Low-Intensity Extracorporeal Shock Wave Therapy in Vascular Disease and Erectile Dysfunction: Theory and Outcomes

Ilan Gruenwald, MD,*† Noam D. Kitrey, MD,*† Boaz Appel, MD,*† and Yoram Vardi, MD*†

*Neuro-Urology Unit, Rambam Healthcare Campus, Haifa, Israel; †Department of Urology, Sheba Medical Center, Ramat-gan, Israel

DOI: 10.1002/smrj.9

ABSTRACT

Introduction. Low-intensity extracorporeal shock wave therapy (LI-ESWT) to the penis has recently emerged as a new and promising modality in the treatment of erectile dysfunction (ED).
Aim. To review the published literature on the mechanism of action of LI-ESWT; and to report our clinical data on its efficacy in men with vasculogenic ED.
Methods. A Medline search using the relevant keywords on this topic has been done.
Results. From the results of numerous preclinical and animal studies that have been done to date, sufficient evidence shows that the underlying mechanism of action of LI-ESWT is probably neovascularization. Therefore, local application of LI-ESWT to the corpora cavernosa may potentially act in the same mechanism and increase corporal blood flow. We found that the application of LI-ESWT to patients who responded to oral therapy (PDE5i) eliminated their dependence on PDE5i and they were able to successfully achieve erections and vaginal penetration (60-75%). Furthermore, PDE5i non-responders became responders and capable of vaginal penetration (72%). Additionally, LI-ESWT resulted in long-term improvement of the erectile mechanism.
Conclusions. LI-ESWT has the potential to improve and permanently restore erectile function by reinstating the penile blood flow. Although these results on LI-ESWT are promising, further multi- centered studies with longer follow-up are needed to confirm these findings. **Gruenwald I, Kitrey ND, Appel B, and Vardi Y. Stem low-intensity extracorporeal shock wave therapy in vascular disease and erectile dysfunction: Theory and outcomes. Sex Med Rev 2013;1:83–90.**

Key Words. Low-Intensity Extracorporeal Shock Waves; Erectile Dysfunction; Therapy

Introduction

Throughout the ages, masculinity and sexual function have always been strongly linked. Erectile dysfunction (ED) is considered a sign of weakness and vulnerability, and men with ED see themselves as impotent in the wide sense of the word. Hence, the impact of ED on self-esteem and self-confidence is enormous and adversely affects quality of life [1]. From a medical standpoint, improving erectile function has always been fundamental to treating these stigmata. Fortunately, the quest for improving erectile function has been quite successful. The discovery in the mid-1980s that nitric oxide (NO) production by penile nerve terminals and vascular endothelium is essential for normal erection improved our understanding of the pathophysiological processes that underlie ED [2]. This discovery also provided an explanation for the link between penile endothelial dysfunction and poor penile blood flow that occurs in atherosclerosis, diabetic vasculopathy, and diabetic neuropathy. This discovery also led to the improvement and development of therapies that specifically targeted penile endothelial cells, such as intracorporal injection of vasodilators and phosphodiesterase-5 inhibitors (PDE5is) [3]. Even so, none of these treatments addressed the problem of impaired blood supply to the corpora, and none of these therapies are curative because they do not restore corporal blood flow and/or endothelial function. Hence, the challenge in ED

management is to develop a therapeutic modality that will reinstate corporal blood flow and improve ED.

Historically, the first therapy that attempted to cure arteriogenic ED by increasing blood flow to the corpora was the surgical revascularization, a technique that was pioneered by Michal et al. in 1973 [4]. Unfortunately, surgical treatment for ED was not further developed because the results were relatively poor (effective in only about 50% of all cases), it was restricted to young men with traumatic arterial occlusion [5], and the data on long-term outcome were limited. Interestingly, a minimally invasive approach to restore corporal blood flow and cure ED has been recently developed, namely the insertion of endovascular stents in the internal pudendal artery in a group of PDE5i nonresponders of whom 50–60% have pudendal artery stenosis. Because these studies are still preliminary, more research is needed to evaluate the efficacy of this procedure and its long-term outcome [6].

Today, new experimental long-lasting treatments of ED [4] are being explored, such as regenerative medicine where (i) the damaged tissue is replaced after laboratory culturing of normal tissue or an autologous stem cell transplant, or (ii) the body's own repair mechanisms are stimulated to heal the damaged tissues. Gene therapy in which plasmids as used to deliver genetic material, such as neuromodulatory factors and brain-derived growth factors (neurotrophins), in order to alter gene expression in the penile smooth muscle, endothelial, or nerve cells is being explored as another potential therapy for ED. Detailed descriptions of these new treatments are beyond the scope of this review and can be found elsewhere [6,7].

Why Did We Choose Low-Intensity Extracorporeal Shock Wave Therapy for ED?

In modern medicine, the use of different types of energy for diagnostics and therapy is widespread. In particular, sound or shock waves (SWs) of various intensities have been used therapeutically for the last two decades in medicine. High-intensity SW therapy has revolutionized the treatment of urinary calculi, and medium-intensity SW therapy is now used for treating joint pain, tendonitis, and bursitis. Low-intensity extracorporeal SW therapy (LI-ESWT) interested us because data from both in vitro and in vivo studies have consistently shown that this energy can stimulate angiogenesis. The idea of applying LI-ESWT to the penis came from animal studies in which shockwave energy was applied to the myocardium of pigs, where it has been reported that LI-ESWT improved ischemia-induced myocardial dysfunction [8]. Extrapolating these findings to ED, we postulated that LI-ESWT of the penis would improve penile blood flow and endothelial function by stimulating angiogenesis in the corpora.

What Do We Know on the Biological Effects of Low-Intensity SWs?

SWs have two important features: they carry energy, and they are able to propagate through a medium. SWs are a sequence of single sonic pulses and are characterized by a fast pressure rise (<10 nanoseconds), a high-pressure peak (100 MPa), and a short lifecycle (10 microseconds) [9]. When SWs are noninvasively focused on an organ or tissue, their energy creates a high-pressure load that only affects the targeted area.

Although the underlying mechanism of their biological action is not completely understood, it is theorized that the tissue is first compressed due to the positive pressure from the energy that is carried by the SW and then expands due to the tensile properties of the tissue [10]. Nishida described this phenomenon as a cavitation because it resembled a micrometer-sized violent collapse of bubbles. Because the physical forces that are generated by cavitation are highly localized, it is thought that SW induces a localized stress on cell membranes in the same way that shear stress affects endothelial cell membranes [11]. This shear stress then triggers a chain of events that cause the release of angiogenic factors, such as increased local NO production through the increased activity of endothelial NO synthase (eNOS) and neuronal NOS (nNOS), platelet-derived growth factor, and vascular endothelial growth factor (VEGF) [12]. In addition to this effect, SWs have been reported to cause membrane hyperpolarization, activation of the Ras signaling pathway [13], non-enzymatic synthesis of NO [14], and induction of stress fibers and intercellular gaps [15].

LI-ESWT: In Vitro and Animal Studies

Wang and his colleagues studied the biological effects of low-intensity SWs (LISWs) extensively [16] and discovered that LISW stimulates endothelial cell proliferation with the expression

of eNOS, VEGF, and proliferating cell nuclear antigen. The angiogenic markers increased after 1 week and continued to rise for 8 weeks, while the processes of neovascularization and cell proliferation started 4 weeks and persisted for more than 12. The same group also reported that LI-ESWT stimulated neovascularization of the tendon-bone junction in dogs [17] and rabbits [16]. LISW can elevate VEGF and VEGF-messenger RNA levels in human umbilical vein endothelial cells as well [8], and it improves angiogenesis, blood flow, and wound repair in nude mice with experimental burns [18].

Stem cells and progenitor cells have the ability to divide and differentiate into specialized cell types. Their pivotal role in the neovascularization of ischemic tissues was widely studied in recent years. LISW affect stem cell recruitment in tissue repair. Chen et al. [19] studied the changes in cell morphology and histology in healing bones of rats following LI-ESWT. They showed that LI-ESWT increased the number of mesenchymal stem cells (MSCs) in the defect, which later differentiated into osteoblasts and chondrocytes. LI-ESWT significantly increased the expressions of growth factors (transforming growth factor β1 and VEGF-A), which have a chemotactic and mitogenic role in the repair process. Aicher et al. [20] investigated the effect of LI-ESWT on the attraction of human autologous circulating progenitor cells (CPCs) in rats with induced chronic ischemia. LISW-treated ischemic muscles attracted significantly more labeled CPCs than the untreated muscles, and the treatment significantly increased the blood flow in the ischemic muscles.

Nishida and colleagues [8] investigated the effects of LI-ESWT in pigs with experimentally induced chronic myocardial ischemia and found that LI-ESWT significantly upregulated VEGF expression in ischemic myocardium. It improved regional myocardial blood flow and left ventricular (LV) ejection fraction. This beneficial effect of LI-ESWT on LV remodeling has also been demonstrated in studies that involved pigs with experimentally induced myocardial infarction [21] and myocardial ischemia-reperfusion injury [22].

The effect of the LI-ESWT on the erectile tissue has only recently been studied. Qiu et al. [23] investigated the effects of LI-ESWT on erectile function in diabetes mellitus rats using a protocol that is similar to the one used to treat men with ED. According to the changes in the intracavernous pressure following electrostimulation of the cavernous nerve to assess erectile function, they found that erectile function was significantly decreased in all diabetic rats and that this effect was less in the LI-ESWT group. Histologically, they found much less nNOS-containing nerves in the dorsal nerves of the penis, around the dorsal arteries, and in the corpora cavernosa. nNOS-containing nerves, endothelial and smooth muscle cells, and MSCs were more abundant in the LI-ESWT group. Such findings support the notion that the mechanism of the therapeutic action of LI-ESWT is the recruitment of MSC, which was postulated by Chen et al. [19].

The Effect of LI-ESWT in Humans

Two well-designed studies have informed on positive effects of LI-ESWT in human patients with severe ischemic heart disease. In the first study, Kikuchi et al. [24] reported that LI-ESWT improved the LV ejection fraction and stroke volume in eight patients, as well as significantly ameliorating the severity of the chest pain after a 6-minute walk. Yang et al. [25] have also reported that LI-ESWT ameliorated the severity of angina pectoris and ischemic heart failure assessments in 25 patients with coronary heart disease. Comparable results have also been reported by Vasyuk et al. [26], Wang et al. [27] and Zimpfer et al. [28] in patients with severe coronary artery disease and refractory angina to whom LI-ESWT was applied. Other reports on the capability of LI-ESWT to heal and repair ischemic wounds were published. Larking et al. [29] examined the effect of LI-ESWT on 16 static chronic ulcers in a placebo-controlled study on a group of patients with complex neurological disabilities. They showed a clear improvement in wound healing and a significant difference compared with placebo after 3 weeks of treatment. A review published on the healing effect of LI-ESWT on chronic ischemic wounds [30] reports very positive results on a wide range of ischemic wounds and ulcers with success rates ranging from the lowest success rate of 36% in venous stasis wounds to 66.7% in decubital ulcers to 100% in burn wounds. In the same publication, they report on success rates of LI-ESWT from nine studies published in peer-reviewed journals on a total of more than 550 patients with chronic soft tissue wounds ranging from 25% [31] to 100% [32].

How Is LI-ESWT Used to Treat ED?

The protocol of LI-ESWT that we selected was based on the accumulated clinical experiences in

which LI-ESWT was used in patients with cardiovascular disease. The protocol required modifications because one of the challenges was to apply LISWs to the whole area of the corpora cavernosa including the crus. Another challenge was to adapt the SW delivery probe to the penis' anatomy because the corpora cavernosa lies immediately under the penile skin. Our final protocol consisted of two treatment sessions per week for three successive weeks, followed by a 3-week no-treatment period, and a repeated twice-weekly treatment session of 3 weeks. After stretching the penis, LISWs (300 SWs/treatment point and 1,500 SWs/session) were applied to three points along the penile shaft and two over the crus at an intensity of 0.09 mJ/mm^2 and a frequency of 120 shocks/minute for about 3 minutes at each point. A water-based gel was spread on and around the penis just before starting the treatment.

The SW Device

For all treatment sessions, LISWs were generated and delivered by an extracorporeal shockwave generator (Omnispec ED1000, Medispec Ltd., Germantown, MD, USA), which is a compact electrohydraulic SW generator with a focused SW source. This device's spark voltage is 10–24 kV and is able to provide SWs with a focal penetration depth of 180 mm and a focal width of 24 mm.

Which Patients Were Eligible for LI-ESWT?

In our studies, only patients who had ED for more than 6 months and were sexually active in a stable heterosexual relationship for more than 3 months were considered for inclusion. Their International Index of Erectile Function questionnaire—Erectile Function (IIEF-EF) domain score had to be below 20, and at least 50% of their sexual intercourse attempts were unsuccessful. Additional inclusion criteria depended on the specific aims of the study (PDE5i responders, PDE5i non-responders, and patients who have had a radical prostatectomy—see Table 1). General exclusion criteria would include ED patients with a neurological pathology, an unstable medical or psychiatric condition, pelvic surgery (other than prostatectomy), or patients who had a spinal cord injury. Patients with an anatomical abnormality of their penis, cancer, or with a cardiovascular condition that prevented normal sexual activity were also excluded.

Evaluation and Outcome Measures

At screening, all patients were thoroughly interviewed about their medical and sexual history and underwent a complete physical examination. The total IIEF questionnaire, the Erection Hardness Scale, the Quality of Erection, the Self-Esteem and Relationship questionnaires, and the Clinical Global Impression of Change rating scale were used to subjectively determine the sexual function of each patient. Objective evaluation parameters included measurement of penile blood flow and endothelial function using plethysmography in all studies, nocturnal penile tumescence (NPT) in some studies, and Doppler ultrasonography to ascertain the cause of ED. All indices of sexual and penile function were obtained before and at least 1 month after LI-ESWT, as well as at 3, 6, 12, 18, and 24 months after treatment completion.

LI-ESWT for ED: Clinical Studies and Results

The aim of our first study was to evaluate the feasibility, efficacy, and safety of LI-ESWT in 20 selected middle-aged men with mild-to-moderate vasculogenic ED [33] who were PDE5i responders. One month after LI-ESWT, erectile function improved in 15 men. The average increase in the IIEF-EF domain score was 7.4 (13.5–20.9, $P = 0.001$). Specifically, the IIEF-EF domain score

Table 1 Study trials

- The Effect of Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction (ED)—Pilot [33]
- The Effect of Low-Intensity Extracorporeal Shock Wave Therapy on Men with ED Who Respond to PDE5 Inhibitors (PDE5i)—a Double-Blind Placebo-Controlled [35]
- The Effect of Low-Intensity Extracorporeal Shockwave Therapy on Men with ED Who Did Not Respond to PDE5i—Pilot [34]
- Low-Intensity Shock Wave Therapy on Men with ED Who Are Nonresponders to PDE5i—a Double-Blind Placebo-Controlled Study (ongoing—ClinicalTrials.gov Identifier NCT01262157)
- The Effect of Low-Intensity Extracorporeal Shock Wave Therapy on Men with ED Who Respond to PDE5i—a Double-Blind Placebo-Controlled Multicenter Study (ongoing—ClinicalTrials.gov Identifier NCT01274923)
- Low-Intensity Extracorporeal Shock Wave Therapy for the Treatment of ED—a 4-Arm Comparator Study (between different new treatment protocols) (ongoing—ClinicalTrials.gov Identifier NCT01442077)

in 15 men increased by more than 5 points and by more than 10 points in seven men. Five men did not respond to LI-ESWT. Ten men reported that they had erections that were sufficiently rigid for vaginal penetration without PDE5i support. In the 15 men who responded to LI-ESWT, all NPT parameters improved as recorded by significant increases in the duration of the erections and penile rigidity. Finally, penile blood flow and endothelial function in these 15 men had improved significantly at the 1-month follow-up examination.

The aim of our second study was to investigate whether LI-ESWT could convert PDE5i nonresponders to PDE5i responders and enable them to achieve vaginal penetration with oral PDE5i therapy. To this end, we investigated the effect of LI-ESWT in 29 men with severe ED, who had multiple cardiovascular risk factors (23), cardiovascular disease (11), and diabetes mellitus (14), and were PDE5i nonresponders [34]. When these men started the study, the average IIEF-EF domain score was 8.8 ± 1 (with PDE5i). Three months after the completion of LI-ESWT, while using PDE5i, the IIEF-EF domain scores improved by at least 5 points in 76%, and the mean IIEF-EF domain score increased to 18.8 ± 1. At the end of the study, eight men achieved normal erections; their IIEF-EF domain score were greater than 25. Overall, 21 of the 29 men were converted to PDE5i responders. Penile blood flow and endothelial function significantly improved ($P = 0.0001$) in the men who responded to LI-ESWT. A significant correlation between the subjective assessment of sexual function using validated sexual function questionnaires and the objective measures of penile blood flow and endothelial function was found in the two studies. None of the men in the two studies reported treatment-associated pain or any adverse events during or after the treatment.

In view of the reassuring results from these first two studies, we then conducted a prospective, randomized, double-blind, sham-controlled study on 60 men with ED [35]. In this study, we found that mean IIEF-EF scores of the treated men were significantly higher than those of the sham-treated men. This increase was also accompanied by improvement in penile and cavernosal blood flows and penile endothelial function.

In order to establish the overall success rate of LI-ESWT, we then analyzed the data from all the study patients who participated in the different clinical trials and for whom we had follow-up data for at least 6 months (Table 1). This cohort comprised 184 patients of which 127 were PDE5i responders and 57 were PDE5i nonresponders with the following characteristics: their mean age was 58.5 years, their mean ED duration was 65.2 months, 51% had severe ED, 37% had moderate ED, and 12% had mild-to-moderate ED according to their IIEF-EF domain scores, 54.3% had cardiovascular risk factors, and 35.3% had diabetes mellitus. The mean IIEF-EF domain scores improved after LI-ESWT by 7 points with the greatest increase occurring in the men with severe ED (Figure 1). We also found that the increases in the IIEF-EF domain scores in the men who were PDE5i nonresponders were higher than those men who were PDE5i responders (Δ 7.52 vs. Δ 5.7 points, $P = 0.04$).

From this group of 184 men, we had data from the 1-year follow-up evaluation for 86 patients. When we compared 6-month and 12-month follow-up IIEF-EF domain scores of these 86 ED patients, we found that the scores had slightly

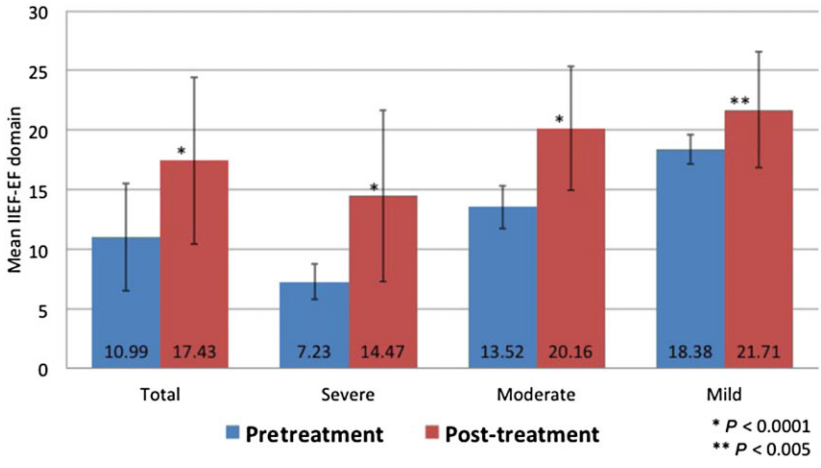

Figure 1 Improvement in International Index of Erectile Function—Erectile Function domain scores from baseline according to severity

increased (17.2 vs. 19.9, $P < 0.01$). We also compared the success of therapy of the treated patients to those who were given the placebo: success, which was defined by an at least 5-point change in the IIEF-EF domain score, occurred in 56% of the treated group, whereas success occurred in only 18% of the placebo-treated men ($P < 0.001$). Because LI-ESWT involves an intense interaction between the patient and the attending physician or nurse, a relatively high placebo effect could be expected. The success rate in 38 men with ED who received the sham-treatment protocol in our study was 21%. This result is less than the 20–35% success rate that is reported in men with ED and pharmacological treatment in other published placebo-controlled studies [36–38].

We are also investigating whether a second round of penile LI-ESWT in patients with ED whose first round of penile LI-ESWT was unsuccessful would be therapeutically beneficial. In this ongoing study, we are witnessing clinical improvements in some of these patients, but analyzed data on both objective and subjective parameters are not yet finalized at this time.

Discussion

After more than a decade of wide experience with oral therapies for ED, it has become evident that PDE5is improve erections but do not treat the underlying mechanism. Undoubtedly, the dependence on drugs for sexual function has its limitations, and a search for a better treatment is the next step in ED management. Although investigations in this direction, such as stem cell therapy or gene therapy are ongoing, no significant progress has yet been made and an ED cure is still being sought. When any new and unconventional therapeutic modality is introduced, it is prone to skepticism and criticism, especially when its mechanism of action is not fully understood and scientifically recognized. This doubt is particularly true when all the published clinical results originate from only one center and the total number of evaluated patients is relatively low. Doubts about any new and controversial therapy can be overcome by conducting larger scale multicenter studies in order to reach conclusive data. Some abstracts have already been published [39–41], and hopefully, this is just the beginning of more studies to come. Although efficacy and safety of LI-ESWT were established in our studies, our protocol was nonstandardized and empirical. Accordingly, information about the optimal treatment protocol, the best anatomical locations to apply the probes, and the amount of energy that needs to be applied at each treatment session still needs to be obtained. We also still do not know which clinical parameters could be used to predict which ED patients would most benefit from LI-ESWT. Finally, there is insufficient data on the mechanism of action of LI-ESWT at the cellular level, a crucial area of further investigation.

In our studies, we have done our best to use strict scientific methodology to collect accurate subjective data from our study population and objective measures in order to validate the efficacy and safety of LI-ESWT in ED. We are also fully aware of the limitations of each of our studies, be it a pilot study or a one-arm comparative study with a small cohort. On the other hand, we have also presented data from well-designed, double-blind, sham-controlled, randomized studies and from a multicenter trial, and the results of these studies are consistent and promising.

Using objective measures, we have shown that LI-ESWT significantly improves penile blood flow and endothelial function, and found that these improvements are positively correlated with the subjective measures of erectile function. These findings, as well as the affirmative reports of improved erection on follow-up visits after LI-ESWT, convey very encouraging indications of treatment success.

Some of the data that we recently collected from patients with 1-year follow-up data after LI-ESWT are reassuring. From their reports, the beneficial effects of LI-ESWT have not diminished or waned. Moreover, some even reported a continual improvement in their erections with time. We would like to emphasize that all our collected data were consistently positive even though they were collected from different studies, with different cohorts, a wide range of ED severity, and a variety of cardiovascular diseases and risk factors. This reproducibility of therapeutic benefit of LI-ESWT in ED adds another layer of evidence that the physiological effect of this unique treatment modality is genuine.

Although our results on the use of LI-ESWT are encouraging, more data from extensive research at both the basic and clinical levels and from other independent studies need to be accumulated before we include this treatment modality in the armamentarium of therapies for ED.

Summary

LI-ESWT is a new therapeutic option for rehabilitating the erectile mechanism and restoring erectile function in men with vasculogenic ED. The main characteristic of this revolutionary treatment is its potential to restore erectile function in these patients without any side effects and the need for a PDE5i. Because of its unique mechanism of action, LI-ESWT could be used to amplify the partial response to current treatments. Finally, LI-ESWT could also be used to prevent the progression of ED. With the acquisition of new knowledge on LI-ESWT, we anticipate that that this novel therapy will be widely used in the future in the clinical management of ED.

Acknowledgment

The authors wish to thank Dr. Arieh Bomzon, ConsulWrite (http://www.consulwrite.com) for his editorial assistance in preparing the manuscript.

Corresponding Author: Yoram Vardi, MD, Neuro-Urology Unit, Rambam Healthcare Campus, Haifa 31096, Israel. Tel: 00972-4-542819; Fax: 00972-4-8542883; E-mail: yvard@rambam.health.gov.il

Statement of Authorship

Category 1

(a) Conception and Design
Ilan Gruenwald; Noam D. Kitrey; Boaz Appel

(b) Acquisition of Data
Ilan Gruenwald; Noam D. Kitrey; Boaz Appel

(c) Analysis and Interpretation of Data
Ilan Gruenwald; Noam D. Kitrey; Boaz Appel

Category 2

(a) Drafting the Article
Ilan Gruenwald; Noam D. Kitrey

(b) Revising It for Intellectual Content
Ilan Gruenwald; Noam D. Kitrey; Yoram Vardi

Category 3

(a) Final Approval of the Completed Article
Ilan Gruenwald; Noam D. Kitrey; Yoram Vardi

References

1 Althof SE. Quality of life and erectile dysfunction. Urology 2002;59:803–10.
2 Burnett AL, Lowenstein CJ, Bredt DS, Chang TS, Snyder SH. Nitric oxide: A physiologic mediator of penile erection. Science 1992;257:401–3.
3 Jonas U. The history of erectile dysfunction management. Int J Impot Res 2001;13(3 suppl):S3–7.
4 Michal V, Kramár R, Pospíchal J, Hejhal L. Direct arterial anastomosis on corpora cavernosa penis in the therapy of erective impotence. Rozhl Chir 1973;52:587–90.
5 Dicks B, Bastuba M, Goldstein I. Penile revascularization-contemporary update. Asian J Androl 2013;15:5–9.
6 Shamloul R, Ghanem H. Erectile dysfunction. Lancet 2012;381:153–65.
7 Hakim L, Van der Aa F, Bivalacqua TJ, Hedlund P, Albersen M. Emerging tools for erectile dysfunction: A role for regenerative medicine. Nature reviews. Urology 2012;9:520–36.
8 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;110:3055–61.
9 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;579:6839–45.
10 Apfel RE. Acoustic cavitation: A possible consequence of biomedical uses of ultrasound. Br J Cancer Suppl 1982;5:140–6.
11 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.
12 Traub O, Berk BC. Laminar shear stress: Mechanisms by which endothelial cells transduce an atheroprotective force. Arterioscler Thromb Vasc Biol 1998;18:677–85.
13 Wang FS, Wang CJ, Huang HJ, Chung H, Chen RF, Yang KD. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochem Biophys Res Commun 2001;287:648–55.
14 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.
15 Seidl M, Steinbach P, Wörle K, Hofstädter F. Induction of stress fibres and intercellular gaps in human vascular endothelium by shock-waves. Ultrasonics 1994;32:397–400.
16 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;21:984–9.
17 Wang CJ, Huang HY, Pai CH. Shock wave-enhanced neovascularization at the tendon-bone junction: An experiment in dogs. J Foot Ankle Surg 2002;41:16–22.
18 Goertz O, Lauer H, Hirsch T, Ring A, Lehnhardt M, Langer S, Steinau HU, Hauser J. Extracorporeal shock waves improve angiogenesis after full thickness burn. Burns 2012;38:1010–8.
19 Chen Y-J, Wurtz T, Wang C-J, Kuo YR, Yang KD, Huang HC, Wang FS. Recruitment of mesenchymal stem cells and expression of TGF-beta 1 and VEGF in the early stage of shock wave-promoted bone regeneration of segmental defect in rats. J Orthop Res 2004;22:526–34.
20 Aicher A, Heeschen C, Sasaki K-I, Urbich C, Zeiher AM, 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.
21 Uwatoku T, Ito K, Abe K, Oi K, Hizume T, Sunagawa K, Shimokawa H. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs. Coron Artery Dis 2007;18:397–404.
22 Ito Y, Ito K, Shiroto T, Tsuburaya R, Yi GJ, Takeda M, Fukumoto Y, Yasuda S, Shimokawa H. Cardiac shock

wave therapy ameliorates left ventricular remodeling after myocardial ischemia-reperfusion injury in pigs in vivo. Coron Artery Dis 2010;21:304–11.
23 Qiu X, Lin G, Xin Z, Ferretti L, Zhang H, Lue TF, Lin CS. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med 2013;10:738–46.
24 Kikuchi Y, Ito K, Ito Y, Shiroto T, Tsuburaya R, Aizawa K, Hao K, Fukumoto Y, Takahashi J, Takeda M, Nakayama M, Yasuda S, Kuriyama S, Tsuji I, Shimokawa H. 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.
25 Yang P, Guo T, Wang W, Peng YZ, Wang Y, Zhou P, Luo ZL, Cai HY, Zhao L, Yang HW. Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. Heart Vessels 2013;28:284–91.
26 Vasyuk YA, Hadzegova AB, Shkolnik EL, Kopeleva MV, Krikunova OV, Iouchtchouk EN, Aronova EM, Ivanova SV. Initial clinical experience with extracorporeal shock wave therapy in treatment of ischemic heart failure. Congest Heart Fail 2010;16:226–30.
27 Wang Y, Guo T, Ma T-K, Cai HY, Tao SM, Peng YZ, Yang P, Chen MQ, Gu Y. A modified regimen of extracorporeal cardiac shock wave therapy for treatment of coronary artery disease. Cardiovascular Ultrasound 2012;10:35–35.
28 Zimpfer D, Aharinejad S, Holfeld J, Thomas A, Dumfarth J, Rosenhek R, Czerny M, Schaden W, Gmeiner M, Wolner E, Grimm M. Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure. J Thorac Cardiovasc Surg 2009;137:963–70.
29 Larking AM, Duport S, Clinton M, Hardy M, Andrews K. Randomized control of extracorporeal shock wave therapy versus placebo for chronic decubitus ulceration. Clin Rehabil 2010;24:222–9.
30 Mittermayr R, Antonic V, Hartinger J, Kaufmann H, Redl H, Téot L, Stojadinovic A, Schaden W. Extracorporeal shock wave therapy (ESWT) for wound healing: Technology, mechanisms, and clinical efficacy. Wound Rep Reg 2012;20: 456–65.
31 Saggini R, Figus A, Troccola A, Cocco V, Saggini A, Scuderi N. Extracorporeal shock wave therapy for management of chronic ulcers in the lower extremities. Ultrasound Med Biol 2008;34:1261–71.
32 Schaden W, Thiele R, Kölpl C, Pusch M, Nissan A, Attinger CE, Maniscalco-Theberge ME, Peoples GE, Elster EA, Stojadinovic A. Shock wave therapy for acute and chronic soft tissue wounds: A feasibility study. J Surg Res 2007;143: 1–12.
33 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.
34 Gruenwald I, Appel B, 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;9:259–64.
35 Vardi Y, Appel B, Kilchevsky A, Gruenwald I. 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. J Urol 2012;187:1769–75.
36 Stuckey BGA, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F, Manzano P, Deerochanawong C. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: Results of a randomized controlled trial. Diabetes Care 2003;26:279–84.
37 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338:1397–404.
38 Lewis RW, Sadovsky R, Eardley I, O'Leary M, Seftel A, Wang WC, Shen W, Walker DJ, Wong DG, Ahuja S. The efficacy of tadalafil in clinical populations. J Sex Med 2005;2:517–31.
39 Hisasue SI, Ide H, China T, Isotani S, Muto S, Yamaguchi R, Horie S. Initial experience of low energy shockwaves for the treatment of erectile dysfunction in Teikyo University Hospital, Japan. J Mens Health 2011;8:211.
40 Srinivas BV, Vasan SS. A paradigm shift in the management of erectile dysfunction: efficacy of low intensity extracorporeal shock wave therapy. The 22nd annual conference of the South Zone USI (SZUSICON-2011). Mahabalipuram, India; 2011.
41 Vasan SS, Srinivas BV. Erectile dysfunction shock wave therapy—a new treatment modality in the management of erectile dysfunction: patient selection and optimizing strategies. 13th Biennial Meeting of the Asia Pacific Society for Sexual Medicine (APSSM). Kaohsiung, Taiwan; 2011.