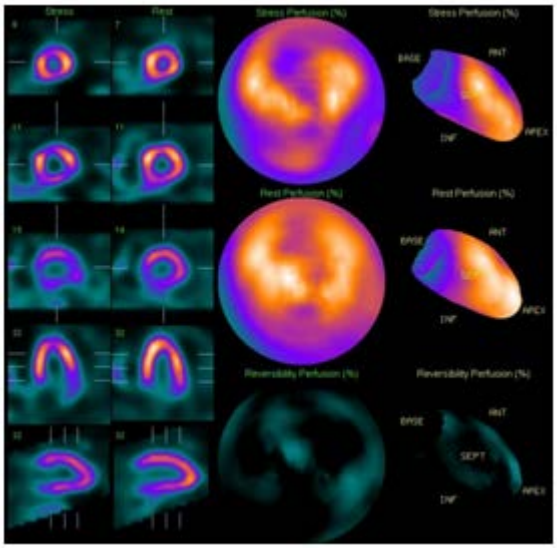
Results:
One month following CSWT, the clinical status of the patients improved significantly. The use of nitrates decreased from 12±7/week pre-CSWT to 2±3/week post-CSWT ($p=0.01$). Simultaneously, angina complaints significantly decreased at least by one NYHA class in all but one patient ($p<0.01$). There was less ischemia burden in 6 patients following CSWT as demonstrated by TS, however, exercise tolerance didn't change. CSWT was well tolerated without side effects apart from transient dizziness and warm sensations shortly after the initial treatment session in 2 pts. Creatine kinase did not rise within the first day after treatment. Compared with baseline, MRI didn't show any increase in scar tissue volume following CSWT and there was no significant change in LV ejection fraction. At 4 months follow-up (4 pts), ischemic burden (TS) increased again in 3 pts compared to the 1 month follow-up assessment.

Conclusions:
CSWT resulted in a short-term improvement of symptoms, decreased use of nitrates and reduced ischemia burden in patients with CRAP. CSWT was well-tolerated with no relevant side effects. The positive expectations based on the 1 month results might be tempered by recurrence of the ischemia burden at 4 months follow-up.

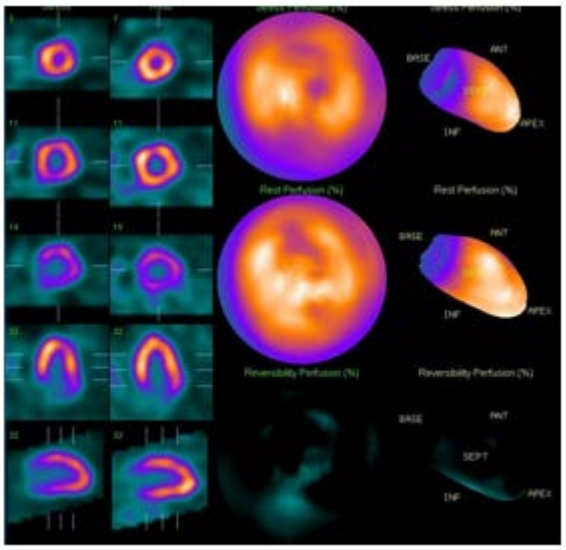

Nitrates Per Week
20
15
10
5
0
n / week
Basline
4 months


AP-CCS
4
3
2
1
0
CCS
P=0.002
P=0.006
Baseline
1 month
4 month

Baseline



4 months



13. Cardiac shock-wave therapy: First Experience

Lyadov Konstantin; Uvarov, Alexey.

Medical and Rehabilitation Center, Moscow, Russia. Presented at the 6th Mediterranean congress of PRM, Oct 2006

Introduction:

We used new treatment modality for patients with coronary arteries disease (CAD) – cardiac shockwave therapy (CSWT) – for the first time in the Eastern Europe. CSWT is a therapy with the series of focused shock waves impacted to the myocardium segments with reversible ischemia. Shock-wave generator was positioned by ultrasound scanner. Sock-wave impact was applied in early diastole phase with ECG control.

Materials and Methods:

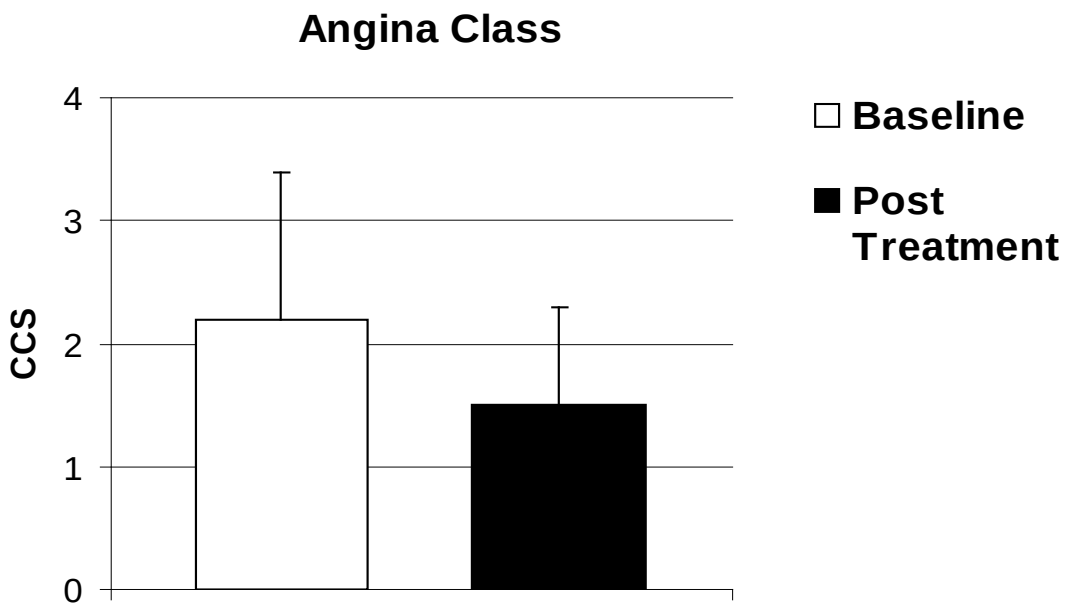
Thirteen patients (11 men, 2 women) received full course of treatment. Mean age was 59.6±6.9. All the patients had myocardial infarction in anamnesis, all had angina. Mean CAD class was 2.2±1.2. Before and after the treatment all was examined with stressechocardiography and cardiopulmonary exercise test (CPET). Patient filled Seattle angina questionnaire (SAQ). After stress-echocardiography there were determined reversible ischemia zones (mean contractility index 4.6±1.7). Therapy was last for 9 weeks in 9 sessions (3 sessions in 1, 5 and 9 week). Every session included 300 shock-wave impulses (totally 2700 impulses). Treatment tolerance was good, there were no complications.

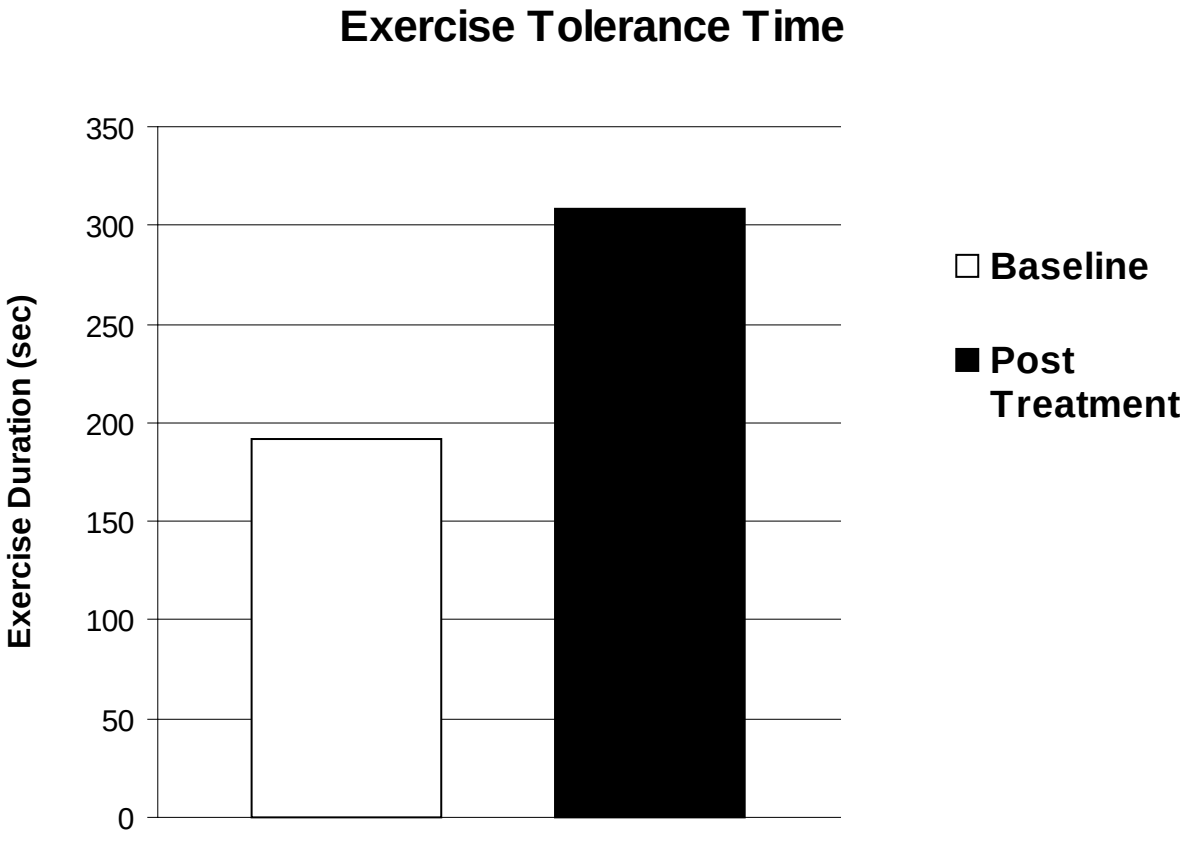
Results:

Mean CAD class after treatment was 1.5±0.8). Mean maximal oxygen uptake increase was 18.5% (11.9±2.2 and 14.1±2.8 ml/kg/min). Mean contractility index after treatment 3.2±1.5). There was decrease in physical activity limitation (by SAQ): 42±11 and 56±13 before and after the treatment.

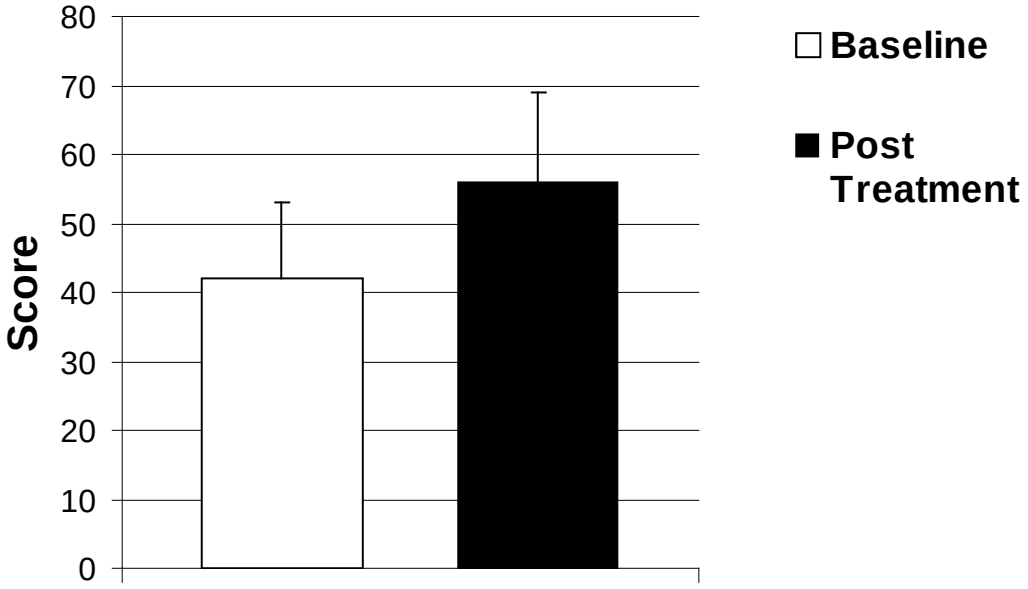
Conclusion:

Our first experience showed hopeful results for patients with CAD. It is non-invasive and safe for patient. So this method can be the new branch in the cardiac rehabilitation. And it is necessary to study the remote effects of this treatment.

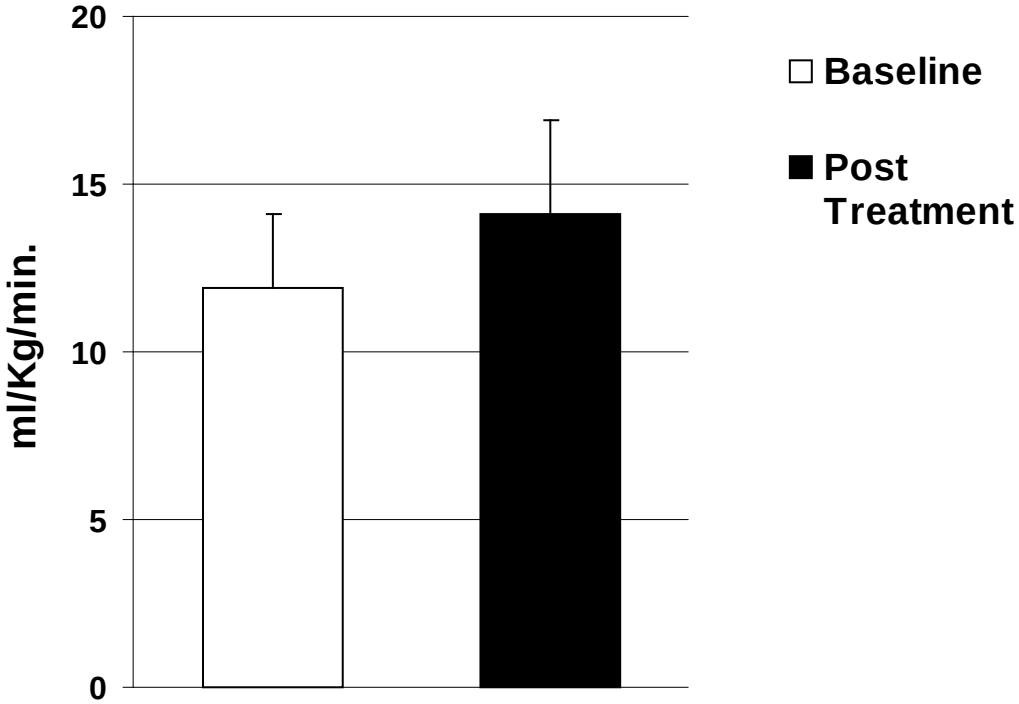

Angina Class
CCS
4
3
2
1
0
Baseline
Post Treatment


Exercise Tolerance Time
Exercise Duration (sec)
350
300
250
200
150
100
50
0
Baseline
Post Treatment

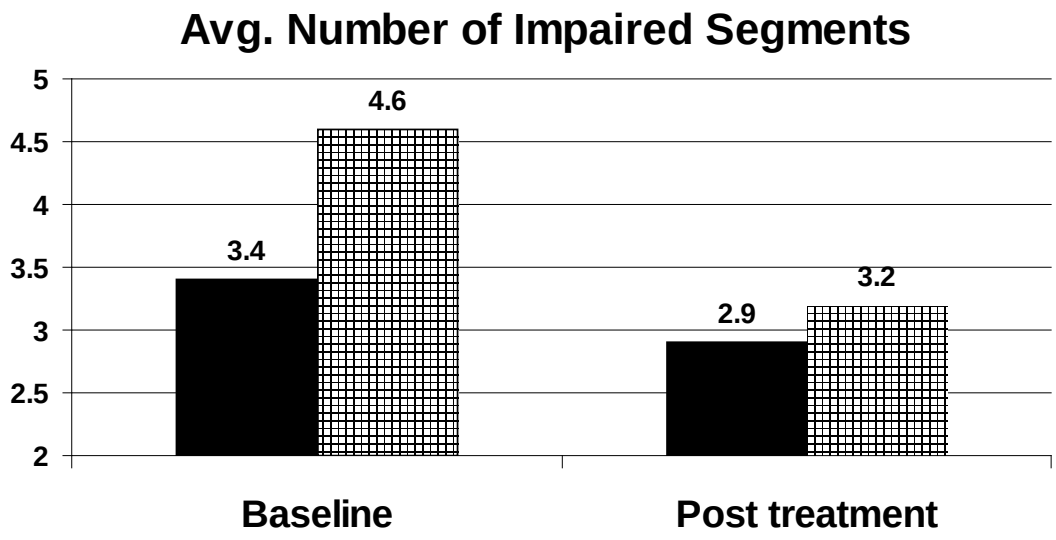
SAQ
(Physical Activitiy Limitation)



Oxygen uptake



:


Avg. Number of Impaired Segments
5
4.5
4
3.5
3
2.5
2
4.6
3.4
3.2
2.9
Baseline
Post treatment

■ - Rest

□ - Stress

14. Initial clinical experience with extracorporeal shock wave therapy in treatment of ischemic heart failure

Yury A. Vasyuk[1], Alla B. Hadzegova[1], Evgeny L. Shkolnik[1], Maya V. Kopeleva[1], Olga V. Krikunova[1], Elena N. Iouchtchouk, Elena M. Aronova[2], Svetlana V. Ivanova[1]

(1) Moscow State University of Medicine & Dentistry, Department of functional methods in internal medicine, Moscow, Russian Federation
(2) Prof. A.A. Ostroumov city hospital 33, Nuclear medicine department, Moscow, Russian Federation

(1) Presented at the EuroEcho 2009, Madrid, Spain, 9th-12th of December and (2) at the Heart failure congress 2009, Nice, France, 30th May- 02nd June.

(1) http://spo.escardio.org/AbstractDetails.aspx?id=73090&eevtid=34*
(2) http://spo.escardio.org/AbstractDetails.aspx?id=60474&eevtid=31*

The study was supported by research grant from Medispec, USA. No other relationship with industry and financial associations that might pose a conflict of interest in connection with the submitted article is present.

The corresponding author: Evgeny L. Shkolnik, M.D. Moscow State University of Medicine & Dentistry, Department of functional methods in internal medicine, ul. Delegatskaya 20/1, 127473, P: 79037709388, Fax: 74952692498, eshkolnik@mail.ru, Moscow, Russian Federation

Background
Previous experimental studies suggested beneficial effect of ESWT in patients with ischemic heart failure.
Methods
24 patients with ischemic heart failure and LVEF<40% received ESWT in addition to their stable treatment. ESWT was performed with 9 sessions with 100 shocks per spot in viable segments detected by dobutamine stress-echocardiography. Patients were evaluated at baseline, 3 and 6 months after ESWT. Tc99m MIBI SPECT was performed on inclusion and 6 months.
Results
ESWT significantly decreased NYHA class from 2.2+/-0.8 to 1.7+/-0.7 at 3 months p<0.01 and 6 months after ESWT (1.7+/-0.7). 6-minute walk test improved from 414+/-141 to 509+/-141 and 538+/-116 p<0.01 at 3 and 6 months, respectively. Steady decrease of CCS angina class from 2.6+/-0.7 to 2.1+/-0.8 and 1.9+/-0.7 p<0.01 at 3 and 6 months, respectively was observed.
Significant increase in left ventricular ejection fraction (LVEF) at rest on 3 and 6 months after ESWT (from 32.2+/-6.0 to 34.8+/-9.6 and 37.7+/-9.5 p=0.03, respectively) was noted. Summed rest score (from 23.9+/-8.1 to 21.4+/-7.1, p=0.03) and stress score improvement (from 28.2+/-8.4 to 24.6+/-6.4, p=0.04) by SPECT was registered.
Conclusions

---

* Link

Significant clinical improvement, accompanied by beneficial changes of LVEF and rest/stress perfusion was found after ESWT.
Key words: ischemic heart failure, shock wave, non-invasive angiogenesis, ejection fraction, hibernation

Abbreviations list:

ESWT = extracorporeal shock wave therapy
LVEF = left ventricular ejection fraction
SPECT = single photon emission computed tomography
MLHF = Minnesota Living with Heart Failure questionnaire
SSS = summed stress score
SRS = summed rest score

Background

About 5.8 million people in the United States have heart failure with 670,000 people diagnosed with it each year. Heart failure is associated with both high level of mortality and cost burden on health care system [1]. The left ventricular ejection fraction (LVEF) is one of the most important predictors of prognosis with substantial mortality increase below 40% [2].

S. Rahimtoola was first to show that many patients with left ventricular dysfunction exhibit improvement of ventricular function after revascularization [3]. To explain the improvement in function, the concept of dysfunctional but viable myocardium with potential to recover function after revascularization was introduced. Viable myocardium has different characteristics and these form the basis for the different imaging modalities that are most frequently used for the assessment of myocardial viability [4]. Cell membrane integrity and mitochondrial function is evaluated by ^{201}Tl and ^{99m}Tc-labeled tracer SPECT respectively, preserved glucose metabolism with ^{18}F-FDG PET, contractile reserve with dobutamine stress-echocardiography. To date there is no agreement for indication of surgical revascularization in patients with viable myocardium and heart failure [5]. Despite possible symptomatic relief and cardiac function improvement surgical treatment is limited in heart failure patients due to high incidence of major adverse events [6]. Extracorporeal shock wave therapy (ESWT) is a new noninvasive angiogenesis-based option in patients with refractory angina pectoris [7-9]. Shock wave therapy is used for decades in urology for lithotripsy. In 1990-s regenerative potential of shockwaves was discovered [10-12]. Despite the fact that exact mechanism of shockwave-induced angiogenesis is unknown it is thought to be mediated through increased production of VEGF and eNOS activation [13, 14]. Taking into account previous experimental study we have suggested beneficial effect of ESWT in patients with ischemic heart failure [15].

Methods

The Ethical committee of Moscow State University of Medicine & Dentistry approved the study protocol and informed consent form was signed by the patients.

24 stable patients (20 men; mean age 63.3±6.1) with ischemic heart failure due to documented acute myocardial infarction (at least 6 months before inclusion) and systolic dysfunction (left ventricular ejection fraction <40% calculated by echocardiography biplane Simpson method) and no planned revascularization in 6 months were included in the study. 12 patients (50,0%) had recurrent myocardial infarction in history. Two patients had previously undergone PCI. The mean duration of heart failure was 6.0 years (3.0; 12.0). 3 patients were in NYHA class I, 13 in class II, 7 in class III, and 1 in class IV. The mean duration of angina was 7.0 years (4.0; 12.0). 1 patient had no angina, 1 was

in CCS class I, 8 in class II, 11 in class III, and 3 in class IV. All patients received optimal stable treatment for heart failure including ACE-inhibitors 24 (100%), beta-blockers 23 (95,8%), aspirin 22 (91,7%), statins 13 (54,2%), prolonged nitrates 15 (62,5%), diuretics 14 (58,3%) for at least 3 months.

The patients were evaluated at baseline, 3 and 6 months with a clinical examination, quality of life assessment (Minnesota living with heart failure - MLHF), 6 minute walk test, echocardiography.

Echocardiography was performed on a Vivid 7 (GE Vingmed, Horton, Norway). The images were stored digitally and analyzed off-line by a single experienced observer. For the assessment of ejection fraction by biplane Simpson method all images were anonimized and were evaluated in a random order by an independent blinded reviewer. To measure intraobserver variability 10 randomly selected studies were evaluated twice.

Low dose dobutamine stress echocardiography was performed at an initial dobutamine dose of 5 mcg/kg/min for 3 minutes, with increase to 10, and 15, and 20 mcg/kg/min for 3 minutes each under continious electrocardiographic and echocardiographic monitoring. Beta-blockers were withdrawn 24 hours before the test. Hibernation was judged to be present if dysfunctional segments showed any improvement on 10 mcg/kg/min stage. In 14 patients (58%) there was an evidence of viability. Others showed only ischemic response.

To assess myocardial perfusion ^{99m}Tc-MIBI single photon emission computed tomography (SPECT) was performed at baseline and 6 months after the last ESWT treatment. The same camera («Entegra», General Electric, USA) was used. Two day rest-stress protocol was used with modified Bruce treadmill protocol with tracer injection on peak exercise (370 mBq). Summed stress score (SSS) and summed rest score (SRS) were calculated semi-quantitatively using a 20-segment model by a blind observer.

ESWT was performed with Cardiospec (Medispec, Germantown, USA) in a standardized protocol of 9 sessions (with 3 sessions every other day in 1, 5, and 9 week) with 100 shocks per spot per session at 0.09 mJ/mm^2 energy level in hibernated or ischemic segments detected by low dose dobutamine stress-echocardiography (Fig. 1). The maximum of 900 shocks per session were applied. Troponin T level was tested qualitatively with Roche CARDIAC TROPT sensitive assay after every third treatment session (Fig. 1).

Data is presented as mean +/-SD. Serial measurements were analyzed with repeated measures ANOVA with post-hoc Bonferroni correction. When non parametrical distribution was found the data was presented as median (25%;75%) and Wilcoxon matched pairs test was used for significance of changes before and after ESWT. Shapiro-Wilk's test was test to determine normality. All statistical tests were performed using Statistica 7.0 (Statsoft, USA). All tests were two-tailed with an alpha level of P =0.05.

The primary endpoint in the study was the change in ejection fraction by biplane Simpson method. Taking into account the 5% change as a clinically significant and 5% for standard deviation of ejection fraction the effective sample size of 17 patients will yield 80% power to detect changes.

Results

Four patients (16,6%) died during follow-up (1 from recurrent myocardial infarction 4 months after the first treatment, 1 from recurrent myocardial infarction 5 months after the first treatment, 1 from sudden death 8 months after the first treatment, and 1 from pulmonary embolism 8 months after the first treatment). One patient withdrew the study

after the first treatment week due to long distance to the hospital. Finally 19 patients were examined 6 months after the last treatment.
Treatment with ESWT significantly decreased NYHA class from 2.2+/-0.8 to 1.7+/-0.7 at 3 months p<0.01 without any worsening to 6 months after ESWT (1.7+/-0.7) (Fig. 2a). Clinical improvement was associated with significant improvement in 6-minute walk test from 414+/-141 to 509+/-141 and 538+/-116 (p<0.01) at 3 and 6 months after ESWT, respectively (Fig. 2b).
ESWT resulted in steady decrease of CCS angina class from 2.6+/-0.7 to 2.1+/-0.8 and 1.9+/-0.7 p<0.01 at 3 and 6 months after ESWT, respectively. Significant decrease of nitroglycerin use per week was observed from 2.0 (1,0;5,0) to 1.0 (0.0; 3.0) at 3 months after ESWT (p<0,01). Antianginal effect lasted up to 6 months after ESWT 1.0 (0.0; 2.0).
Significant improvement of MLHF from 35.4+/-15.7 to 27.8+/-15.1 and 28.2+/-17.0, p=0.01 was observed. Improvement in quality of life was mainly due to physical subscore: from 16,9+/-8,1 to 12.2+/-6.8 and 12.9+/-7.3 (p<0,01), respectively.
The functional improvement of ESWT-treated patients was associated with significant increase in left ventricular ejection fraction (LVEF) at rest on 3 and 6 months after ESWT (from 32.2+/-6.0 to 34.8+/-9.6 and 37.7+/-9.5 p=0.03, respectively). Intraobserver variability was 5%.
Small, but significant improvement of summed rest score by SPECT was observed (from 23.9+/-8.1 to 21.4+/-7.1 at 6 months after the last treatment, p=0.03) (Fig. 4). In patients able to exercise (modified Bruce protocol, n=12) significant improvement of summed stress score was registered (from 28.2+/-8.4 to 24.6+/-6.4 at 6 months after the last treatment, p=0.04) despite increased exercise tolerance from 4,0+/-2,2 to 4,7+/-2,4 MET (p=0,05).
ESWT was safe in our patients with ischemic heart failure. No adverse events were registered. Troponin T level was always negative (<0.1 ng/ml) in all of the patients.

Discussion

High prevalence of hibernated myocardium in patients with ischemic heart failure and limited revascularization options in this population lead to unfavorable prognosis [16-17]. 4 patients (16.7%) died during follow-up which is consistent with mortality in heart failure patients with viability on medical treatment (16%) [18]. Negative troponin T values during the treatment of these patients combined with clinical improvement of angina and prolonged time period between start of the treatment and death make the association of ESWT with deaths doubtful. The present study demonstrates that ESWT non-invasively improves left ventricular function and perfusion in patients with ischemic heart failure. Associated increase of LVEF and clinical improvement was observed early after the treatment and persisted for 6 months follow-up. To our knowledge this is the first clinical study of ESWT in heart failure population. Recently published experimental study of direct epicardial shock wave therapy showed marked improvement of LVEF and decline of NT-proBNP on a rat model of chronic heart failure [15]. Authors were able to confirm upregulation of VEGF and ESWT- induced angiogenesis in heart failure similar to previous clinical and animal studies in stable angina [13, 15]. But direct epicardial shock wave therapy can be used only in combination with CABG due to low penetration depth of unfocused shock waves. Higher energies of shock waves used in this study require additional safety confirmation. Energy levels used in our study were safe and didn't produce any damage to myocardium (confirmed by negative troponin T). Similar to other studies in refractory angina our shock wave therapy produced marked improvement of 6-minute walk test and treadmill exercise tolerance [7]. Significant improvement of

SPECT stress and rest perfusion confirms angiogenesis based mechanism of ESWT in chronic heart failure, as it was shown in several clinical studies before [7,8].

Limitations of the study

Study included limited number of patients. Due to exploratory nature this study didn't have placebo arm and was not designed for assessment of long-term safety of ESWT. But early clinical and functional improvement confirmed objectively by echocardiography and SPECT was stable for 6 months after ESWT.
However, properly powered randomized controlled trial is needed to confirm beneficial effects of ESWT in ischemic heart failure.

Conclusions

Significant clinical improvement, accompanied by beneficial changes of LVEF and rest/stress perfusion was found after ESWT. In this small trial ESWT was effective in patients with ischemic heart failure and systolic dysfunction. If safety and efficacy are confirmed in a larger randomized controlled trial ESWT may become effective addition to traditional treatment of ischemic heart failure.

Financial Disclosure:

The study was supported by research grant from Medispec, USA.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.* Circulation. 2010;121:e1-e170.
2. Volpi A, DeVita C, Franzosi G, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: results of the GISSI-2 data base. Circulation 1993;88:416-29.
3. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985;72(Suppl V):V123-V135.
4. Underwood SR, Bax JJ, vom Dahl J, et al. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. Eur Heart J 2004; 25(10):815-36.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.
6. P. Buszman Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. Am J Cardiol 2007;99:36–41
7. Y. Fukumoto et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis 17:63–70
8. Khattab AA, Brodersen B, Schuermann-Kuchenbrandt D, et al. Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol. 2007 Sep 14;121(1):84-5.

9. Kikuchi Y, Ito K., Ito Y. et al. Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris Circ J 2010; 74: 589 – 591
10. Reher P., Doan N., Bradnock B., Meghji S., Harris M.: Effect of Ultrasound on the Production of IL-8, basic FGF and VEGF. Cytokine, 11(6): 416-23. Jun 1999
11. Doan N., Reher P., Meghji S., Harris M.: In Vitro Effects of Therapeutic Ultrasound On Cell Proliferation, Protein Synthesis, and Cytokine Production By Human Fibroblasts, Osteoblasts and Momocytes. J Oral Maxillofac Surg. 57(4): 409-19; Apr 1999.
12. Young SR., Dyson M.: The Effect of Therapeutic Ultrasound On Angiogenesis. Ultrasound Med Biol., 16(3): 261-9; 1990.
13. Nishida T, Shimokawa H, Oi K et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation. 2004 Nov 9;110(19):3055-61.
14. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, Russo S, Suzuki H. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide. 2005 Mar;12(2):89-96.
15. D. Zimpfer et al. Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure. J Thorac Cardiovasc Surg 2009;137:963-70
16. Auerbach MA, Schoder H, Hoh C, et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. Circulation 1999;99:2921-6.
17. Cleland JG, Pennel D, Ray D, et al. Prevalence of hibernation and reversible ischemia in patients with heart failure due to ischemic heart disease: baseline data from the CHRISTMAS study. Eur J Heart Fail 2001; 3: S75
18. Allman KC, Shaw LJ, Hachamovitch R, Udelson Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol. 2002 Apr 3;39(7):1151-8.

Figure 1. Title – Study design.
Caption - 24 patients with ischemic heart failure and LVEF<40% received ESWT in addition to their stable treatment. ESWT was performed with 9 sessions with 100 shocks per spot in hibernated or ischemic segments detected by low dose dobutamine stress-echocardiography.

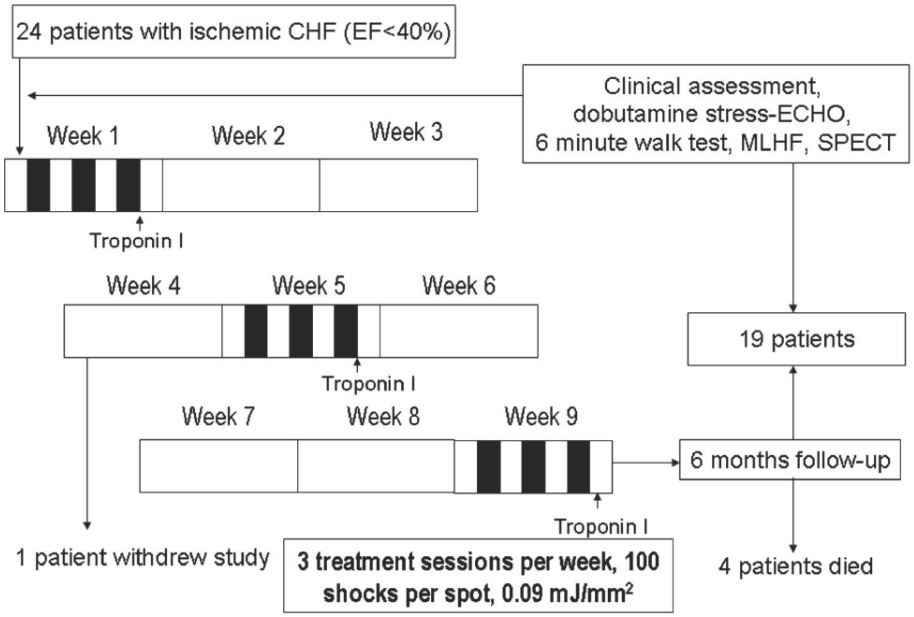


Figure 2. Title – Clinical improvement.
Caption - ESWT significantly improved NYHA class (a) and 6-minute walk test distance (b). * - P<0.01 vs. baseline.

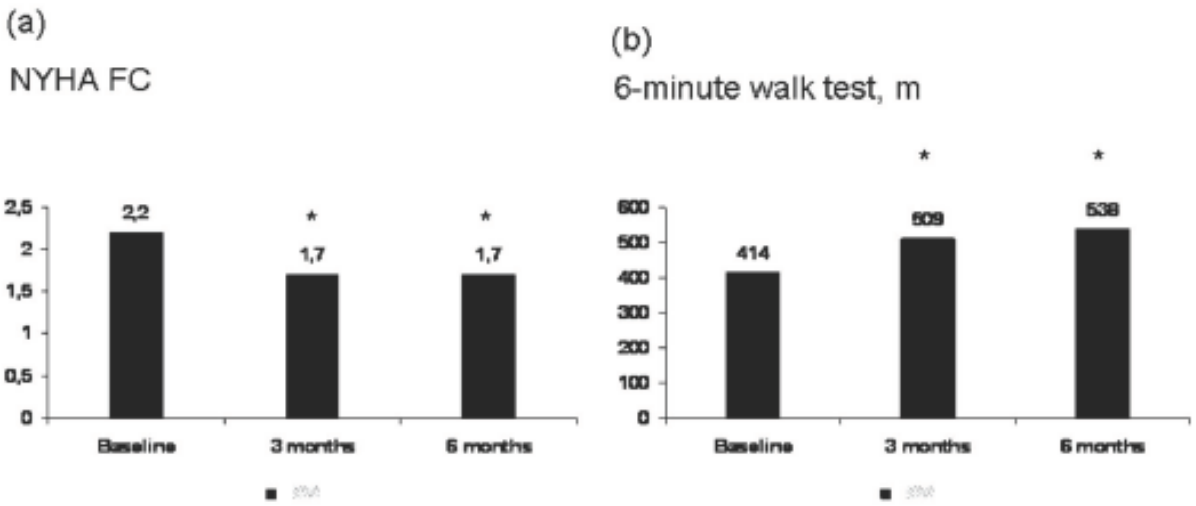


Figure 3. Title – LV function.
Caption - ESWT was associated with significant and stable increase in left ventricular ejection fraction. * - p=0.03 vs. baseline.

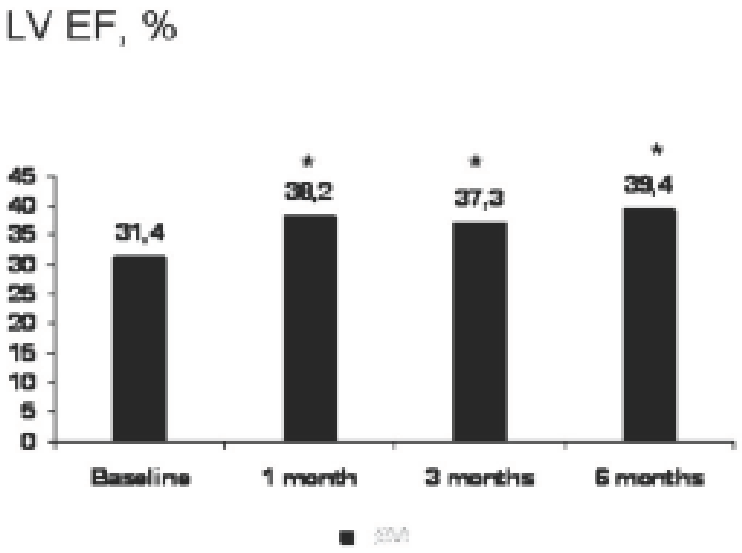
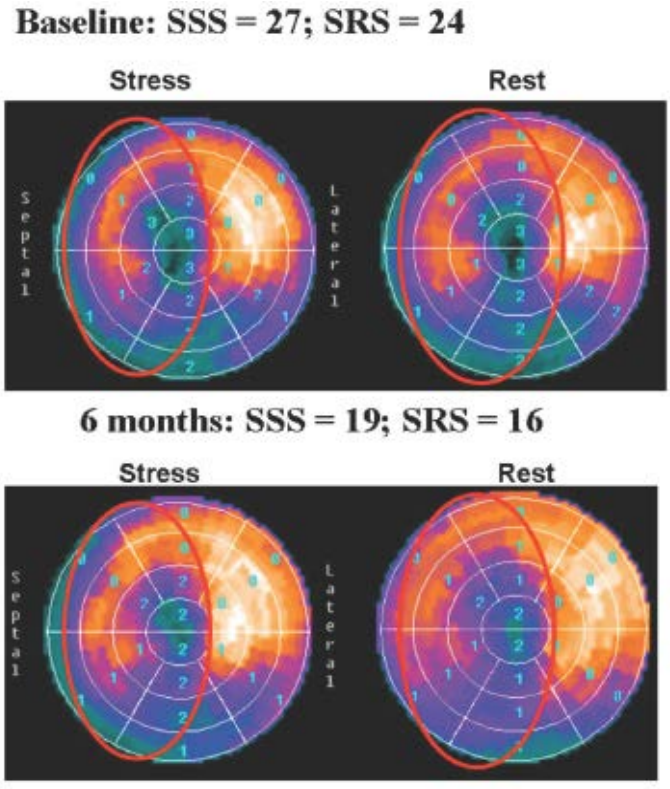


Figure 4. Title - Typical SPECT polar maps of the patient M.
Caption – Marked improvement of SSS and SRS scores was observed despite increase of exercise tolerance from 2.0 to 3.4 MET. Treated area is shown with red line.



References:

1. CURRAGE trial research group: Optimal Medical Therapy with or without PCI for Stable Coronary Disease. N Engl J Med 2007;356.
2. Kadowaki MH, Levett JM. Sympathectomy in the treatment of angina and arrhythmias. Ann Thoracic Surg 41, 1986: 572-8
3. Arora RR, Chou TM, Jain D, et al.: The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and angina episodes. J Am Coll Cardiol 1999; 33:1833-42.
4. Mannheimer C, Eliasson T, Augustinsson LE, et al.: Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. The ESBY Study. Circulation 1998; 97:1157-63.
5. Leschke M, Schoebel FC, Mecklenbeck W, et al.: Long-term intermittent urokinase therapy in patients with end-stage coronary artery disease and refractory angina pectoris: a randomized dose-response trial. J Am Coll Cardiol 1996; 27: 757-84.
6. Oesterle SN, Reifart NJ, Meier B, et al.: Initial results of laser-based percutaneous myocardial revascularization for angina pectoris. Am J Cardiol 1998; 82:659-62.
7. Henry TD, Annex BH, McKendall GR, Azrin MA, Lopez JJ, Giordano FJ, Shah PK, Willerson JT, Benza RL, Berman DS, Gibson CM, Bajamonde A, Rundle AC, Fine J, McCluskey ER; VIVA Investigators. The VIVA trial: Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. Circulation. 2003;107:1359-65.
8. Kastrup J, Jørgensen E, Rück A, Tägil K, Glogar D, Ruzyllo W, Bøtker HE, Dudek D, Drvota V, Hesse B, Thuesen L, Blomberg P, Gyöngyösi M, Sylvén C; Euroinject One Group. Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris A randomized double-blind placebo-controlled study: the Euroinject One trial. J Am Coll Cardiol. 2005;45:982-8.
9. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel HC Jr, Kormos R, Benetti F. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005;130:1631-8.
10. Wang CJ, Huang HY, Pai CH: Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg. 2002 Jan-Feb;41(1):16-22.
11. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, Yang LC: Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res. 2003 Nov;21(6):984-9 .
12. Wang CJ: An overview of shock wave therapy in musculoskeletal disorders. Chang Gung Med J. 2003 Apr;26(4):220-32.
13. Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. : Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett. 2002 Jun 5;520(1-3):153-5.
14. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, Russo S, Suzuki H. Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production. Nitric Oxide. 2005 Mar;12(2):89-96.
15. Ciampa AR, de Prati AC, Amelio E, Cavalieri E, Persichini T, Colasanti M, Musci G, Marlinghaus E, Suzuki H, Mariotto S. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett. 2005 Dec 19;579(30):6839-45. Epub 2005 Nov 28
16. Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, Matsumoto Y, Kajihara N, Eto M, Matsuda T, Yasui H, Takeshita A, Sunagawa K. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004; 110: 3055-3061
17. Umatoku T, Ito K, Kohtaro A, Oi K, Hizume T, Sunagawa K, Shimokawa H: Extracorporeal cardiac shockwave therapy improves left ventricular remodelling after acute myocardial infarction in pigs. Coron Artery Dis. 2007, 18:397-404
18. Fukumoto Y, Ito A, Uwatoku T, Matoba T, Kishi T, Tanaka H, Takeshita A, Sunagawa K, Shimokawa H. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coronary Artery Disease 2006, 17:63–70
19. Berman DS, Kiat H, Van Train K, Friedman JD, Wang FP, Germano G. Dual-isotope myocardial perfusion SPECT with rest thallium-201 and stress Tc-99m sestamibi. Cardiol Clin. 1994 May;12(2):261-70.

20. Wieneke H, Zander C, Eising EG, et al.: Non-invasive characterization of cardiac microvascular disease by nuclear medicine using single-photon emission tomography. Herz 1999; 24: 515-21.
21. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS: Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, Circulation 2002;105;539-542
22. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two dimensional echocardiography: J Am Soc Echocardiogr 1989; 2: 358-67.
23. Spertus J, Winder J, Dewhurst T, et al.: Development and evaluation of the Seattle angina questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol, 1995; 15: 333-41.
24. Gibbson RJ, Balady GJ, Beasley JW, et al: ACC / AHA guidelines for exercise testing – a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997; 30: 260-315.
25. Haupt G, Haupt A, Ekkernkamp A, et al.: Influence of shock waves on fracture healing. Endourology 1992; 39: 529-532.
26. Rompe JD, Rumler F, Hopf C, et al.: Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. Clin Orthop 1995; 321: 196-201.
27. Rompe JD, Hopf C, Kuellmer K, et al.: Low-energy extracorporeal shock wave therapy for persistent tennis elbow. Int Orthop 1996; 20: 23-27.
28. Rompe JD, Hopf C, Nafe B, et al.: Low-energy extracorporeal shock wave therapy for painful heel: A prospective controlled single-blind study. Arch Orthop Trauma Surg 1996; 115: 75-79.
29. De Sabctis M.T., Belcaro G., et al.: Effects of Shock Waves on the Microcirculation in Critical Limb Ischemia (CLI) (8 Week Study). Angiology 51 (8-2): 69-78, August 2000.
30. G. Belcaro, MR. Cesarone, M. Dugall, AD Renzo, BM. Errichi, M. Cacchio, A. Ricci, S. Stuard, E. Ippolito, F. Fano, A. Theng, M. Kasai, G. Hakim, G. Acerbi : Effects of Shock Waves on the Microcirculation, Perfusion, and Pain Management in Critical Limb Ischemia. Angiology, 56, No. 4, 403-407 (2005)
31. Keiji Oi, Yoshihiro Fukumoto, Kenta Ito, Toyokazu Uwatoku, Kohtaro Abe, Takatoshi Hizume, Hiroaki Shimokawa. Extracorporeal shock wave therapy ameliorates hind limb ischemia in rabbits. Tohoku J Exp Med. 2008 Feb ;214 (2):151-8
32. Seemann O, Rassweiler J, Chvapil M, Alken P, Drach GW. The effect of single shock waves on the vascular system of artificially perfused rabbit kidneys. kidneys. J Stone Dis. 1993 Jul;5(3):172-8