

## 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,<sup>\*,†</sup> 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  $\pm$  SEM  $6.7 \pm 0.9$  vs  $3.0 \pm 1.4$ ,  $p = 0.0322$ ). 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

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.<sup>1</sup> Gene and stem cell therapies are current examples of treatment strategies whose therapeutic goals are to restore erec-

### 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.

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tile function as part of the present trend to shift the field of ED treatments away from on demand palliative treatments.<sup>2,3</sup>

Adopting this new treatment strategy we began exploring the use of LI-ESWT to achieve this goal.<sup>4,5</sup> 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.<sup>6–8</sup> This finding led clinicians to begin using shock wave therapy in the treatment of coronary artery disease,<sup>9</sup> bone fractures,<sup>10</sup> calcifying tendonitis<sup>11</sup> and diabetic foot ulcers.<sup>12</sup>

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.<sup>4</sup> We also reported that LI-ESWT effectively converted PDE5i nonresponders to responders.<sup>5</sup> 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 tech-

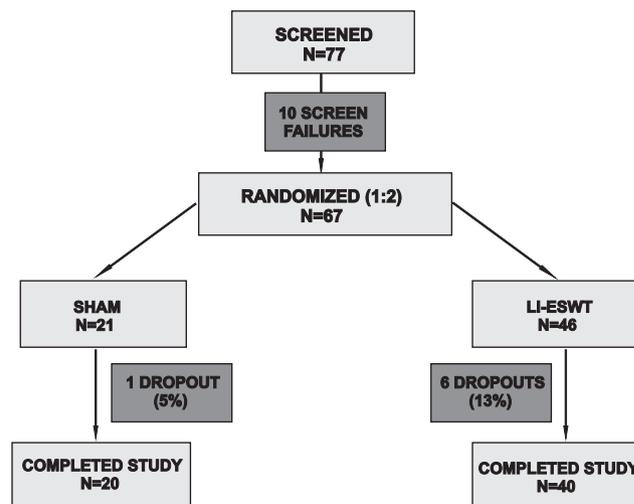


Figure 1. Patient screening and randomization flowchart

nique in which penile blood flow is measured at rest and after a 5-minute ischemic period using venoocclusive strain gauge plethysmography.<sup>13,14</sup> 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).

### Specifics of LI-ESWT

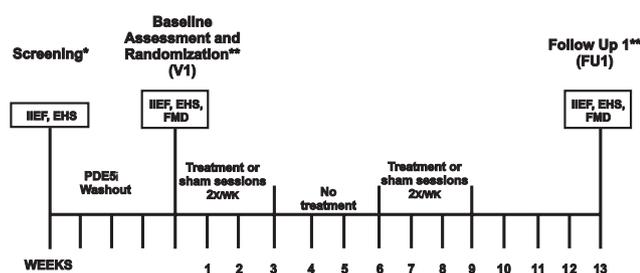
We applied a standard commercial gel normally used for sonography to the penis. The shock waves were delivered to the distal, mid and proximal penile shaft, and the left and right crura using a specialized focused shock wave probe (Omnispec ED1000, Medispec Ltd., Yehud, Israel) as described in our previous studies (fig. 3).<sup>4,5</sup> 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<sup>2</sup> 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

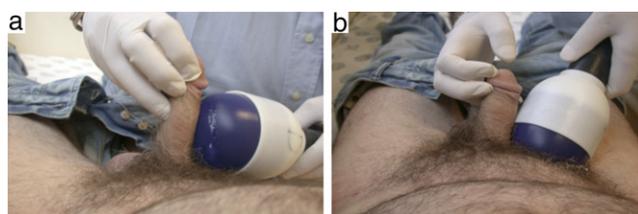
We used the IIEF-EF to evaluate erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF between V1 and FU1 because this value indicates an improvement of erectile function by at least 1 severity category. The secondary outcome measures were defined as significant 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  $\pm$  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 $\pm$ SEM IIEF-EF domain scores	11.5 $\pm$ 0.86	12.6 $\pm$ 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).

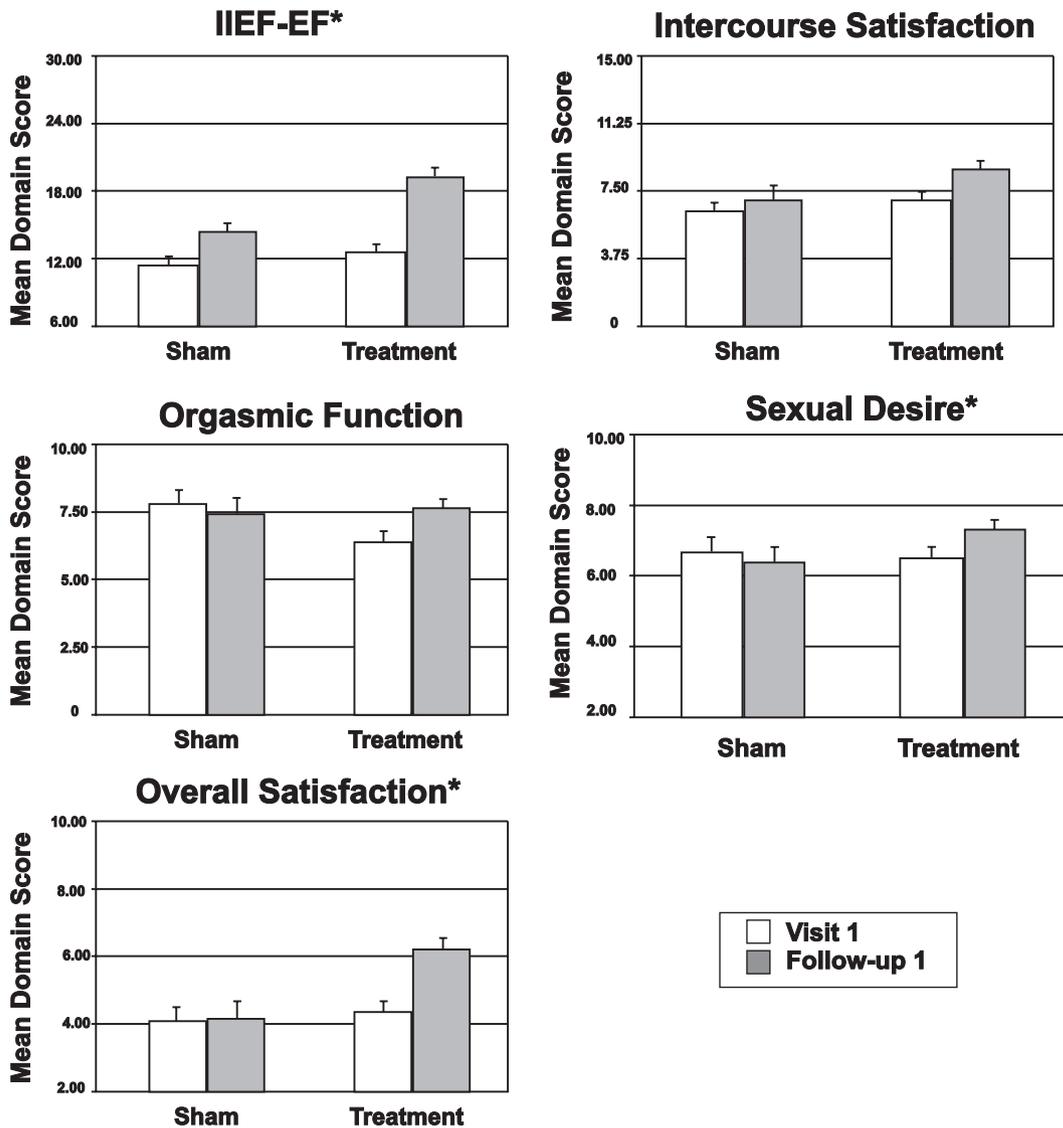
Penile hemodynamics were assessed in 59 of the 60 men who presented at FU1 (1 man in the treated group refused this assessment after treatment). Penile hemodynamics improved significantly in the treated group (table 2,  $p < 0.0001$ ). Furthermore, we noted a strong positive correlation between changes 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<sup>2</sup>), the low intensity shock wave energy (0.09 mJ/mm<sup>2</sup>) 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.

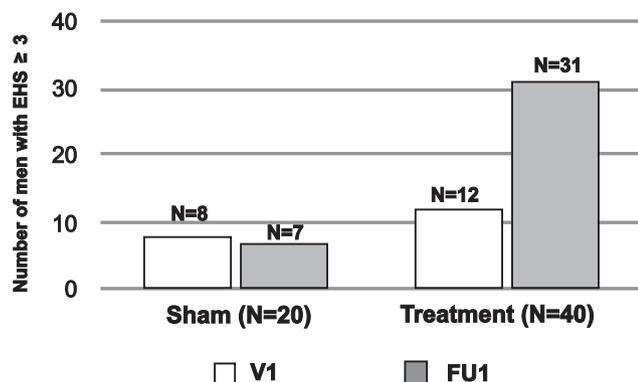
without knowing their original group (fig. 6). Mean IIEF-EF of men continuing on to a second round of treatments was 12.2 at FU1, while the remaining 36 men who had followup at 3 months had an additional increase in mean IIEF-EF from 20.7 at FU1 to 22.1 at FU2.

**DISCUSSION**

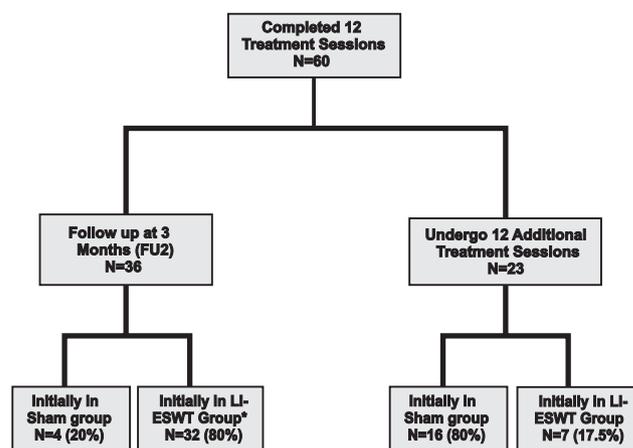
Due to the skepticism surrounding this novel treatment, insufficient scientific background and disappointing results of penile shock wave therapy in Peyronie disease, it was crucial to further establish the validity of LI-ESWT by conducting a randomized, double-blind, sham controlled study. We chose 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.<sup>15-17</sup> 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.

parameter 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.<sup>13,14</sup> 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.<sup>18–20</sup> 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.<sup>21</sup> 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.<sup>22,23</sup> Nevertheless, it is possible that our empirical LI-ESWT protocol is less effective than PDE5i therapy.

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.<sup>19</sup> 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.

**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  $p < 0.0001$ .

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.<sup>4</sup>

The treatment protocol that we used in all our studies to date was based on that described in the cardiology literature.<sup>24,25</sup> 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 determin-

ing 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,<sup>26,27</sup> despite findings that such shock waves may lead to the collagenization of corporal smooth muscle in the rat.<sup>28</sup> 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.

## ACKNOWLEDGMENTS

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

## REFERENCES

- 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.
- 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.
- Deng W, Bivalacqua TJ, Hellstrom WJ et al: Gene and stem cell therapy for erectile dysfunction. *Int J Impot Res* 2005; **17**: S57.
- 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.
- Gruenewald 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.
- Young SR and Dyson M: The effect of therapeutic ultrasound on angiogenesis. *Ultrasound Med Biol* 1990; **16**: 261.
- 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.
- Wang CJ: An overview of shock wave therapy in musculoskeletal disorders. *Chang Gung Med J* 2003; **26**: 220.
- 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.
- Haupt G, Haupt A, Ekkernkamp A et al: Influence of shock waves on fracture healing. *Urology* 1992; **39**: 529.
- Rompe JD, Rumler F, Hopf C et al: Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. *Clin Orthop Relat Res* 1995; **321**: 196.
- Wang CJ, Kuo YR, Wu RW et al: Extracorporeal shockwave treatment for chronic diabetic foot ulcers. *J Surg Res* 2009; **152**: 96.
- Dayan L, Gruenewald 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.