SEXUAL MEDICINE REVIEWS REVIEWS

Review of the Current Status of Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) in Erectile Dysfunction (ED), Peyronie's Disease (PD), and Sexual Rehabilitation After Radical Prostatectomy With Special Focus on Technical Aspects of the Different Marketed ESWT Devices Including Personal Experiences in 350 Patients

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ABSTRACT

Introduction: Although the literature of the positive effects of penile low intensity extracorporeal shockwave therapy is meanwhile substantial, there are substantial differences regarding both the sources of energies and extracorporeal shockwave therapy (ESWT) devices.

Objectives: To provide an overview on the energy range and energy differences of the 6 currently marketed ESWT devices along with personal ESWT experiences in 350 patients.

Methods: This review includes all published preclinical and clinical penile ESWT studies with evaluation of the technical differences of the 6 ESWT devices and the personal experiences with these 6 devices in ED and PD. The main outcomes measures were success rates in ED (International Index of Erectile Function-erectile function change, conversion of phosphodiesterase type 5 inhibitors non-responders) and PD (change in deviation and plaque size), differences of used sources of energy, and energy flux densities (EFDs).

Results: 3 different sources of energies are used, that is electromagnetic, electrohydraulic, and piezoelectric .The devices markedly distinguish in the available spectrum of the EFD ranging between 0.09 and 0.55 mJ/mm^2. In terms of the biological effects, the relevant energy parameters are −6 dB and the 5 MPa focus, which differ substantially between the ESWT devices. In addition, a great variability in the treatment protocols and applied energy is obvious. The preliminary own experiences with low intensity extracorporeal shockwave therapy in 160 ED non-responders and 190 patients with PD with success rates of 45% and 47%, respectively, are reported.

Conclusion: Positive results were published with all 6 ESWT devices in question in patients with organic ED but with huge differences regarding the EFD and the total energies applied. There is growing evidence that concentrated treatment protocols and increasing energies may yield better results. In this context, it may be argued that at least some of the published studies were markedly underpowered .Owing to the paucity of published studies, the literature of the effects of ESWT in PD and for penile rehabilitation after pelvic surgery is currently not conclusive. **Porst H. Review of the Current Status of Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) in Erectile Dysfunction (ED), Peyronie's Disease (PD), and Sexual Rehabilitation After Radical Prostatectomy With Special Focus on Technical Aspects of the Different Marketed ESWT Devices Including Personal Experiences in 350 Patients. Sex Med 2020;XX:XXX−XXX.**

Key Words: Extracorporeal Shockwave Therapy; Erectile Dysfunction; Peyronie's Disease; Penile Rehabilitation

INTRODUCTION

The history of extracorporeal shockwave therapy (ESWT) in medicine dates back to the late 70s of the last century when together with the German company Dornier the clinical research group of Chaussy et al[1,2] from the urological

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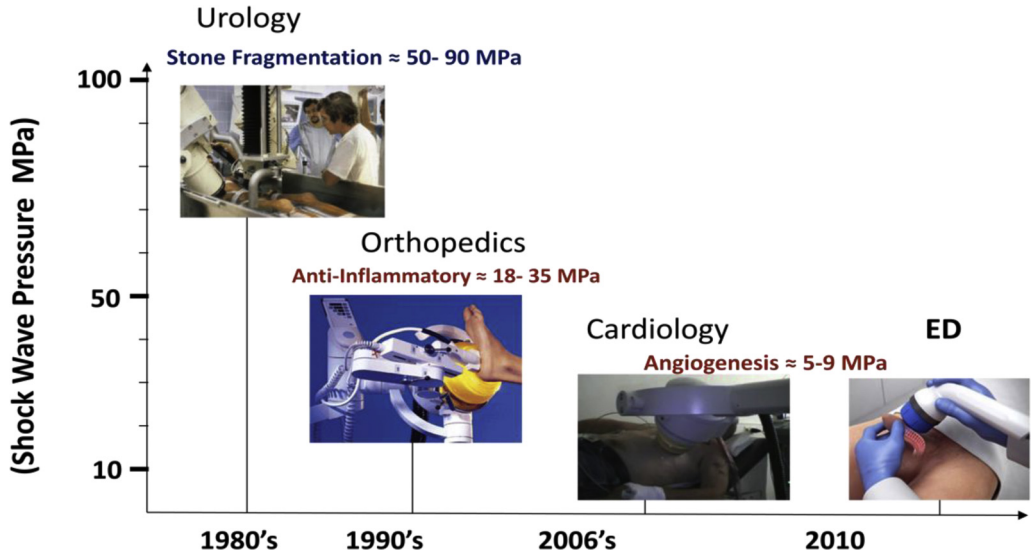


Figure 1. The history of shockwave therapy in medicine using different energies depending on the underlying energy. ED = erectile dysfunction. Source: Dornier MedTech Systems Wessling, Germany (credit: Dornier, Germany).

department of the University Hospital Großhadern in Munich, Germany for the first time developed a shockwave machine for extracorporeal destruction of kidney stones. This development with the introduction of non-surgical and successful treatment of kidney stones marked a breakthrough in urology regarding the management of kidney and later also of ureteral stones and research on this is ongoing even now. Later, ESWT was utilized for the treatment of gallbladder and salivary gland stones but with uncertain results. Finally, ESWT was introduced in the field of orthopedics where it became an established treatment for some musculoskeletal disorders and tendinopathies like proximal plantar fasciitis of the heel, lateral epicondylitis of the elbow, and calcific or non-calcific tendonitis of the shoulder and patella with success rates ranging from 65% to 91%[3] (Figures 1 and 2).

In Andrology and Sexual Medicine, the principles of low intensity ESWT (Li-ESWT) for erectile dysfunction (ED) were introduced by the pioneering clinical research work of Vardi et al[4] who were able to show for the first time that ESWT can successfully treat patients suffering from ED. 2 years later the same research group reported on the successful outcome of ESWT in 29 patients with organic ED, poorly or not responding to phosphodiesterase type 5 inhibitors (PDE5i), and reported a conversion rate to responders of 72% after 12 sessions.[5]

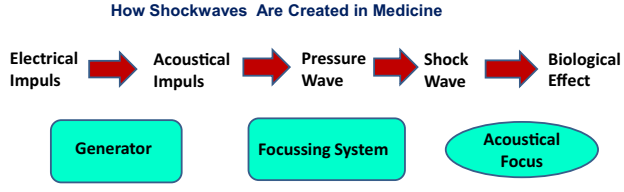


Figure 2. Technical principles of shockwave generation. HV = high voltage.

The author has, in his institute, used over the last 6 years all 6 ESWT devices which are marketed in Europe and with which studies were conducted and published worldwide (Table 1).

MATERIALS AND METHODS

The main objective of this comprehensive review on both preclinical and clinical ESWT studies is to provide readers for the first time with the technical details and differences of the 6 currently, in Europe and elsewhere, marketed shockwave devices as reported by the manufacturers on personal request of the author. Furthermore, the relevant results of preclinical and clinical studies conducted with these ESWT devices in question and their possible consequences for the clinical routine are described in detail. For this purpose, by using PubMed and Medline search engines, relevant literature regarding both the preclinical and clinical use of ESWT on the penis and other body components has been reviewed starting with the year of introduction of ESWT in urology. In addition, this survey provides temporary personal experiences in more than 350 patients in whom these devices were used for ED, Peyronie's disease (PD), or sexual rehabilitation after radical prostatectomy (RRP).

Preclinical Results of Li-ESWT

The effects of Li-ESWT on both penis structure and function of the cavernous bodies were the subject of a variety of preclinical in vivo and in vitro studies and recently summarized by Sokolakis et al[6] in a comprehensive review. In this review, 15 experimental studies regarding the effects of Li-ESWT only on ED and 44 experimental ESWT studies in other fields/indications such as cardiology/orthopedics and wound healing were considered. Interestingly, it is noteworthy that the authors excluded from this review all papers which did not provide either detailed technical

Table 1. Results of short-term outcomes in published Li-ESWT trials

Author	Study design	No of patients eligible	Device, energy	EFD (mJ/mm^2)	Total no of sessions Shocks/session	No of sessions per week	ED population	Diagnostic work-up	Follow-up (mo)	Outcome/success rate
Vardi et al[4]	Monoc.	20	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	Organic/vascular PDE5i resp.	IIEF-EF EHS/QEQ History	1	Mean IIEF-EF increase: 13.5–20.9
Vardi et al[16]	Monoc. RCT	67	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	IIEF-EF>19 on PDE5i.	IIEF-EF EHS/QEQ FMD penis History	4 wk	Mean IIEF-EF increase: Sham: 3.0 Active: 6.7
Kitrey et al[17]	Monoc. RCT	55	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	PDE5i non-resp. EHS ≤2 on PDE5i	IIEF-EF EHS/QEQ FMD penis History	1	IIEF-EF MCID: Active: 40.5% Sham: 0% EHS 3: Active: 54.1% Sham: 0%
Gruenwald et al[5]	Monoc. open label	29	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	Vascular PDE5i non-resp.	IIEF-EF EHS/QEQ FMD penis History	3	IIEF-EF increase: >5 in 76%, conversion to PDE5i resp. 21/29
Olsen et al[18]	Monoc. RCT	105	Duolith SD1/ Storz, Electromagnetic	0.15 12.8 J per sess.	5 3,000	1	IIEF-EF < 20 EHS <2	IIEF-EF EHS Organic ED > 6 mo	5 wk	EHS 3–4: Active: 57% (29/51) Sham: 9% (5/54) IIEF-EF ≥ 5 Active: 43%(19/51) Sham: 38% (19/54)
Bechara et al[19]	Monoc. open label	40	Renova Direx, Electromagnetic	0.09	4 3,600	1	PDE5i non-resp.	IIEF-EF, EHS SEP 2/3	3	IIEF-EF increase: 14.8–24.1 SEP 3: 30.2–75.3%
Reisman et al[20]	Multic. open label	56	Renova Direx, Electromagnetic	0.09	4 3,600	1	Mixed/vascular	IIEF-EF < 25 History	6	Mean IIEF-EF increase: 14.78–22.26

(continued)

Table 1. Continued

Author	Study design	No of patients eligible	Device, energy	EFD (mJ/mm^2)	Total no of sessions Shocks/session	No of sessions per week	ED population	Diagnostic work-up	Follow-up (mo)	Outcome/success rate
Srini et al[21]	Monoc. RCT	135	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	ED > 6 mo Non-psychogenic ED	IIEF-EF EHS Color Doppler	1	IIEF-EF change: Active: 9.2 Sham: 1.1 EHS ≥3: Active: 0–90% (54/60) Sham: 0%
Chung and Cartmill[22]	Monoc. open label	30	Duolith SD1/ Storz, Electromagnetic	0.25	12 3,000	2	PDE5i non- or poor resp. IIEF-5 ≥ 12	IIEF-5 History	1.5 and 4	IIEF-5 increase ≥ 5 points: 60% (18) EDITS increase > 50%: 70% (21)
Motil et al[23]	Multic. RCT	125	Wolf, PiezoWave, Piezoelectric	0.16 Total: 2,560 mJ	4 4,000	1	PDE5i resp. ED > 6 mo IIEF-5 score: 7–21 on PDE5i	IIEF-5 TSQ	1	IIEF-5 increase: Active: 81% (61/75) Sham: 10% (5/50) TSQ-success: Active: 77% (58/75) Sham: 16% (8/50)
Tsai et al[24]	Monoc. open label	52	Duolith SD1/ Storz, Electromagnetic	0.15	12 3,000	1	PDE5 non-resp.	IIEF-5 EHS	1 3 1 3	IIEF-5 increase: 5.4 5.8 EHS 3 or 4 0–67.3% 0–62.4%
Frey et al[25]	Monoc.	16	Duolith SD1/ Storz, Electromagnetic	0.12–0.20	6 3,000	2 every other week	Post RRP (Ø 24 mo)	IIEF-5	1	IIEF-5 median change: 9.5–14.5
Yee et al[65]	Monoc. RCT	58	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	ED > 6 mo IIEF-5 ≤ 21	IIEF-EF EHS	1	IIEF-EF increase: Active: 5.3 Sham: 3.8 EHS score: Active: 2.7 Sham: 2.4

(continued)

Table 1. Continued

Author	Study design	No of patients eligible	Device, energy	EFD (mJ/mm^2)	Total no of sessions Shocks/session	No of sessions per week	ED population	Diagnostic work-up	Follow-up (mo)	Outcome/success rate
Fojecki et al[26]	Monoc. RCT	118	Wolf, PiezoWave, Piezoelectric	0.09	10 600	1 (10 wk)	ED > 6 mo Age > 40 y IIEF-EF < 25	IIEF-EF EHS EDITS	None, outcome at 10th session	IIEF-EF increase: Active: 0.9 Sham: 1.1 EHS score 3: Active: 3.5% Sham: 6.7%
Kalyvianakis and Hatzichristou[27]	Monoc. RCT	46	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	ED > 6 mo Age >18 y IIEF-EF: 6–21	IIEF-EF History Trimix color Doppler	1	IIEF-EF: MCID Active: 56.7% Sham: 12.5%

ED = erectile dysfunction; EFD = energy flux density; EHS = Erection Hardness Scale; FMD = flow mediated dilation; IIEF-EF = International Index for Erectile Function-erectile function domain; Li-ESWT = low intensity extracorporeal shockwave therapy; MCID = minimally clinical important difference; Monoc. = monocenter; Multic. = multicenter; non-resp. = non-responders; PDE5i = phosphodiesterase type 5 inhibitors; QEQ = Quality of Erection Questionnaire; RCT = randomized controlled trial; resp. = responders; RRP = radical retropubic prostatectomy; SEP = sexual encounter profile; TSQ = Treatment Satisfaction Questionnaire.

information, such as number of shockwaves, energy flux density (EFD), and total energy applied, or plausible outcome measures.

Immediate Effects of Li-ESWT on Erectile Function

In the pathological setting, that is animals/rats with ED and compared to controls, Li-ESWT resulted in an improvement of the intracavernosal pressure/mean arterial pressure ratio indicating an immediate improvement of erectile function. Of note, the positive effects of Li-ESWT on erectile function were potentiated by the PDE5i sildenafil. Taking together all these preclinical findings, the positive effects of Li-ESWT on cavernosal function seemed to be the result of enhanced nitric oxide (NO) and in turn cyclic guanosine monophosphate production by activation and upregulation of endothelial NO synthase (NOS) and neuronal NOS (nNOS). This early activation of the NO-mediated vasodilation and increase of arterial inflow may be translated into the clinical observation that some patients report on improved morning and coital erections already 1 or 2 days after the first ESWT session.[6]

Mid-Term/Long-Term Effects of Li-ESWT on Erectile Function

Neoangiogenesis

Increasing expression of the vasoactive endothelial growth factor has been observed in nearly all experimental ESWT studies investigating this parameter. In both streptozotocin induced diabetic rats and bilateral cavernous nerve injury rat models, mimicking a post-prostatectomy situation, histology of the penile tissue revealed greatly reduced endothelial cell content in the cavernosal sinusoids with significant recovery after Li-ESWT in contrast to the control group.[7,8] Moreover, the authors also reported an increase of endothelial progenitor cells after Li-ESWT in the bilateral cavernous nerve injury model.[7] In addition, some of the reviewed preclinical studies investigated the effect of Li-ESWT on stem and progenitor cells in the cavernosal tissue and observed either increased recruitment of progenitor cells and enhancement of the pro-erectile effects of stem cell transplantation or longer survival of transplanted stem cells. Both of the mechanisms increased vasoactive endothelial growth factor expression and activity, and the increased number of progenitor cells finally resulted in an improved arterial blood flow in the clinical setting and may therefore have a positive impact on arteriogenic/vascular ED.

Nerve Recovery/Regeneration

The effects of Li-ESWT on penile nerves were investigated in 5 in vivo or in vitro studies in the diabetic or cavernous nerve injury rat model.

Li-ESWT resulted in an increase and restoration of nNOS-positive nerve fibers in the sinusoids, dorsal arteries, and cavernous nerves.[6–8] Moreover, Li-ESWT either led to the activation of Schwann cell proliferation or showed in in vivo and in vitro settings a stimulation of the brain-derived neurotrophic factor.[7–10] The same research group was also able to prove that delayed Li-ESWT, applied 4 weeks after cavernous nerve injury, was able to produce regeneration of damaged tissue and nerve structures when nerve and tissue atrophy had already occurred.[11] These results imply that Li-ESWT can be successfully used for regenerative therapy even after tissue and functional damages have occurred after cavernous nerve injury in patients after RRP.[11]

Reduction of Fibrotic Changes and Cavernous Tissue Remodeling

In summary, immunohistochemistry or immunofluorescence studies showed that Li-ESWT resulted in an increase of cavernosal smooth muscle/collagen ratio, an increase in elastin fibers, and a downregulation of the transforming growth factor-ß1/Smad/connective tissue growth factor signaling pathway and thus in anti-fibrotic tissue remodeling properties of Li-ESWT.[6] In light of these findings, it is more than justified to speculate that Li-ESWT might be an appropriate method to prevent or at least delay structural changes in the aging penis, finally resulting in deterioration of erectile function or penile shrinking.

Reduction of Sympathetic/Adrenergic Tone

In a recently published study, in naturally aged rats, alteration of the expression's ratio of alpha-1/alpha-2 adrenoceptors in favor of alpha-2 receptors was observed after application of Li-ESWT.[12] In this context, alpha-2 receptors located preterminally on alpha-1 adrenoceptor terminals modulate/inhibit the sympathetic tone and make cavernosal smooth muscle relaxation and thus induction of erection easier (Figure 3). If these preliminary findings are confirmed in further clinical studies, then Li-ESWT may also become a suitable and promising treatment option for all these ED patients suffering from a permanently elevated sympathetic/adrenergic tone finally resulting in performance anxiety and erectile failure.

The positive effects of Li-ESWT on cavernosal tissue and function in the preclinical setting as described earlier occurred with a great variation of EFDs and total number of shockwaves, with EFDs varying between 0.01 and 0.11 mJ/mm^2, shockwaves per session between 300 and 2,000, and the total number of shockwaves between 300 and 24,000 depending on the investigational topic in question and the shockwave machine used.[6]

This huge heterogeneity in the treatment protocols and energies applied makes the interpretation and comparison of the results of all preclinical studies difficult and leaves many questions open/unanswered regarding the best sources of energies, the optimum EFDs, the optimum number of shockwaves per session, the optimum intervals between the sessions, and the optimum total number of shockwaves. Some studies in which

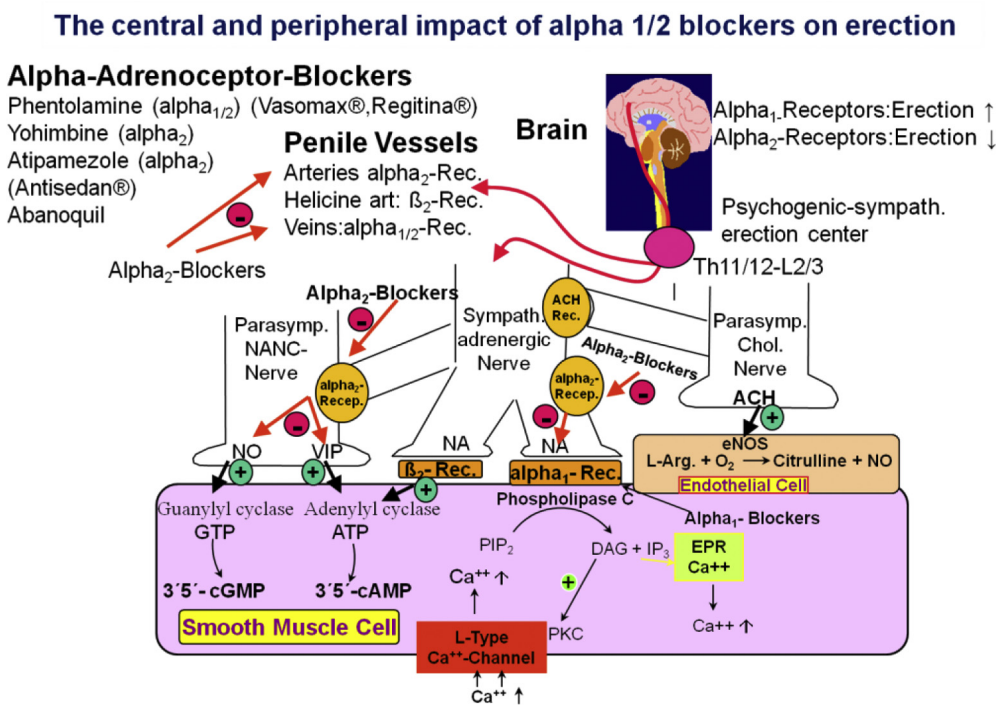


Figure 3. The sympathetic-adrenergic innervation of the cavernous bodies and the possible impact of ESWT on "psychogenic"-sympathetic/adrenergic ED (unpublished source: author). The alpha-2 adrenergic receptors which are located preterminally at the alpha-1 adrenergic receptors modulate/inhibit the sympathetic tone and thus make the onset of erections easier. By changing the ratio of alpha-1/alpha-2 adrenergic receptors in favor of alpha-2 adrenergic receptors, ESWT may be able to decrease the sympathetic activity within the cavernous bodies and finally may facilitate erection in the so-called psychogenic ED patients with an increased sympathetic tone.[12] ACH = acetyl choline; ATP = adenosine triphosphate; ED = erectile dysfunction; EPR = endoplasmatic reticulum; ESWT = extracorporeal shockwave therapy; GTP = guanosine triphosphate; NA = noradrenaline; NANC = non adrenergic non cholinergic.

different EFDs and different protocols were compared provided at least some evidence that higher EFDs and a higher total number of shockwaves may result in a better final outcome.[6,7,9]

Finally, nearly all preclinical studies in ED except one have shown beneficial effects of Li-ESWT on a variety of parameters related to cavernosal/erectile function such as restoration of aging or damaged arteries/nerves and fibrotic tissue changes in the aging penis, including the impact of increased sympathetic activity in the aging man justifying the use of Li-ESWT in the clinical/practical setting.[6,12]

Clinical Results of Li-ESWT in ED

Until now a variety of Li-ESWT studies in different ED populations has been published and has been the subject of several recent review papers.[13–15] As shown in Table 1, an overwhelming majority of these studies, some of them conducted as randomized placebo (sham)-controlled double-blind trials (RCT), provided evidence that Li-ESWT is able to yield positive results in patients with more organic ED and corresponding risk factors (Tables 1 and 2).

Many of the currently published ESWT trials were conducted with Omnispec ED1000 from Medispec, Gaithersburg, USA, the original prototype for ED treatment with which the first pilot trials were carried out, and therefore used relatively low EFDs of 0.09 mJ/mm^2 due to the device design with a maximum possible EFD of 0.09 mJ/mm^2.

Studies using other sources of energies and other ESWT machines applied EFDs between 0.10 and 0.25 mJ/mm^2, nearly 2–3 fold higher compared to the electrohydraulic Omnispec machine. As listed in Tables 1 and 2, not only the EFDs but also the number of shockwaves per session and the total number of shockwaves were quite different ranging between 600 and 4,000 shots per session and between 6,000 and 36,000 total number of shots applied over one treatment period.[22,26]

Moreover, similar to the variability of energies and number of sessions between the studies, there were also great differences regarding the study populations treated. This statement applies especially for 2 completely different target populations—PDE5i responders and PDE5i non-responders. Although these 2 ED populations must be considered completely different in terms of the underlying ED etiologies, ESWT treatment with the same EFDs and study protocols yielded positive results in both groups.[17–24]

Although nearly all authors claimed that only patients with vascular/organic ED were included in their studies, they did not

provide any objective findings such as the outcome of intracorporeal (ic) injection of maximum doses of vasoactive drugs combined with color Doppler of the deep penile arteries with the determination of the peak systolic velocity and end diastolic flow to support this claim. Therefore, it must be argued that the definition of vascular ED does not at all apply for many of the recruited patients.

Considering these huge discrepancies of both applied energies and involved patients in the study protocols it is surprising that nearly all the studies were completed with a positive outcome in the active arms after a short-term follow-up of 1−3 months. The only exception in this regard was the RCT from Fojecki et al[26] in which no differences could be observed between the sham and the active group. There are some important limitations in this trial which may explain these arguable findings. First, despite using a low EFD of only 0.09 mJ/mm^2, the authors applied only 600 shockwaves per session and only a total number of 6,000 shockwaves over the entire treatment period of 10 weeks. When compared to all the other ESWT trials applying between 1,500 and 4,000 shots per session and a total number of between 14,400 and 36,000 shockwaves, it is obvious that this trial was considerably underpowered. Second, the authors evaluated the outcome only after the last shockwave session and not after an interval of 1−3 months like all the other trials.[26]

An important topic of major clinical relevance is the question of how long the positive effects of ESWT can last and after which period the positive effects can be expected to wane. This special topic of interest was investigated in 5 different trials analyzing the outcome of ESWT over 6−24 months after completion (Table 2).[19,21,25,27,29] Whereas in 2 trials after 12 and 24 months no relevant decrease or even a small increase of the efficacy parameters was observed, the 3 other trials reported a clinically meaningful decrease over time of the short-term improved erection function.

Without any exception, in none of the published trials relevant side effects of ESWT were observed so far.

Technical Considerations of ESWT

Sources of Energy

In general, the ESWT devices currently marketed and used in the field of Andrology and Sexual Medicine make use of 3 different sources of energy. (Figures 4−21)

Electromagnetic sources of energy: *Duolith SD1* (Storz Medical, Switzerland), *Aries 2* (Dornier, Germany), and *Renova* (Direx, Germany). Generally speaking, devices enabling electromagnetic shockwave generation use either the so-called flat coil/lens arrangement or a cylinder/parabolic configuration (Figure 5− 8, 12, 16−19, 21)

Electrohydraulic source of energy (Figure 4A): *Omnispec ED1000* (Medispec) and *MTS Urogold 100* (MTS, Konstanz, Germany) (Figures 4A, 13−15, 20).

Piezoelectric source of energy (Figure 4B): *PiezoWave* (ELvation, Germany) (Figures 4B, 9−11).

Important Energy Parameters

The EFD (Figures 5 and 8) is a widely used measure in ESWT studies, and is defined by the energy per area and indicated in mJ/mm^2. In general, the EFD values contain both the positive and negative pressure parts of the shockwave. The maximum applied energy flux density represents a local variable for the acoustic pressure signal measured at the central focal point. In addition, this figure also provides information about the energy acting in the focal area of the acoustic field. The provided EFD depends on the extent of focusing and focus size: small focus sizes increase the EFD and the effect of the shockwave and vice versa (Figures 5 and 8).[30]

The −6 dB zone (Figures 6−9) is often reported in studies and refers to the focal zone where pressure amplitudes of at least 50% of the maximum pressure are reached. According to current knowledge and opinion, the figures of the focal zone do not provide any information about the real therapeutic impact zone of the shockwave treatment. Based on the assumption that a pressure amplitude of at least 5 MPa is necessary in conventional ESWT applications to achieve a therapeutic effect on tissue, the 5 MPa zone is increasingly considered to be the therapeutic impact zone.[30,31]

The 5 MPa zone (Figures 6−8) is defined as the focal area in an acoustic field where the pressure amplitude is 5 MPa. There is increasing agreement in the ESWT literature that the 5 MPa zone should be considered as the therapeutic impact zone of the respective shockwaves.

Both the reported −6 dB and 5 MPa zones depend on the different energy levels with their corresponding EFD. However, as shown in Figure 8, the therapeutic 5 MPa increases much more with increasing EFD than is the case with the −6 dB area.[30,31]

The maximum penetration depth in the −6 dB and 5 MPa zone refers to the distance between the skin surface and the distal end of the focal zone. The penetration depths can be reduced and precisely adjusted by using gel pads as spacers.

To our knowledge, until now there are no comparable studies published regarding the critical question of whether the different sources of energy—electromagnetic, electrohydraulic, and piezoelectric—used for ESWT may produce different outcomes of the biological effects if the same EFD levels are compared.

This topic is of utmost interest because our personal experiences with all the 6 shockwave machines in the market definitely show that the direct effects of shockwaves are differently experienced or felt by the patients when comparing shockwaves of the same EFD but generated by different sources of energy.

Therefore, according to these personal observations, obviously, it has to be argued whether the biological effects of all the

Table 2. Results of Li-ESWT trials over time

Author	Study design	No of patients	Device/source of energy	EFD (mJ/mm^2)	Total no of sessions Shocks/session	No of sessions per week	ED population	Diagnostic work-up	Follow-up (mo)	Outcome/success rate
Kitrey et al[28]	Monoc. mixed	156	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	Heterogenous several studies	IIEF-EF EHS FMD/QEQ FMD penis History	1 6 12 18 24	MCID of IIEF-EF: 63.5% (99) 52.6% 42.9% 38.5% 34%
Bechara et al[19]	Monoc. open label	40	Renova Direx, electromagnetic	0.09	4 3,600	1	PDE5i non-resp.	IIEF-EF, EHS SEP 2/3	3 6 9 12	IIEF-EF increase: 14.8–24.1 SEP 3: 30.2–75.3% IIEF-EF increase: 14.8–24.3 SEP 3: 30.2–78.8% IIEF-EF increase: 14.8–23.2 SEP 3: 30.2–83.6% IIEF-EF increase: 14.8–23.9 SEP 3: 30.2–83.2%
Srini et al[21]	Monoc. RCT	135	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	ED > 6 mo Non-psychogenic ED	IIEF-EF EHS Color Doppler	1 3 6 9 12	IIEF-EF increase: Active: 12.5 Sham: 1.4 Active: 12.0 Active: 10.7 Active: 9.6 Active: 8.7
Frey et al[25]	Monoc. open label	16	Duolith SD1/ Storz, Electromagnetic	0.12–0.20	6 3,000	2 every other week	Post BNSP RRP (Ø 24 mo)	IIEF-5	 1 12	IIEF-5 median change: 9.5–14.5 9.5–10.0

(continued)

Table 2. Continued

Author	Study design	No of patients	Device/source of energy	EFD (mJ/mm^2)	Total no of sessions Shocks/session	No of sessions per week	ED population	Diagnostic work-up	Follow-up (mo)	Outcome/success rate
Kalyvianakis and Hatzichristou[27]	Monoc. RCT	46	Omnispec/ Medispec, Electrohydraulic	0.09	12 1,500	2 with 3-wk interval after 3 wk	ED > 6 mo Age > 18 y IIEF-EF: 6–21	IIEF-EF History Trimix color Doppler		IIEF-EF: MCID
									1	Active: 56.7% Sham: 12.5%
									3	Active: 56.7% Sham: 12.5%
									6	Active: 63.3% Sham: 18.8%
									9	Active: 66.7% Sham: 31.3%
									12	Active: 75% Sham: 25%

BNSP RRP = bilateral nerve-sparing radical prostatectomy; ED = erectile dysfunction; EHS = Erection Hardness Scale; FMD = flow mediated dilation; IIEF-EF = International Index for Erectile Function-erectile function domain; Li-ESWT = low intensity extracorporeal shockwave therapy; MCID = minimally clinical important difference; Monoc = monocenter; non-resp. = non-responders; PDE5i = phosphodiesterase type 5 inhibitors; QEQ = Quality of Erection Questionnaire; RCT = randomized controlled trial; SEP = sexual encounter profile.

shockwave devices at defined levels of energy (EFD) are really identical and comparable.

Technical and Economical Differences Between 6 ESWT Machines

The differences of the respective 6 shockwave devices regarding the technical details and especially in terms of energy differences are shown in Tables 3–14. In addition, there are also marked differences regarding the pricing of the devices and applicators. Furthermore, from an economic standpoint, there are 2 further aspects to be considered, that is the longevity of the applicators and the time needed per session because in general in many settings ESWT is performed by the physician himself and costs his own manpower and time which he cannot use for other activities while performing this therapy. In this regard, it, of course, makes a difference whether an ED session takes only about 15 minutes, when a linear focused applicator is used which is able to cover the whole penis shaft, or takes up to 30 minutes, when 6 or even more different applicator positions are needed (Figures 10–22).

Moreover, it has to be taken into account whether the country of the potential ESWT user has at its disposal a reliable and quick national service team/system or not, and how fast defective machines or applicators can be replaced.

Temporary Personal Experiences with ESWT in ED Treatment Failures/PDE5i Non-Responders (n = 160)

All the patients in the ED group undergoing ESWT were without any exception unresponsive to PDE5i and were typical candidates for either vacuum therapy or penile

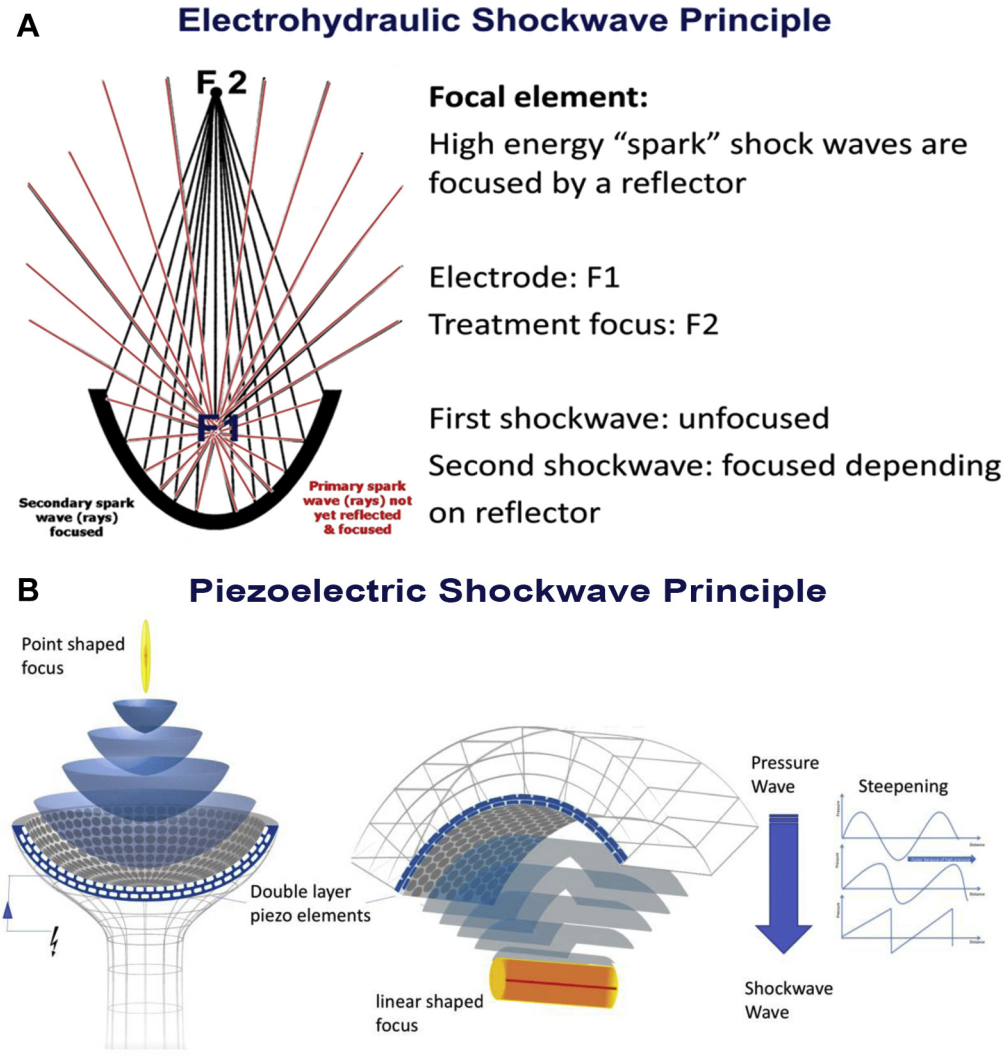


Figure 4. A: Electrohydraulic shockwave generation (credit: MTS, Germany). Generator: high-energy spark discharge in water quench (electrode) explosive water evaporation produces "spark" shockwave, which is spherically spreading out into the surrounding medium. B: Piezoelectric shockwave generation (PiezoWave; credit: ELvation Medical GmbH, Germany). Generator: piezo elements generate pressure waves by voltage pulses which need to be transformed to a shockwave by focusing (steepening effect). Focal element: layer of piezo elements located on a spherical surface.

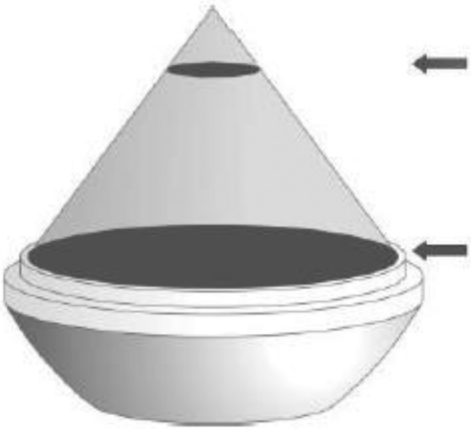


Figure 5. With comparable total energy, the EFD increases by focusing: reduction of a larger area (lower arrow) to a smaller one (upper arrow) results in the concentration of energy, which is an increase of the EFD and enhances the efficacy of the shockwave (credit: Storz Medical, Switzerland, Wess[30]). EFD = energy flux density.

implants. Both therapeutic options were explicitly not wanted by these patients. The rationale for that approach to use ESWT only in PDE5i non-responders was the fact that in our center roughly 1,000 patients with ED are treated every year, with many of them being referred because of non-responsiveness to PDE5i.

Prior to ESWT salvage therapy, all these patients underwent a 3 months trial with daily dosing of tadalafil 5 mg combined with a short-term PDE5i as needed in the highest dose like 100 mg sildenafil, 20 mg vardenafil film-coated or 10 mg oro-dispersible tablet, or 200 mg avanafil; despite this oral combination therapy, they were unable to penetrate. All these non-responders underwent intracavernosal testing with either 20 μg prostaglandin E1 or the trimix combination (20 μg prostaglandin E1 + 30 mg papaverine + 1 mg phentolamine) combined with color Doppler with >90% of them non-responding with a rigid erection sufficient for vaginal penetration and were therefore entitled to suffer from severe veno-occlusive dysfunction. In this context, we have to emphasize that in this heterogeneous group we did not apply a fixed ESWT protocol with a fixed number of sessions and a defined EFD but were instead following an individualized approach depending on the outcome of the diagnostic work-up, that is especially on the severity of the veno-occlusive dysfunction. Moreover, the patients' individual housing location, with many of them having to travel between 200 and 600 km per session, played an important role. Finally, the number of sessions chosen by the patients also depended on the individual economic background. All patients underwent at least 6 sessions with between 2,500 and 5,000 shockwaves per session depending on the ESWT device and EFD used. In addition, the EFD per shot was adjusted to the patients' convenience/tolerance that is from which energy level onward the patients felt the applied energy to be painful or at least very inconvenient. In many patients, within the same session, we used 2 or even 3 different devices with 3 different energy sources to learn whether the susceptibility of the patients may be different by using different energy sources but with the same EFD. The majority of patients underwent at least 1 session per week, some undertook 2 sessions, and depending on the efficacy and the economical background many patients underwent 8–12 or even up to 20 sessions, some with between 3 and 6 months breaks in between. Given this diversity of treatment characteristics in a very heterogeneous PDE5i non-responder population, scientifically speaking this group represents a "dirty" group, and it is therefore a matter of course that no real evidence-based medicine data can be provided but otherwise a lot of useful personal observations

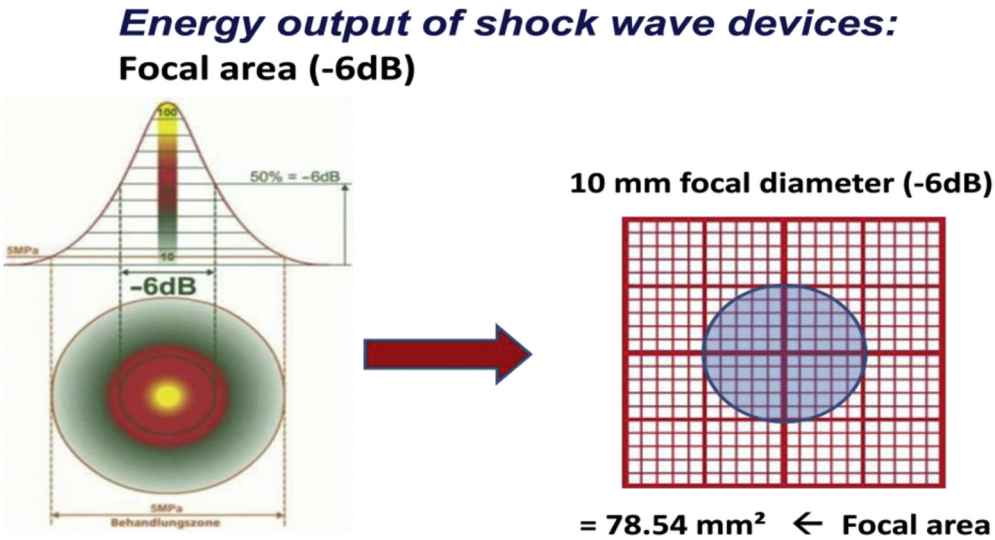


Figure 6. The −6 dB area describes the area exposed to pressure values above half of the maximum pressure where the treatment energy reaches 50% of the maximal power (credit: Storz Medical, Switzerland, Wess,[30] and MTS Medical, Konstanz, Germany).

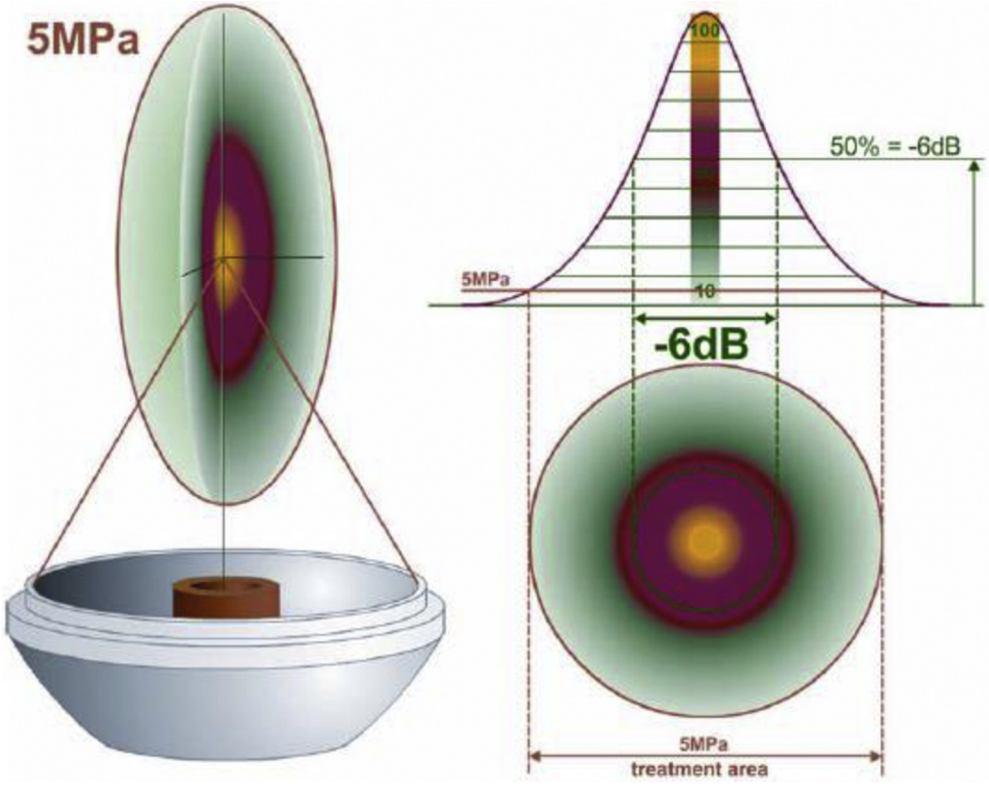


Figure 7. The 5 MPa treatment zone is defined by maximum pressures >5 MPa (50 bar) and is considered the main responsible efficacy zone (credit: Haecker and Wess[31]).

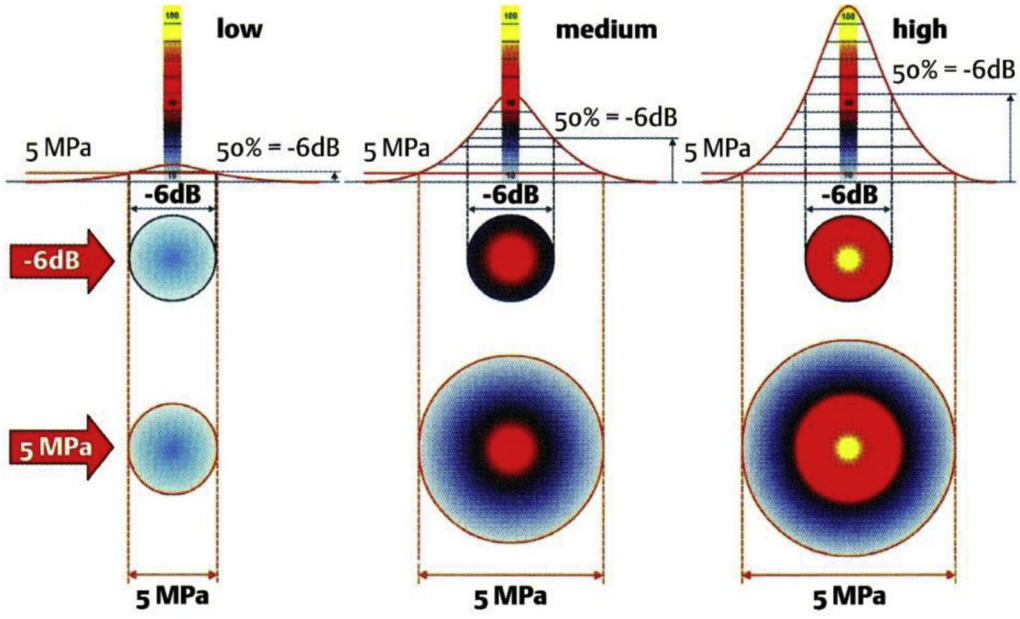


Figure 8. −6 dB Focus compared to 5 MPa therapeutic zone when different energy levels with different EFDs are used: despite different energies with different EFDs delivered, the −6 dB zone remains relatively unchanged whereas the therapeutic 5 MPa focus zone is clearly increasing, reflecting an expanded therapeutic area of shockwaves with increasing level (credit: Storz Medical, Switzerland, and Wess[30]). EFDs = energy flux densities.

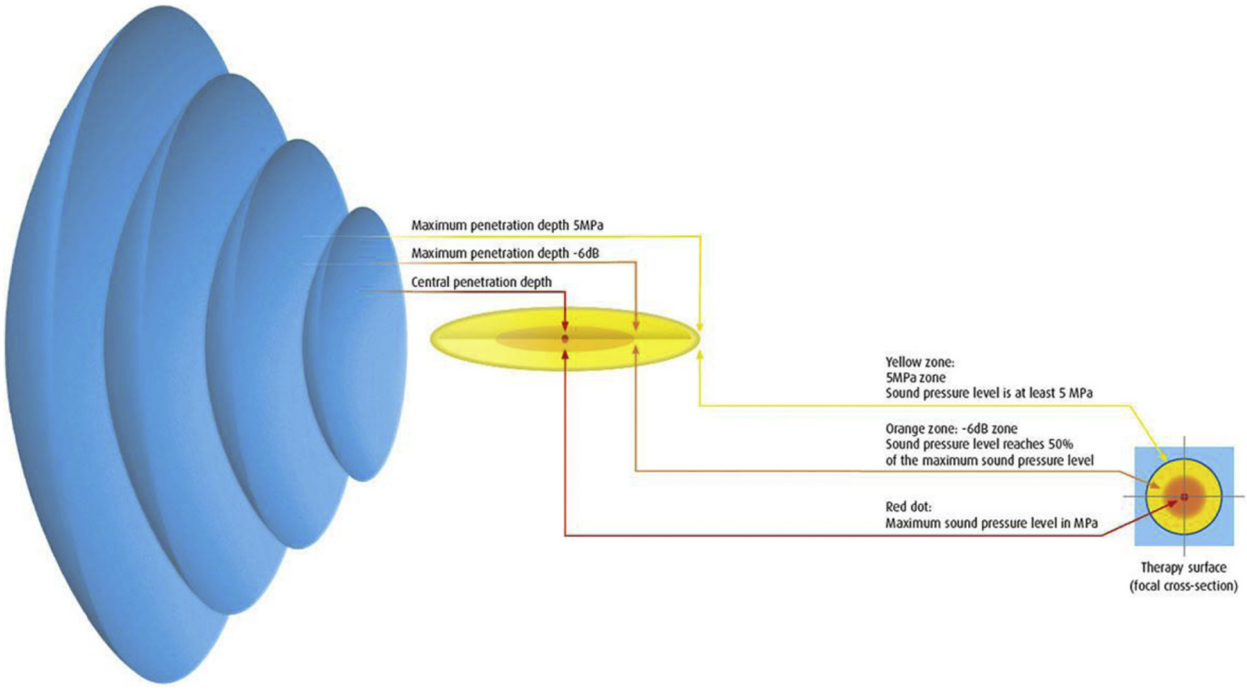


Figure 9. Distribution of central focal zone, −6 dB zone, and 5 MPa zone. The central maximum penetration depth refers to the distance between the skin surface and the point of maximum acoustic pressure when using a gel pad, which allows the greatest penetration depth. The maximum penetration depth in the −6 dB zone and 5 MPa zone refers to the distance between the skin surface and the distal end of the focal zone. The penetration depth can be reduced and precisely adjusted by using gel pads as spacers (credit: ELvation Medical, Germany).

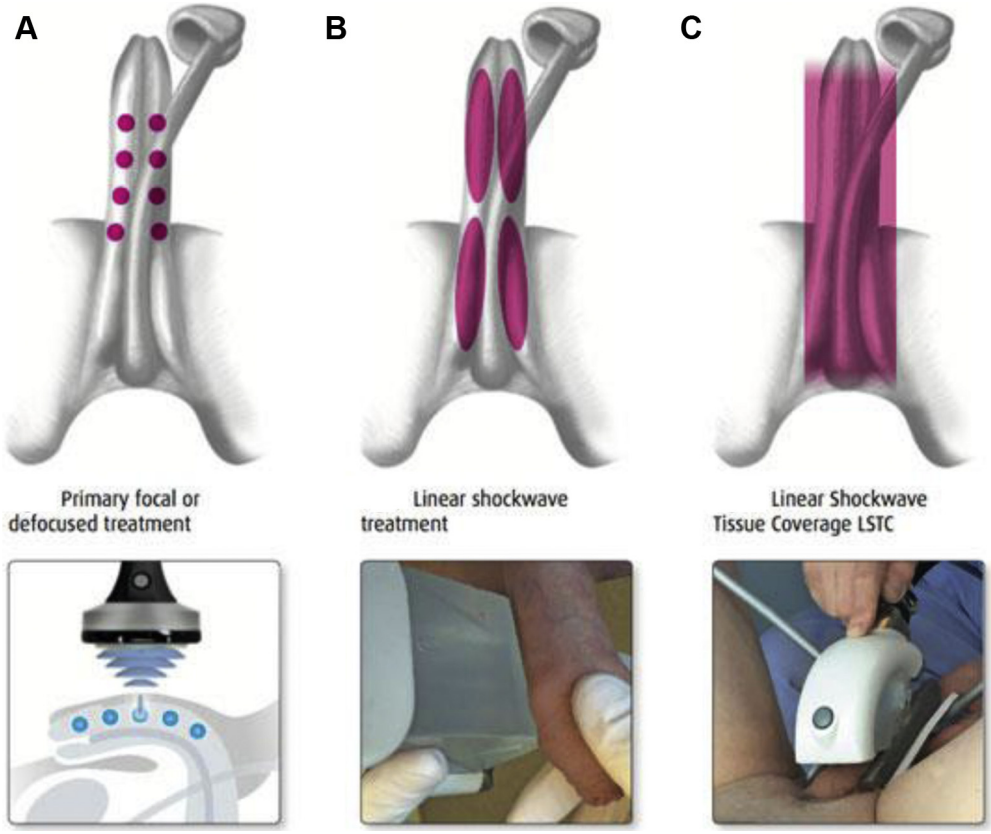


Figure 10. A: Focused or defocused therapy. B: Linear focused shockwave therapy. C: Linear focused shockwave therapy in LSTC-ED technique (Piezoelectric ESWT with PiezoWave in LSTC-ED technique; credit: ELvation Medical, Germany). ED = erectile dysfunction; ESWT = extracorporeal shockwave therapy; LSTC = linear shockwave tissue coverage.

Figure 11. The piezoelectric shockwave principle creates a unique range of shockwave modulations. PiezoWave allows to choose between classic focused shockwaves, linear focused shockwaves, and planar shockwaves (credit: ELvation Medical, Germany).

and individual findings can be observed, which is the subject of another special publication.

The only efficacy endpoint for all patients after completing the ESWT was whether they were able for at least 3 months to perform vaginal intercourse by using the same PDE5i treatment regimen they used prior to ESWT but failed at that time.

In total, we were able to convert 45% of previous PDE5i non-responders to responders. There were no side effects observed during and after ESWT and the applied EFDs ranged between 0.08 and 0.31 mJ/mm^2.

Results of Clinical Li-ESWT Studies in PD

Li-ESWT was introduced in Andrology for PD at the end of the last millennium long before it was investigated for ED.[32]

Meanwhile, there are 3 meta-analyses on the efficacy of ESWT published reviewing always the same limited number of papers available in this indication.[33–35]

The review by Gao et al[33] considered 3 case-control studies published by Hauck, Mirone, and Poulakis and 3 randomized controlled trials published by Chitale, Hatzichristodoulou, and Palmieri and came to the conclusion that ESWT may be an effective and safe treatment for lessening of penile plaques and relieving pain but not for improving penile curvature.[36–41] The combined review of Fojecki et al on the efficacy of ESWT on ED, PD, and chronic pelvic pain only considered the 3 published RCT in PD.[33,39–41] The recently published review by Krieger et al considered, besides the 3 already cited RCT and 3 case-control studies, 6 other case-control studies involving a total of 191 patients and ended up with the conclusion that ESWT may

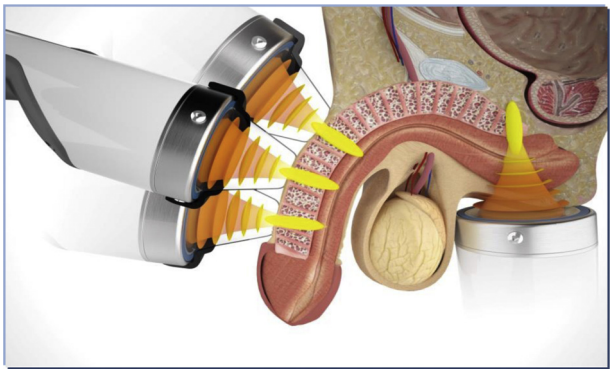


Figure 12. Principle of ESWT for ED treatment at 3 different locations along the penile shaft and one at the crura penis (credit: Storz Medical, Switzerland). ED = erectile dysfunction; ESWT = extracorporeal shockwave therapy.

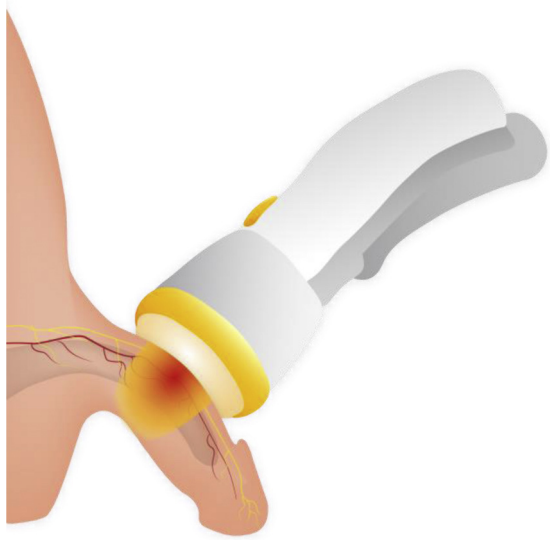


Figure 13. Principle of focal ESWT for PD plaques and fibrotic areas (credit: MTS Medical, Germany). ESWT = extracorporeal shockwave therapy; PD = Peyronie's disease.

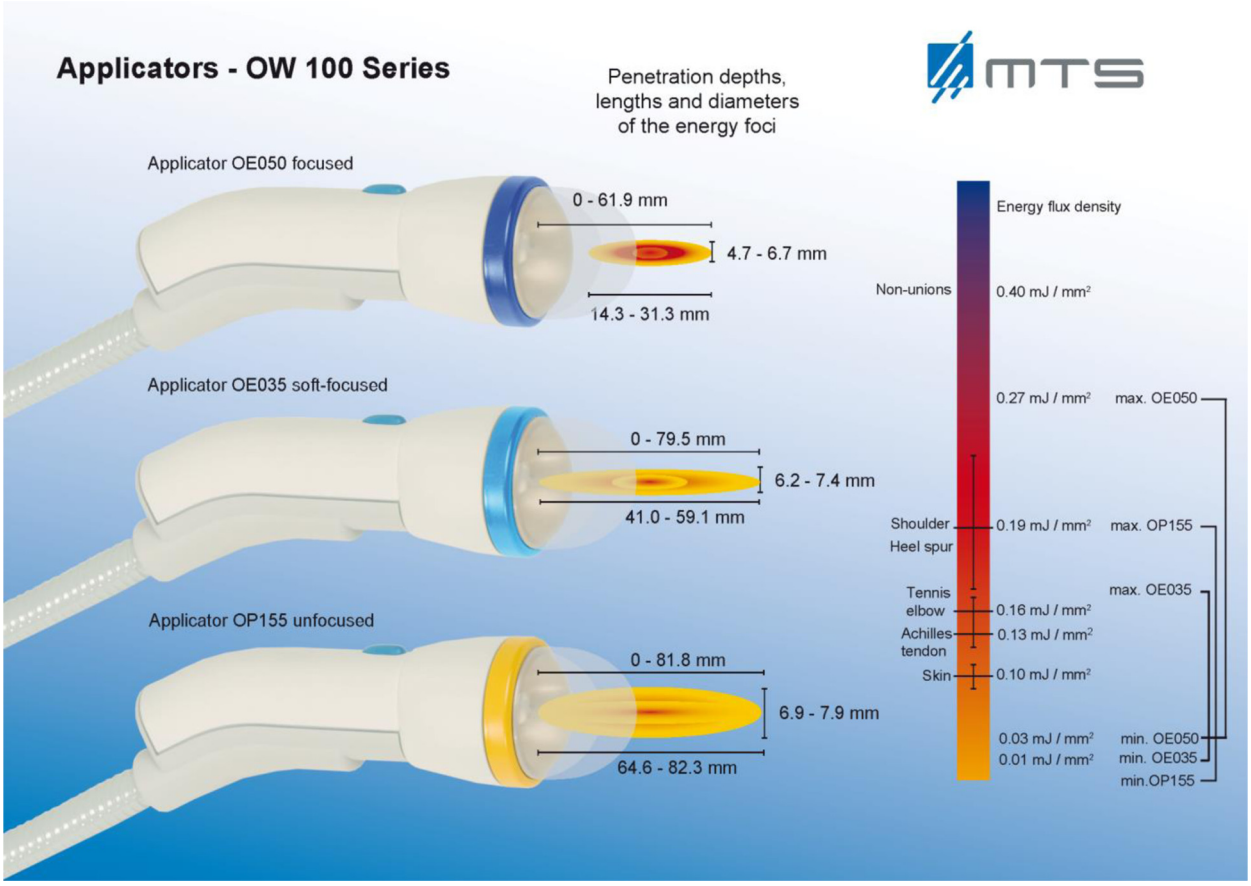


Figure 14. The various MTS Urogold applicators with their technical details: applicator dependent EFDs and penetration depths (credit: MTS Medical, Germany). EFD = energy flux densities.

be beneficial in the management of PD for refractory pain and plaque-size reduction.[35,42–47]

Considering the design of the studies analyzed in these 3 reviews on ESWT in PD, the disparity regarding the energies, shockwave machines, number of shockwaves per session, and total number of shockwaves applied was even much greater than has been the case with all the published ESWT ED studies. Therefore, no noteworthy conclusions can be drawn on the rationale and especially potential of ESWT in PD. In addition, the ESWT machines used in the older studies are meanwhile replaced by new and technically refined devices, a statement which especially applies to the focused applicators for PD. So, for example, the often cited RCT by Hatzichristodoulou conducted between 2002 and 2004 was performed with a PiezoSon

Figure 15. The electrohydraulic MTS Urogold 100 device (credit: MTS Medical, Germany).

Figure 16. The electromagnetic Storz Duolith SD1 (credit: Storz Medical, Switzerland).

Figure 17. The electromagnetic Aries 2 device from Dornier, Germany.

lithotripter, not developed for the treatment of the penis, and the median follow-up was only 4 weeks![41] In addition, it is more than strange that the results of this study were published nearly 10 years later, a very uncommon procedure in scientific literature. In the 3 available RCT studies, only a total of 4–6 weekly sessions with EFDs between 0.25 and 0.29 mJ/mm^2 and with between 2,000 and 3,000 shockwaves per session were applied.[39–41]

Personal Experiences with ESWT in 190 Patients with PD

After having successfully introduced Li-ESWT in a difficult-to-treat ED population, we decided to offer ESWT therapy also to a subset of our new PD patients presenting at our institute because of "new-acute" or not successfully treated "old" PD and specifically asking for ESWT. In this context, it has to be stated that we are counseling and treating about 300 patients with PD per year and therefore we used an admittedly arbitrary definition for patients with new and old PD.

Defining Patients with "Acute"/New and Stable PD

Patients with a history of still ongoing PD within the last 6 months with changes of plaque locations and sizes and/or change of direction or degree of curvature were allocated to the acute or new PD group and those with a history of at least 12 months including 6 months of stagnation with no change at all and no improvement were categorized as the old PD group. This personal definition is more or less in line with the current literature on this subject mostly distinguishing between the acute and the stable phase of PD by defining stable phase as a period of at least 6 months.[48] The overwhelming majority of our patients with new PD had a history of <15 months, a period which in most patients comprises the so-called acute phase. A minority of those patients allocated to the new PD group had a history of more than $1^1/_2$ or even 2–5 years, but were suffering from a new progress after a longer (>12 months) period of stable phase. None of the PD patients to whom ESWT was finally offered had a history of PD surgery. The scientific rationale behind our new policy to offer at least special patient groups with PD ESWT as a new conservative treatment option before considering more invasive or even surgical treatment methods was based on the publications from Gao et al[33] and Mirone et al[37] as described earlier. In the study by Mirone et al,[37] 380 patients with PD were undergoing either ESWT 3 times a week for 20 minutes followed by a complete cycle of 12 intralesional verapamil 10 mg injections (group A) or only the verapamil injection cycle and serving as control group (group B; N = 92). 3 months after the treatment penile biopsy was performed with Acu-Punch (Acuderm Inc, Fort Lauderdale). Reduction of plaque volume was found in 260/380 (68.4%) patients in the ESWT-group A compared to only 30.4% (28/92) in the non-ESWT group. In those 260 patients with a successful outcome of ESWT, the histological evaluation of the specimens conducted by means of transmission electron microscopy revealed a reduction in packing and clumping of the collagen fibers.

The problem with ESWT therapy in PD patients is not only that PD does not represent a stable but phase-wise continuing disease, but also the much more challenging fact that even within the same phase PD may present with different clinical features that can quite reliably be distinguished by high-resolution sonography but not at all by mere palpation. Figures 22–26 provide a better understanding of the individual differences of the sonographic presentations of PD within the acute phase.

First of all, it has to be emphasized that a reliable assessment of the size and thickness of fibrotic plaques and areas can in the majority of cases only be performed in a fully tumescent state after ic injection of vasoactive drugs (eg, Figures 22 and 23).

The huge interindividual differences in PD manifestations make it clear that there cannot be one fixed ESWT protocol with fixed energies and sessions which may fit all the PD patients with their different characteristics. Because of this huge variability among the different PD patients we are still in an experimental stage where we are individually adjusting the energy, number of shots and sessions, and the devices and applicators preferred, depending on the individual sonographic findings. Until 1 year

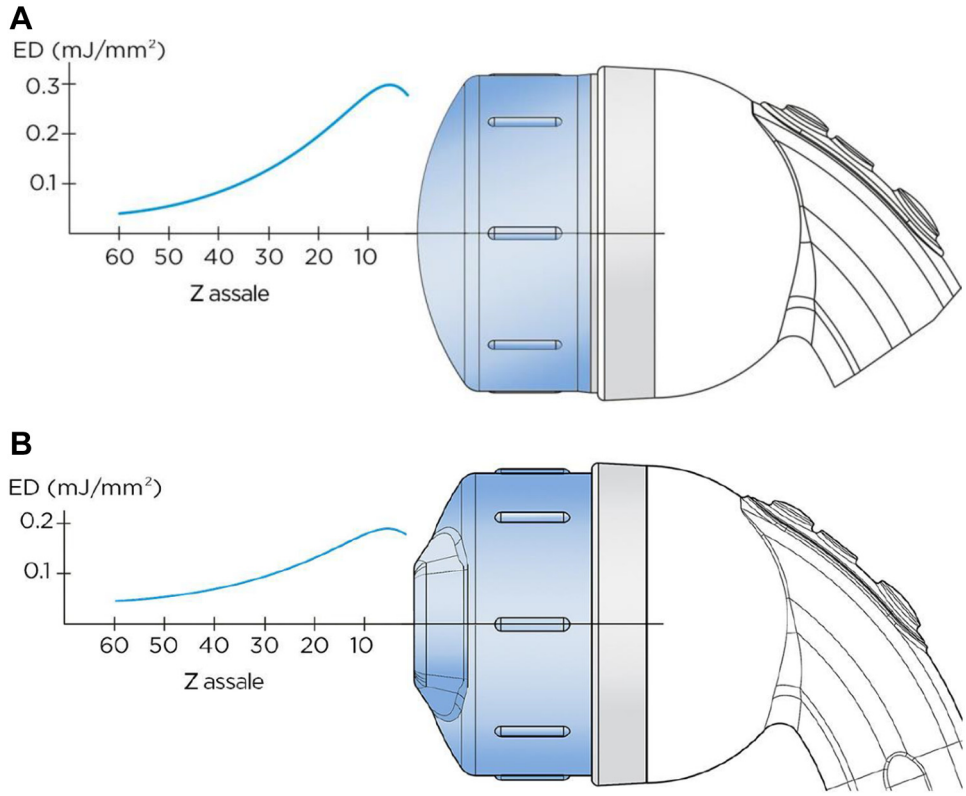
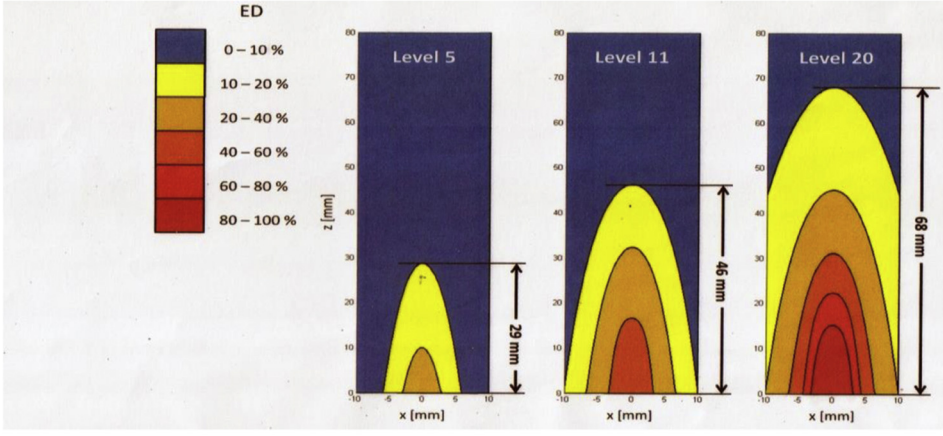


Figure 18. A: Energy distribution at energy level 20 with Smart Focus applicator standard of the Aries 2 used for example also for Peyronie's Disease (credit: Dornier, Germany). B: Energy distribution at energy level 20 with the Aries 2 Smart Focus applicator standard (credit: Dornier, Germany). ED = erectile dysfunction.



Energy Level	Max. trigger frequency (Hz)	Max.Energy Flux Density (EFD in mJ/mm²)	Max. Energy (12mm) (mJ)
5	6	0,062	4,67
11	4	0,169	11,80
20	2,5	0,306	21,6

Figure 19. Percentage related distribution of energy at different levels of energy. Level 20 represents the highest energy level of the electromagnetic Dornier Aries 2 device (credit: Dornier, Germany). ED = erectile dysfunction; EFD = energy flux densities.

Figure 20. The electrohydraulic ED1000 EDSWT device from Medispec, Gaithersburg, USA. EDSWT = erectile dysfunction shockwave therapy.

ago we only used ESWT in patients with well-defined calcified plaques irrespective of their location—dorsal, ventral, or intraseptal. For septal plaques, bigger fibrotic areas within the cavernous bodies, and thick calcified dorsal or ventral plaques we are now administering EFDs ranging between 0.15 and up to 0.50 mJ/mm^2, depending on the patient's individual tolerance level.(see Figures 24–26) These energies are much higher than those described for ED treatment in the literature and can therefore not be provided with each of the different marketed ESWT devices (see Table 14). The number of shockwaves and sessions varied too, depending on the sonographic findings, reaching up to 20 sessions with a variation of between 3,000 and 5,000 shots per session depending on the machine and applicator used, the number of plaques found, the degree of calcification, and extent of intracavernous fibrotic alterations.

In total, 90 (47%) of the 190 patients treated for PD in this own very heterogenous series showed success defined by significant (>50%) plaque reduction or even complete resolution and by at least 30% improvement of penile curvature as measured 6–12 months after ESWT (Figure 27).

Personal Multimodal Therapy Strategy in Patients with PD Undergoing ESWT

- All patients are prescribed for 18–24 months tadalafil 5 mg.
- All patients with penile curvatures >30° are prescribed either a medical vacuum device for penile curvatures <60° or a penile extender (Andropeyronie [Andromedical, Madrid, Spain] or Penimaster [Pro-MSP Concept, Berlin Germany]) for penile curvatures >60°.
- In all patients with or without penile curvature < 30° but erect penile lengths < 11 cm penile extenders are prescribed too.
- All patients with penile curvatures >30° are introduced in penile modeling as has been described in the collagenase histolyticum IMPRESS 1 and 2 trials.[49]

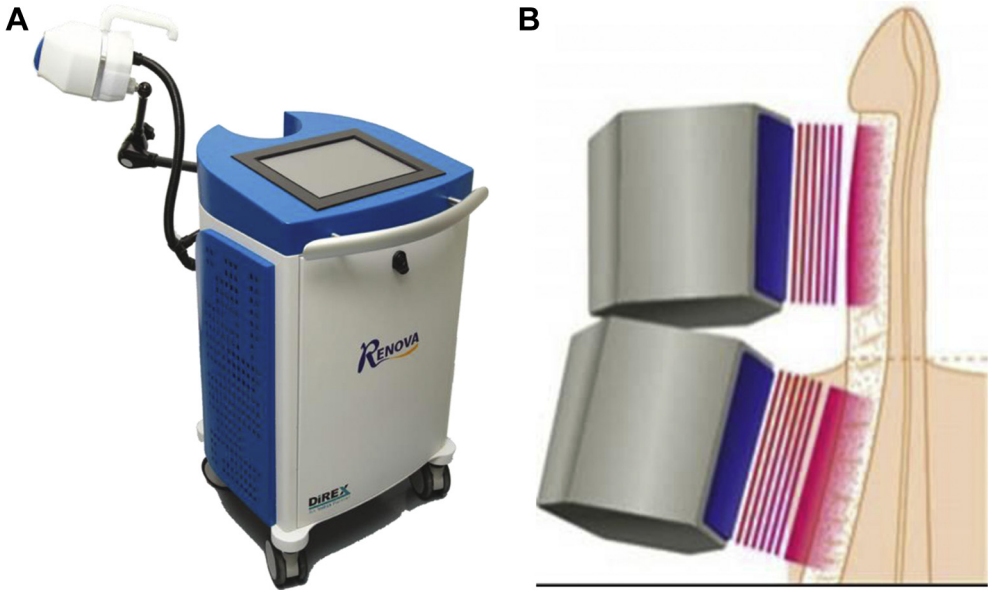


Figure 21. A: The electromagnetic Renova System from Direx Group, Israel. B: In situ application of the Renova System (credit: Direx, Israel).

Table 3. Energy levels and corresponding provided energies with the PiezoWave FBL10x5G2 Applicator (credit: ELvation Medical, Kieselbronn, Germany)

Energy level	Energy flux density (mJ/mm^2)
0.1–1	0.018
2	0.021
3	0.027
4	0.029
5	0.034
6	0.041
7	0.046
8	0.051
9	0.060
10	0.064
11	0.069
12	0.079
13	0.087
14	0.097
15	0.106
16	0.113
17	0.126
18	0.139
19	0.147
20	0.160

Early ESWT for Sexual Rehabilitation After Bilateral Nerve-Sparing Radical Prostatectomy (BNSP RRP)—General Considerations and Preliminary Results

After introduction of the nerve-sparing technique by Walsh and co-workers over decades incredibly high potency preservation rates with this new surgical technique were reiterated by many other surgeons.[50–55] In reality the figures of potency preservation in daily practice were quite different with the majority of patients never reaching their preoperative erectile status even after meticulous BNSP and with PDE5i.[50–55] First doubts about the incredibly high potency rates after nerve-sparing RRP arose with the publication of Catalona et al.[51] In their series with 236 patients undergoing BNSP RRP potency was preserved in 63% (149/236) and after unilateral nerve-sparing RRP in only 41% (24/59). Over a decade later in a review/meta-analysis publication on the erection status after RRP, Montorsi and McCullough reported sildenafil response rates after nerve-sparing surgery ranging between 35% and 75% and after non-nerve sparing surgery of only 0–15%.[52] Finally, the publication of an international multicenter study involving nearly all the worldwide leading centers of excellence regarding BNSP surgery for prostate cancer revealed the truth and put into perspective the data of all the previous publications: 2 months after study drug termination, that is at least 12 months after BNSP surgery, the

Table 4. Technical details of the piezoelectric PiezoWave device from Wolf (ELvation, Germany) (based on 11MPa measurement settings)

Company	Richard Wolf GmbH/ELvation medical GmbH	
Device name	PiezoWave 2 ED	
Official price of device	€25,000–€45,000 (depending on the nation/market in question)	
Official price of probe	€5,000–€8,000 (depending on the nation/market in question)	
Guaranteed probe longevity (shots)	5 Mio	
Range EFD (mJ/mm^2)	0.018–0.160 (linear along the focus length)	
Experienced EFD (mJ/mm^2) for ED	0.160	
Experienced shots/impulses per session for ED	4,000–6,000 (we recommend using the algorithm at the website https://ed-shockwave.com/userarea/)	
Recommended total number of sessions for ED	4–6 (we recommend using the algorithm at the website https://ed-shockwave.com/userarea/)	
−6 dB Focus diameter (mm)		
5 MPa Focus diameter (mm)		
	Focus length	Focus width
−6 dB Focus	45.6 mm	22 mm
5 MPa Focus	50.2 mm	23.4 mm
EFD (mJ/mm^2)	Standard focus	Linear focus
Total EFD (mJ/mm^2)		0.16
Positive EFD (EFD+; mJ/mm^2)		0.07
Total energy per shot in −6 dB focus (mJ)	circa 15.00 mJ (of note: −6 dB and 5 MPa are nearly identical)	
Total energy per shot in 5 MPa focus (mJ)	15.45	
Positive pressure (MPa)	11	
Negative pressure (MPa)		
Rise time shockwave (nS)	40–440	

ED = erectile dysfunction; EFD = energy flux density.

Table 5. Energy levels and corresponding provided energies with the MTS Urogold 100 Applicator OP155, recommended for erectile dysfunction (credit: MTS Medical, Konstanz, Germany)

Energy level	Energy flux density (mJ/mm^2)	Total energy in −6 dB focus	Total energy in 5 MPa zone (mJ)
1	0.005	0.40	0.40
2	0.008	0.53	0.60
3	0.019	0.67	0.85
4	0.030	0.83	1.05
5	0.041	1.00	1.64
6	0.053	1.19	2.35
7	0.064	1.40	3.18
8	0.076	1.62	4.13
9	0.088	1.85	5.22
10	0.100	2.10	6.45
11	0.112	2.36	7.82
12	0.125	2.64	9.33
13	0.138	2.93	11.00
14	0.150	3.23	12.80
15	0.163	3.55	14.80
16	0.176	3.88	17.00

respective data in the 3 treatment arms for the International Index of Erectile Function-erectile function (IIEF-EF) domain were $\geq$ 22, between 24% and 29%, and for SEP 3 between 32% and 42%.[53] This large multicenter study in which only the

Table 6. Energy levels and corresponding provided energies with the MTS Urogold 100 Applicator OE050, recommended for Peyronie's disease

Energy level	Energy flux density (mJ/mm^2)	Total energy in −6 dB focus	Total energy in 5 MPa zone (mJ)
1	0.031	0.30	0.61
2	0.042	0.52	1.12
3	0.054	0.78	1.74
4	0.066	1.08	2.48
5	0.079	1.41	3.32
6	0.093	1.76	4.28
7	0.108	2.15	5.34
8	0.123	2.55	6.51
9	0.139	2.97	7.77
10	0.156	3.41	9.15
11	0.172	3.86	10.60
12	0.191	4.31	12.20
13	0.210	4.78	13.90
14	0.229	5.24	15.60
15	0.249	5.70	17.50
16	0.270	6.15	19.50

Table 7. Focus −6 dB sizes dependent of energy levels with the MTS Urogold 100 Applicator OE050

Energy level	Focus volume (mm^3)	Focus diameter fxy (mm)	Focus length fz (mm)
1	165.4	4.7	14.3
9	503.2	6.2	25.0
16	735.7	6.7	31.3

worldwide leading centers of excellence were enrolling their patients with prostate carcinoma for BNSP RRP impressively showed the fact that in the overwhelming majority of patients the final goal of potency preservation was not reached. Another study analyzed the number/percentages of patients with baseline IIEF-EF $\geq$24 who underwent RRP and achieved back to baseline IIEF-EF.[54] Of 132 patients, 12% (16/132) reached the baseline IIEF-EF after 2 year follow-up without medications and 27% (36/132) with PDE5i. Of patients $\geq$60 years, the respective data after 2 years were 8% (4/51) without medication and 31% with PDE5i. The reason for these disappointing findings is the fact that even with non-nerve cutting techniques the majority of patients undergoing nerve-sparing procedures seems to suffer from long-term sequelae of neuropraxia because of intraoperative nerve compression or traction, or due to use of thermal energy close to the cavernous nerves.

The final biochemical and histological long-term consequences for the cavernous bodies and erectile capacity of at least in part irreversible neuropraxia are smooth muscle cell apoptosis and increase of collagen with in turn a decrease of the cavernous compliance finally resulting in veno-occlusive dysfunction (Figure 28).[55] Already over 20 years ago, it has been proven in the animal cavernous neurotomy model with Sprague Dawley rats that in contrast to sham-operated rats the group with cavernous nerve injury already showed within 1 week a high rate of intra-nucleosomal DNA fragmentation, which is a marker for progressive apoptosis.[56] In this context, pre- and postoperative cavernous biopsies before and 2 and 12 months after RRP were able to show that smooth muscle fibers were significantly decreased and collagen content increased with continuing progression after 1 year.[57] All these data provided convincing evidence that within days after RRP, sequelae of cavernous injury/neuropraxia can be seen implying the obvious need for a very early rehabilitation/treatment strategy to preserve postoperatively erectile function after RRP and pelvic surgery. So far, these findings from both animal and human studies were ignored by all the authors who initiated their PDE5i studies several weeks or even some months after RRP with a corresponding discouraging outcome regarding the promised potency preservation. Meanwhile, there is growing evidence in the literature that early initiation of rehabilitation strategies starting even with the time of RRP may finally result in higher rates of preservation of

Table 8. Dependence of total energy on focus size (−6 dB) with MTS Urogold 100

Size of focus (−6 dB)	Focal area (−6 dB) (mm^2)	Energy flux density (mJ/mm^2)	Total energy/shock (mJ; −6 dB)	Number of shocks	Total energy/treatment (mJ; −6 dB)
3 mm diameter	7.07	0.09	0.64	5,000	3,200
8 mm diameter	50.27	0.09	4.52	1,500	6,780
3 mm diameter	7.07	0.25	1.77	5,000	8,850
8 mm diameter	50.27	0.25	12.57	1,500	18,855

functional cavernous tissue and therefore of potency. In this context, it has been shown by several author groups that early, that is simultaneously with or immediately after RRP, administration of the PDE5i sildenafil, tadalafil, or vardenafil has been able to avoid most of the detrimental effects of cavernous neurotomy with the prevention of loss of smooth muscle cell and corporal fibrosis due to increase of collagen content.[58–62]

With reference to these studies and their unanimous findings we changed our rehabilitation strategies and started from 2007 onward with daily tadalafil 5 mg 5 days prior to RRP in all those men who were sexually active and interested in the preservation of their potency after surgery.

Finally in 2016, the research group of Tom Lue's laboratory in San Francisco reported for the first time the impact of early low energy shockwave treatment in 32 12-week-old Sprague Dawley rats starting 48 hours after bilateral cavernous nerve injury.[7] The shockwaves were delivered for 4 weeks to the pelvic region with a special probe and the group was divided into 2 study arms: one low energy group with 0.06 mJ/mm^2 with 300 pulses at 3 Hz and one high energy group with 0.09 mJ/mm^2 with 1,000 pulses at 3 Hz and the treatment was conducted with the electrohydraulic device from MTS. Furthermore, for the in vitro experiment cell cultures from Schwann cells received low energy shockwaves with 0.02 mJ/mm^2, 200 pulses at 3 Hz. The essential findings of this pilot study on the effect of Li-ESWT were as follows: Li-ESWT resulted in angiogenesis, tissue restoration, and nerve regeneration with more endogenous progenitor cells recruited to the damaged area and Schwann cells. Li-ESWT facilitated more complete reinnervation of penile tissue with regeneration of

Table 9. Technical details of the electrohydraulic MTS Urogold 100 device from MTS, Konstanz, Germany

Company	MTS medical	
Device name	Urogold 100	
Official price of device	Not reported	
Official price of probe	Not reported	
Guaranteed probe longevity (shots)	500,000 (0.1 mJ/mm^2 with new model 2019)	
Range EFD (mJ/mm^2)	ED applicator unfocussed, OP155: 0.005–0.176	(E1–E16)
	PD applicator focussed, OE050: 0.03–0.27	
Recommended EFD (mJ/mm^2) for ED	Unfocussed–0.1	
Recommended shots/impulses per session for ED	1,500–2,500	
Recommended total number of sessions for ED	4–6	
ED applicator unfocussed OP155		
−6 dB beam diameter (mm; E16)	6.9	
5 MPa beam diameter (mm; E16)	**27.5**	
	Beam length	Beam width
−6 dB beam (E16)	64.6 mm	6.9 mm
5 MPa beam (E16)	71 mm	27.5 mm
EFD (mJ/mm^2)	Standard beam	
Total EFD (mJ/mm^2)	0.005–0.176	(E1–E16)
Positive EFD (EFD+; mJ/mm^2)	0.004–0.16	(E1–E16)
Total energy per shot in −6 dB beam (mJ)	0.40–3.88	(E1–E16)
Total energy per shot in 5 MPa beam (mJ)	0.40–17.00	(E1–E16)
Positive pressure (MPa)	4.6–24.0	(E1–E16)
Negative pressure (MPa)	−0.7 to −5.6	(E1–E16)
Rise time shockwave (nS)	1.89 μs–280 ns	(E1–E16)

ED = erectile dysfunction; EFD = energy flux density; NA = not applicable; PD = Peyronie's disease.

Table 10. Technical details of the electromagnetic Duolith SD1 device from Storz, Switzerland

Company	Storz Medical AG	
Device name	Duolith SD1 T-TOP "ultra"	
Official price of device	€23,500 (including VAT)	
Official price of probe	€5,900 (including VAT)	
Guaranteed probe longevity (shots)	Handpiece 5mio	
	Revision 1mio	
Range EFD (mJ/mm^2)	0.01–0.55	
Recommended EFD (mJ/mm^2) for ED	0.01–0.25	Depending on pain level
Recommended shots/impulses per session for ED	3,000	
Recommended total number of sessions for ED	6	
Depends on energy level	0.55 mJ/mm^2	
−6 dB Focus diameter	2.8 mm	
5 MPa Focus diameter	18 mm	
Treatment depth	50 mm	
Focus length	34 mm	
Focus width	2.8 mm	
−6 dB Focus	2.8 mm	
5 MPa Focus	18 mm	
EFD (mJ/mm^2)	0.01–0.55	Linear focus
Total EFD (mJ/mm^2)	0.01–0.55	
Positive EFD (EFD+; mJ/mm^2)	0.004–0.37	
Total energy per shot in −6 dB focus (mJ)	3.5	
Total energy per shot in 5 MPa focus (mJ)	33	
Positive pressure (MPa)	62	
Negative pressure (MPa)	15	
Rise time shockwave (nS)	100	

ED = erectile dysfunction; EFD = energy flux density; VAT = value added tax.

Table 11. Technical details of the electromagnetic Aries 2 device from Dornier, Germany

Company	Dornier
Device name	Aries 2 with standard applicator
Official price of device	Not stated, depending on the market/nation
Official price of probe	Not stated, depending on the market/nation
Guaranteed probe longevity (shots)	3 million shockwaves (pro rata; max 12 months)
Range EFD (mJ/mm^2)	0.01–0.306
Recommended EFD (mJ/mm^2) for ED	0.096 (level 7)
Recommended shots/impulses per session for ED	5,000
Recommended total number of sessions for ED	12
Probe name	Standard applicator
−6 dB Focus diameter (mm)	10–11
5 MPa Focus diameter (mm)	
−6 dB Focus	Not applicable to Aries 2 with smart focus
5 MPa Focus	
EFD (mJ/mm^2)	
Total EFD (mJ/mm^2)	0.01–0.306
Positive EFD (EFD+; mJ/mm^2)	
Total energy per shot in −6 dB focus (mJ)	(Similar to 12 mm zone, since −6 dB focus is close to 12 mm)
Total energy per shot in 5 MPa focus (mJ)	
Total energy per shot in 12 mm zone (mJ)	0.28–21.6
Positive pressure (MPa)	1.4–17.3
Negative pressure (MPa)	−0.3 to −6.6
Rise time shockwave (nS)	

ED = erectile dysfunction; EFD = energy flux density.

Table 12. Technical details of the electrohydraulic ED1000 EDSWT device from Medispec, Gaithersburg, USA

Company	Medispec*	
Device name	ED1000	
Official price of device		
Official price of probe		
Guaranteed probe longevity (shots)	180,000	
Range EFD (mJ/mm^2)	0.09	
Recommended EFD (mJ/mm^2) for ED	0.09	
Recommended shots/impulses per session for ED	1,500	
Recommended total number of sessions for ED	6	
−6 dB Focus diameter (mm)		
5 MPa Focus diameter (mm)		
Therapeutic area length (penetration depth)	135 mm	
Therapeutic area diametric (width)	15 mm	
−6 dB Focus		
5 MPa Focus		
EFD (mJ/mm^2)	Standard focus	Linear focus
Total EFD (mJ/mm^2)	0.09	
Positive EFD (EFD+; mJ/mm^2)		
Total energy per shot in −6 dB focus (mJ)		
Total energy per shot in 5 MPa focus (mJ)	12.37	
Positive pressure (MPa)		
Negative pressure (MPa)		
Rise time shockwave (nS)	40	

ED = erectile dysfunction; EFD = energy flux density; EDSWT = erectile dysfunction shockwave therapy.
*Several missing data were not reported by the company despite repeated requests.

nNOS positive nerves from the major pelvic ganglion to the penis. In addition, a direct effect of the shockwaves on Schwann cell proliferation could be observed. These positive effects were more enhanced in the group treated with higher energy shockwaves.[7] The same research group reported 1 year later in the same rat animal model that Li-ESWT significantly increased 5-ethynyl-2′-deoxyuridine cells indicating the activation of local progenitor cells, a mechanism which may contribute to the beneficial effects of Li-ESWT for ED.[9]

Based on the findings of the literature cited earlier and especially on the recent findings of the positive effects of Li-ESWT on penile rehabilitation after RRP, we changed our strategy from 2018 onward and are offering all patients scheduled for RRP and interested in the best effective rehabilitation program a combination of tadalafil 5 mg daily starting 5 days prior to surgery and early Li-ESWT starting within 8−14 days after surgery when the indwelling catheter has been removed.

Table 13. Data as provided by the respective ESWT device companies

Company/device	Price of device¶	Price of applicator¶	Guaranteed applicator longevity (shots)	Recommended shots per session	Recommended sessions for ED
Medispec ED1000*	Not rep.	Not rep.	180,000	1,500	6
MTS Urogold 100*	Not rep.	Not rep.	500,000§	1,500−2,500	4−6
ELvation PiezoWave†	25,000−40,000	5,000−8,000	5 Mio	4,000−6,000	4−6
Dornier Aries 2‡	Not rep.	Not rep.	3 Mio	5,000	12
Storz Duolith SD1 T-TOP "ultra"‡	23,500	5,900	5 Mio	3,000	6
Direx Renova‡	Not rep.	Not rep.	1 Mio	3,600	4

ED = erectile dysfunction; ESWT = extracorporeal shockwave therapy; rep = reported.
*Electrohydraulic source of energy.
†Piezoelectric source of energy.
‡Electromagnetic source of energy.
§With new MTS Urogold Model 2019.
¶Reported prices are in Euro and are subject to variations between nations and market situations.

Table 14. Energy data as provided by the respective ESWT device companies

Company/device	Range EFD (mJ/mm^2)*	Recommended EFD for ED	Total energy per shot in −6 dB focus (mJ)†	Total energy per shot in 5 MPa focus (mJ)†
Medispec ED 1000	Not rep.	0.09	Not rep.	12.37
MTS Urogold 100	0.005–0.176	0.10	0.40–3.88‡	0.40–17.00‡
ELvation PiezoWave	0.018–0.16§	0.16	15.00 mJ§	15.45
Dornier Aries 2	0.01–0.30	0.096	0.28–21.6	0.28–21.6
Storz Duolith SD1 T-TOP "ultra"	0.001–0.55	0.01–0.25	3.5	33
Direx	0.02–0.09	0.09	21.27¶	Not rep.

ED = erectile dysfunction; EFD = energy flux density; ESWT = extracorporeal shockwave therapy; rep = reported.
*The range of EFD as reported depends on the respective energy level options per ESWT device.
†The total energy per shot in 12 mm zone. With Aries 2 the −6 dB focus is close to 12 mm.
‡The range of energy is related to the energy level chosen (level 1–16).
§Linear along the focus length, −6 dB and 5 MPa are nearly identical.
¶Total energy is spread over the linear focal height of 60 mm.

So far, we have treated 12 patients after nerve sparing radical prostetctomy with the new rehabilitation strategy and reached in 10 after 6–10 sessions complete return of potency to baseline, that is they were able to perform sexual intercourse with vaginal penetration under tadalafil 5 mg daily.

In 2 older patients (67 and 78 years old) with impaired erectile function (IIEF-EF 15 and 12 with tadalafil 5 mg), prior to RRP the combination of tadalafil 5 mg with 12 and 24 shockwave sessions, respectively, was not able to rescue these patients. We were alternating in all these patients both the shockwave devices—Dornier Aries 2, MTS Urogold 100, and PiezoWave—and energies with increasing EFDs up to 0.30 mJ/mm^2 depending on the penile size as established by intracavernosal injection test with Invicorp (Evolan Pharma, Danderyd, Sweden) prior to ESWT and depending on the individual patient's tolerance level.

DISCUSSION

As summarized in Tables 1 and 2, there is convincing evidence in the literature that Li-ESWT is able to generate efficacy data in many patients with the so-called organic ED of vasculogenic origin and that in subsets of patients these positive effects are durable up to 2 years.[19–21,28,29] Regarding the underlying etiology of ED, most publications have not stated by which objective criteria this definition has been finally elucidated and, therefore, it must be speculated that this diagnosis is in the majority of publications exclusively based on patients' history and not on objective criteria such as color Doppler with the determination of peak systolic velocity/resistance index, combined with ic testing with increasing doses to learn the extent of veno-occlusive dysfunction and the degree of cavernous compliance. Furthermore, it has to be stated that with all the different ESWT machines successful outcome in ED studies has been reported but with a huge variation regarding protocols and energies applied (Table 1). Regarding the original protocol with 6 ESWT sessions over 3 weeks followed by a break of 3 weeks and then by another 3 weeks of 2 weekly sessions as introduced by Vardi's research group, it turned out that in the practical setting such a protocol is too complicated and not user friendly.[4]

Therefore, it was not surprising that recently other study protocols were tried, mostly with weekly sessions. As recently

Table 15. Efficacy data of Li-ESWT achieved with different energies and protocols over 1 and 3 months[64]

Total no. of sessions: 12; 5,000 shots/session Dornier Aries 2 (electromagnetic)	EFD 0.05 mJ/mm^2: 2× weekly, over 6 weeks	EFD 0.05 mJ/mm^2: 3× weekly, over 4 weeks	EFD 0.10 mJ/mm^2: 2× weekly, over 6 weeks	EFD 0.10 mJ/mm^2: 3× weekly, over 4 weeks
IIEF-EF increase 1 mo (total n = 80)	4.2	3.8	4.3	4.7
IIEF-EF increase 3 mo (total n = 75)	4.6	4.5	5.4	5.2
MCID met 1 mo (%)	68	76	67	58
MCID met 3 mo (%)	73	86	94	67
SEP 3 increase 1 mo (%)	24.9	22.1	29.2	35.2
SEP 3 increase 3 mo (%)	24.1	28.2	31.6	37.0

EFD = energy flux density; IIEF-EF = International Index of Erectile Function-erectile function domain; Li-ESWT = low intensity extracorporeal shockwave therapy; MCID = minimal clinically important difference; SEP = sexual encounter profile.

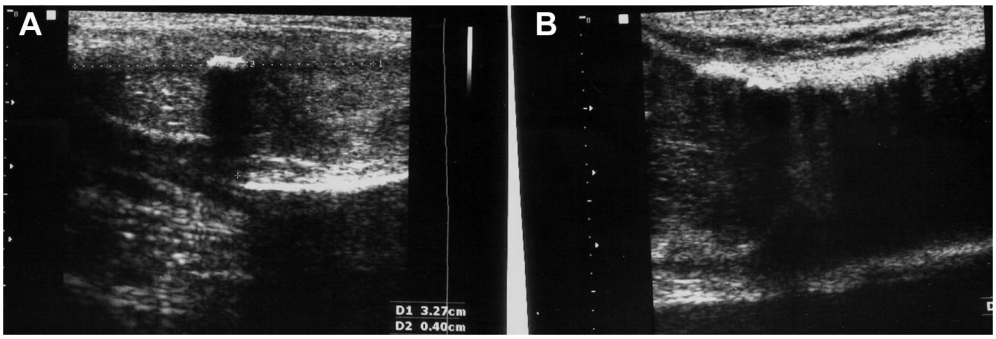


Figure 22. Sonography of a PD patient with palpable plaque on the dorsal surface. (A) Sonography in the flaccid state only shows a small calcified plaque. (B) Sonography in the full tumescent state after intracavernosal injection of PGE1 shows a much bigger fibrotic plaque with a small embedded calcified area. PD = Peyronie's disease; PGE1 = prostaglandin E1.

introduced by the clinical research group of Hatzichristou, we are now focusing more on concentrated protocols with 2–3 sessions weekly over 4 weeks with impressive results (Table 15).[63,64] However, these treatment protocols also are not really meeting many patients' needs, with most of them being engaged in a daily job and unable to manage during their business hours 3 sessions a week over 4 weeks with distances of 100–200 km or even more depending on their home location.

The first personal experiences with such more concentrated protocols are very promising and encouraging. With respect to the EFDs used in the published studies with the different devices, there was a broad variation between 0.05 and 0.25 mJ/mm^2, which also applies for the number of shots per session ranging between 600 and 5,000. As has been illustrated in Tables 3–14 and described in the text, the biological effects that yielded the crucial energy are not the EFD but the total energy in the −6 dB focus and even more importantly in the 5 MPa focus. As outlined earlier, regarding these well-established technical parameters, there are considerable differences between the ESWT machines and energy sources.

With these facts in mind it is really difficult to expect that only one energy and one protocol may be able to sufficiently accommodate all our patients irrespective of the underlying ED etiology. The same statement applies for the huge variability of individual PD features as reflected by the different sonographic features.

At present all the patients in the published studies were treated with the same protocol regardless of the ED severity and the diagnostic findings, ignoring the huge variation in penile sizes and volumes. The same statement applies for the fact that the same treatment protocols were used for PDE5i responders and non-responders ignoring the huge variation in cavernous residual capacity and cavernosal structure changes.

So far there is increasing evidence that ESWT may yield better results in studies administering more shots per session and shorter duration, that is more sessions per time period.[7,13,14]

Considering all these individual differences in ED and PD patients, the future of ESWT will be a more individualized than a fixed treatment protocol with individually determined energies, number of shots, and number of sessions depending on the diagnostic findings, including ic vasoactive drug testing with color Doppler, measurement of penile size, measurement of number, structure and thickness of plaques, and degree of penile curvature in PD patients.

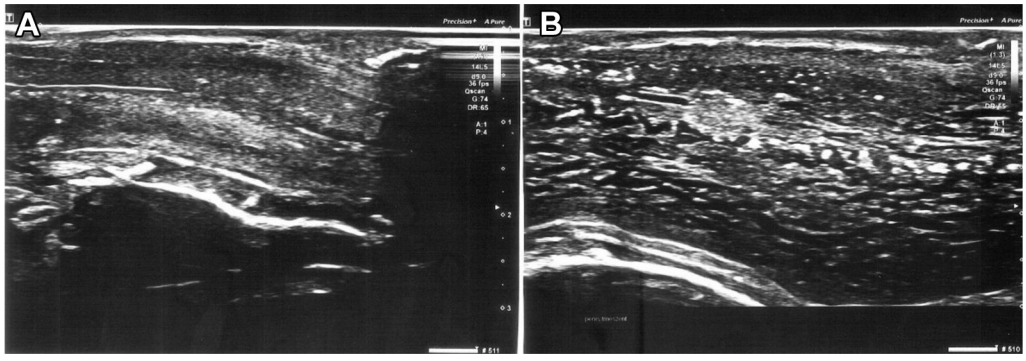


Figure 23. A, B: 58-year-old patient with a 6 months history of PD and palpable induration: the fibrotic septum plaque is only shown in the full tumescent state after PGE1 injection. PD = Peyronie's disease; PGE1 = prostaglandin E1.

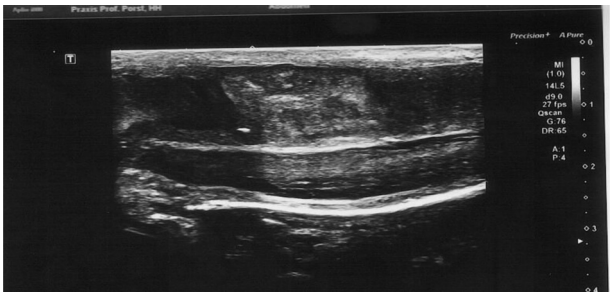


Figure 24. Severe intracavernous fibrosis in a 45-year-old patient with a 4 months history of PD. PD = Peyronie's disease.

Last but not least, there is convincing evidence that the combination of ESWT with daily dosing PDE5i is clearly superior to ESWT alone as has been shown in the preclinical and clinical setting, a strategy we are consequently pursuing in each of our patients since the initiation of ESWT in our institute.[6,14]

Based on the very recent findings in naturally aged rats, in whom Li-ESWT was able to modulate the expression's ratio of alpha-1/alpha-2 adrenoceptors in favor of the erection supporting alpha-2 receptors with subsequent decrease of the erection inhibiting effects of the alpha-1 adrenergic nerve terminals, ESWT may also be suitable for all men with chronically increased sympathetic activity and performance anxiety resulting in the so-called psychogenic ED.[12]

In several animal model settings earlier, that is with the onset of cavernosal nerve injury, administration of daily PDE5i was able to avoid or at least attenuate most of its negative consequences.[58–62] In addition, Tom Lue's research group was able to prove that early Li-ESWT after cavernous nerve injury resulted in angiogenesis, tissue restoration, and nerve

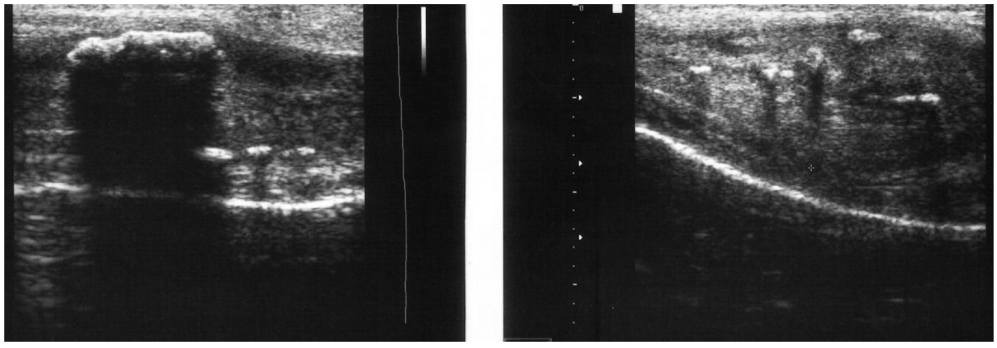


Figure 25. Sonograpy of the penile shaft mid and distal parts: one of the many challenging PD cases with a history of 9 months, calcified plaques at the dorsal and ventral surface (left half) as well as scattered intracavernous calcifications. PD = Peyronie's disease.

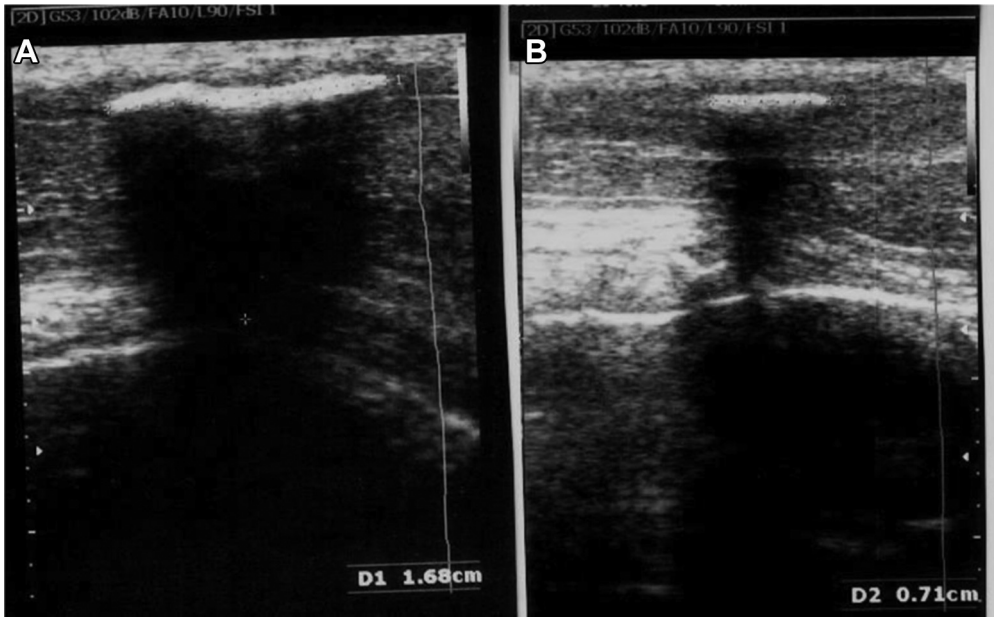


Figure 26. A: 55-year-old patient with a 6 months history of PD: big palpable, ventrally located and calcified plaque, and 65° ventral curvature (left side). Sonography probe was located on the ventral surface. B: After 6 weekly ESWT sessions with the Dornier Aries 2 device and under tadalafil 5 mg, plaque reduction from 1.68 to 0.71 cm and decrease of ventral deviation from 65° to 15° occurred. ESWT = extracorporeal shockwave therapy; PD = Peyronie's disease.

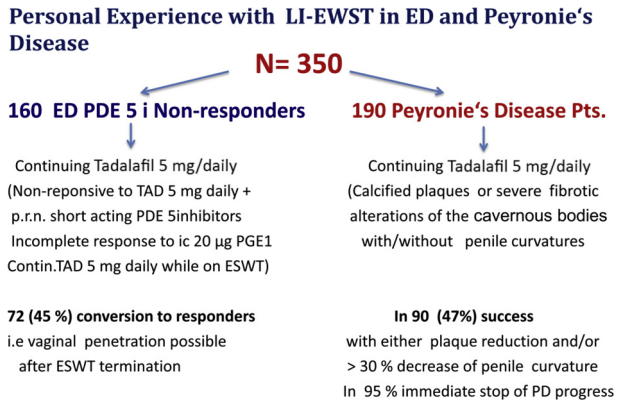


Figure 27. Personal experience with Li-ESWT in ED and PD over the past 4 years. ED = erectile dysfunction; ic = intracavernosal; Li-ESWT = low intensity extracorporeal shockwave therapy; PD = Peyronie's disease; PDE5 inhibitors = phosphodiesterase type 5 inhibitors; PGE1 = prostaglandin E1; p.r.n. = when necessary; TAD = tadalafil.

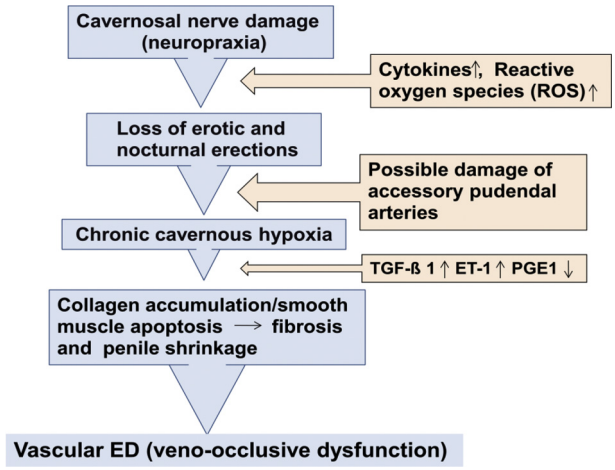


Figure 28. The detrimental cascade after pelvic surgery resulting in vascular (veno-occlusive) ED. Modified after Hatzimouratides et al.[55] ED = erectile dysfunction; ET = endothelin; PGE1 = prostaglandin E1; TGF = transforming growth factor.

regeneration with more endogenous progenitor cells recruited to the damaged area and Schwann cells. This means that Li-ESWT facilitated more complete rehabilitation of penile tissue with regeneration of nNOS positive nerves from the major pelvic ganglion to the penis.[7,9] It is interesting to note that these positive findings were even more pronounced with higher energies used (EFD 0.09 mJ/mm^2 with 1,000 pulses at 3 Hz instead of EFD 0.06 mJ/mm^2 with 300 pulses at 3 Hz).[7]

At present there is only one small clinical study published on this subject starting with Li-ESWT only 1 year after surgery and showing no positive outcome of ESWT.[25] Based on preclinical animal findings, Li-ESWT should therefore ideally start very early within weeks after pelvic surgery and under daily PDE5i medication like tadalafil 5 mg.

As outlined earlier, the situation with patients with PD is quite different as compared to patients with ED because of the variety of clinical features with different sonographic findings (Figures 23–26). Based on both some studies in the literature and own experiences, ESWT is able to show promising results but only in special patient groups.[34] According to our temporary results, patients with a relatively short history of PD < 12–15 months and with calcified plaques, severe fibrotic thickening of the septum, or extensive intracavernosal fibrosis are the most promising candidates for Li-ESWT treatment in PD.

Without any doubt the future of penile ESWT lies in individualized treatment protocols based on a thorough diagnostic work-up. The chosen energies as well as the number of shockwaves and sessions including the applicators—linear focused or focal focused—depend on the individual findings and also on the individual patient's tolerance and may exceed EFDs beyond 0.25–0.30 mJ/mm^2, energies which are not available with each of the currently marketed ESWT machines. And regardless of the indication, Li-ESWT on the penis should always be combined with daily dosing of a PDE5i, preferably with tadalafil 5 mg.

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