THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

ERECTILE FUNCTION

# Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial

Dimitrios Kalyvianakis, MD, FECSM, and Dimitrios Hatzichristou, MD, PhD, FECSM

## ABSTRACT

**Background:** Although several reports have documented the subjective improvement of erectile function after low-intensity extracorporeal shockwave therapy (LI-ESWT) in patients with vasculogenic erectile dysfunction (ED), objective assessment data of penile hemodynamics are lacking.

**Aim:** To assess penile hemodynamics before and 3 months after LI-ESWT in a group of patients with documented vasculogenic ED.

**Methods:** This was a double-blinded, randomized, sham-controlled trial. Forty-six patients with ED were randomized; 30 underwent LI-ESWT and 16 had a sham procedure in double-blinded fashion. All patients underwent penile triplex ultrasonography by the same investigator immediately before and 3 months after treatment. Patient demographics, International Index of Erectile Function erectile function domain (IIEF-ED) score, and minimal clinically important difference were assessed at baseline and 1, 3, 6, 9, and 12 months after treatment.

**Outcomes:** Changes in peak systolic velocity and resistance index as measured by triplex ultrasonography at baseline and 3 months after treatment were the main outcomes of the study. Secondary outcomes were changes in the IIEF-EF score from baseline to 1, 3, 6, 9, and 12 months after treatment and the percentage of patients reaching a minimal clinically important difference during the same period for the two groups.

**Results:** IIEF-EF minimal clinically important differences for the active vs sham group were observed for 56.7% vs 12.5% ($P = .005$) at 1 month, 56.7% vs 12.5% ($P = .003$) at 3 months, 63.3% vs 18.8% ($P = .006$) at 6 months, 66.7% vs 31.3% ($P = .022$) at 9 months, and 75% vs 25% ($P = .008$) at 12 months. Mean peak systolic velocity increased by 4.5 and 0.6 cm/s in the LI-ESWT and sham groups, respectively ($P < .001$).

**Clinical Implications:** Such results offer objective and subjective documentation of the value of this novel treatment modality for men with vasculogenic ED.

**Strengths and Limitations:** Strengths include the prospective, randomized, sham-controlled type of study and the assessment of penile hemodynamics. Limitations include the small sample and strict inclusion criteria that do not reflect everyday clinical practice.

**Conclusion:** The present study confirms the beneficial effect of LI-ESWT on penile hemodynamics and the beneficial effect of this treatment up to 12 months. **Kalyvianakis D, Hatzichristou D. Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial. J Sex Med 2017;14:891−897.**



**Key Words:** Low-Intensity Shockwave Therapy; Erectile Dysfunction; Peak Systolic Velocity; Penile Doppler

## INTRODUCTION

Several treatment effective options are available for vasculogenic erectile dysfunction (ED); phosphodiesterase type 5 (PDE5) inhibitors and intracavernosal injections are effective and safe vasodilating agents.[1] The main disadvantage of currently available pharmacotherapy is the inability to alter the underlying predominant pathology in patients with vasculogenic ED (eg, cavernosal artery insufficiency). Furthermore, PDE5 inhibitors might be contraindicated or should be used with caution in some patients.[2]

Low-intensity extracorporeal shockwave therapy (LI-ESWT) has shown encouraging results for patients with ischemic heart

Received December 13, 2016. Accepted May 19, 2017.

Center for Sexual and Reproductive Health, Aristotle University of Thessaloniki Greece, Thessaloniki, Greece



http://dx.doi.org/10.1016/j.jsxm.2017.05.012

disease,[3] chronic diabetic foot ulcers, or wound healing.[4,5] Basic research has shown that low-intensity shockwaves act by provoking microtrauma in the endothelium of the helicine arteries, leading to the release of angiogenic factors, such as nitric oxide synthase and vascular endothelial growth factor, and endothelial cell proliferation factors, such as proliferating cell nuclear antigen.[6,7]

Recent sham-controlled clinical trials have reported subjective improvement in erectile function and systemic endothelial function measured by nocturnal penile tumescence and flow-mediated dilatation, respectively.[8–10] However, most of the published studies did not assess penile hemodynamics. The purpose of the study was to assess penile hemodynamics before and after LI-ESWT and subjective long-term improvement of erectile function.

## METHODS

We recruited men who a history of vasculogenic ED for at least 6 months. Diagnosis was based on sexual and medical history, clinical examination, and laboratory test results. Eligible subjects were at least 18 years old, had ED for at least 6 months, and were at least partial responders to PDE5 inhibitors (able to penetrate at least half the time while taking a PDE5 inhibitor). For inclusion in the study, after a 4-week washout period, the baseline International Index of Erectile Function erectile function domain (IIEF-EF) score had to be at least 6 (mild to moderate ED) to 21 (moderate and severe ED). Patients with no ED or with mild ED were excluded. All subjects had been in a stable heterosexual relationship with the same partner for more than 3 months. The exclusion criteria were radical prostatectomy; psychogenic ED; penile anatomic abnormalities; neurogenic ED; hormonal abnormalities; antiandrogen therapy; history of heart attack, stroke, or life-threatening arrhythmia within 6 months before enrollment in the study; and recovery from any cancer within the past 5 years. All patients accepted and signed the informed consent form for the study, which was approved by the institutional review board.

### Study Sample

Sample size calculation was based on a difference of at least 3.5 in changes from baseline to month 12 in IIEF-EF score between the study groups, with 80% power and 5% statistical significance. The calculation assumes a common SD of the change of 3.5 and a ratio of 2:1 between the groups. A two-group t-test with a 0.05 two-sided significance level would have 80% power to detect the difference of at least 3.5 in IIEF-EF score between groups when the sample sizes were 15 for the sham group and 30 for the active treatment group.

### Study Protocol

The study consisted of the following phases. The screening phase included a 4-week run-in phase of using PDE5 inhibitors to identify at least partial response to PDE5 inhibitors. Subjects who met the inclusion criteria underwent a 4-week PDE5 inhibitor washout period and completed the IIEF questionnaire, and data were selected by a research assistant. At the end of the washout phase, eligible patients underwent triplex ultrasonography of the cavernosal arteries by the same investigator to assess penile hemodynamics.[11] All patients were blindly randomized to one of two active treatment groups or to a sham control group. The groups were marked as A, B, and C, two of which indicated active treatment groups and one of which indicated a sham control group. The treatment protocol was applied by two investigators in double-blinded fashion and included biweekly treatment sessions at the first, second, third, seventh, eighth, and ninth weeks after the washout period, for a total of 12 treatments (sessions). All patients underwent penile triplex ultrasonography by the same investigator at baseline and 3 months after treatment. Side effect profile was assessed at every visit during the treatment period, and the IIEF score was assessed before and at 1, 3, 6, 9, and 12 months after treatment (Figure 1).

### Blinding and Randomization

Study procedures were identical for the active treatment and sham control groups, but the sham treatment was conducted using a distinctively designed shockwave applicator. The sham shockwave applicator contained an element that blocked delivery of shockwaves. The two types of shockwave applicator (active and sham) looked identical. All patients were blindly randomized using specific computer software into one of two active treatment groups or into a sham control group in a 2:1 ratio, respectively.

### LI-ESWT Methodology

We applied a standard commercial gel normally used for sonography on the subject's penis and on the membrane of the shockwave applicator. The treatment included a standard protocol of 300 shocks to each treatment location (three locations on the penile shaft and two locations on the penile crura for a total of 1,500 shocks) using a specialized focused shockwave probe (Omnispec ED1000, Medispec Ltd, Yehud, Israel) as described in previous studies.[9,10] The treatment was performed at an energy intensity of 0.09 mJ/mm$^2$; the energy level was automatically predetermined by the device. The treatment was performed at an energy intensity of 0.09 mJ/mm$^2$ and frequency of 160 pulses/min. Each treatment session lasted approximately 20 minutes without local or systemic analgesia.

### Penile Triplex Ultrasonography Protocol

Penile triplex ultrasonography was performed (BK Flex Focus 400, BK Ultrasound, Peabody, MA, USA) to assess penile hemodynamics at baseline and 3 months after the final LI-ESWT treatment. The test was performed as follows: 0.5 mL of vasoactive agent (tri-mix solution) was injected into the corpus cavernosum and the time of injection was recorded. Then, the ultrasound B-mode probe was placed on the left and right