Extracorporeal Shock Waves in the Treatment of Nonunions

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Background: **Nonunion remains a major complication after skeletal trauma. In the last decade, extracorporeal shock wave therapy has become a common tool for the treatment of nonunions. To date, no prospective, randomized trial has been conducted to show the efficacy of this form of treatment.**

Methods: **This study was performed to determine the value of extracorporeal shock wave therapy for nonunions. Previous published results in the literature and our own clinical results were analyzed and related to the natural history of bony union.**

Results: **No study has proven that extracorporeal shock wave therapy improves bone healing. Clinical studies reporting the acceleration of union after application of shock waves instead seem to misinterpret the natural history of bony union.**

Conclusion: **No evidence supports the treatment of pseudarthroses with extracorporeal shock waves. A randomized, prospective, clinical trial with a control group has to be performed before a final decision can be made regarding this indication for extracorporeal shock wave therapy.**

Key Words: **Extracorporeal shock wave therapy (ESWT), Extracorporeal shock waves, Nonunion, Delayed union, Pseudarthrosis.**

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Nonunion remains one of the major complications after skeletal trauma or elective surgery despite advanced operative techniques and osteosynthesis material. Very often, revision surgery is needed, sometimes even requiring reoperations with autogenous bone grafts. Observing donor-site morbidity, Younger and Chapman found "major complications" in 8.6% and "minor complications" in more than 20%.[1] This explains the necessity for alternative treatments of nonunions such as pulsed electromagnetic fields and electrically pulsed current stimulation, of which promising results were reported 15 years ago.[2,3]

Extracorporeal shock wave therapy (ESWT), usually used for disintegration of stones in urolithiasis, has become a common therapy for orthopedic disorders in the last decade, mainly in central European countries. In 1996, the number of shock wave treatments for orthopedic indications in a single country were similar to the number of shock wave therapies used for urolithiasis (66,000 vs. 70,000). Manufacturers have already developed specific devices for orthopedic indications. At a consensus meeting in 1995, the indications for shock wave therapy were defined by an orthopedic group of a national lithotripsy society as enthesiopathies and pseudarthrosis. For pseudarthrosis, shock wave therapy was even the first-choice treatment, which was also confirmed in a recent study.[4,5]

The efficacy of ESWT has been demonstrated in a prospective, randomized trial with a control group for chronic calcifying tendonitis of the shoulder.[6] The benefit of shock wave therapy for nonunions has already been reported in various experimental[7–10] and clinical studies.[11–19] Acceptance for this kind of therapy has reached such an extent that a randomized, placebo-controlled, clinical trial was recently even not allowed by an ethical committee.[16]

The aim of the present study was to determine the value of extracorporeal shock waves for the treatment of nonunions, analyzing previous published studies and our own clinical results. For the first time in the literature, these results have been compared with the natural history of union.

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MATERIALS AND METHODS

Extracorporeal Shock Waves

The basic mechanism of shock waves consists of a single-impulse acoustic wave with a high amplitude and short length. There are three different types that produce the shock wave (piezoelectric, electromagnetic, and electrohydraulic). The diverging vectors of this wave are focused by an acoustic lens or a reflector shield. These components are situated in a water-filled balloon that is applied to the body at the location of the nonunion. The sound wave is transformed into mechanical force at the boundary of tissues with different rigidity, such as bone and muscle, leading to local tension.[15] A linear relationship between the energy level of shock waves applied to bone specimens and the severity of the resulting cortical bone defects is demonstrated. With high-energy shock waves, microfractures and gross cortical changes were detected, such as bone chips peeled from the cortex.[10] In vitro, destruction of bone cells as a short-term effect and cell stimulation as a medium-term effect are reported.[20] Other authors have suggested bone marrow stromal cell differentiation toward osteogenic lineage via membrane hyperpolarization.[21]

The power at the focus point is defined as the energy flux density (EFD) per impulse and is measured in millijoules per square millimeter. For some devices, the EFD is not defined and the energy level of shock waves is specified in kilovolts. High-energy shock wave therapy was performed in the present study with an electrohydraulic MFL 5000 Lithotriptor (Dornier Medizintechnik GmbH, Wessling, Germany).

The number of shock waves varied with the location and length of the nonunion (approximately 1,000/cm). A mean of 2,900 shock waves with an average of 23 kV was applied.

The exact EFD has not been evaluated for the MFL 5000, but approximations, imparted by the Dornier Company in comparison with the newer Epos Fluoro Lithotriptor, confirmed the high energy level of the shock waves applied with more than 0.7 mJ/mm^2 EFD. During the treatment, repetitive radiographic controls with image intensifier were performed. For localization, the entire x-ray C-arm could be revolved around the shock wave focus as indicated by the cross-hair on the x-ray monitor.

Patients

Between September 1995 and November 1999, shock wave therapy was performed on 73 consecutive patients, 34 women and 39 men, with the diagnosis of delayed union (n = 16) or nonunion (n = 57). In this study, nonunion was defined as a failed bone healing of more than 6 months.[22,23] Mean age was 42 years. A follow-up could not be performed on three patients. One moved to an unknown address after callus formation was seen 6 weeks after shock wave therapy of a posttraumatic nonunion of the forearm. Two patients in the delayed bone-healing group with metatarsal stress fractures refused radiographic controls, as they were free of complaint 6 weeks after therapy. All except one patient had aseptic lesions, although infection is one of the commonest causes for nonunion. The rationale are the exclusion criteria, which were bone tumors, pathologic fractures, recent infections, dysfunction of coagulation, nonunions close to the epiphyseal growth plate, pregnancy, nonunions of the thoracic bones, and nonunions close to the central nervous system.[15] This kind of therapy cannot be used for open fractures. Detailed information regarding primary diagnosis, location, and type of nonunion are listed in Table 1.

For ESWT, regional anesthesia is reported to be effective and well accepted by patients.[24] Therefore, regional anesthesia was offered to the patients in our study. However, more than half of the patients opted for general anesthesia. Twelve patients were treated twice, so a total of 85 ESWTs were performed: 46 with general anesthesia and 39 with local, plexus, or spinal anesthesia.

Immobilization was carried out with plaster or brace for 6 weeks to 3 months after therapy except in cases of sufficient internal stabilization. Radiographic controls were performed 6 weeks and 3 months after therapy and then intermittently in the event of persistent nonunion.

Table 1 **Detailed Information of All Patients Treated with Extracorporeal Shock Waves in the Present Study, Divided into Two Categories: Nonunions and Delayed Unions**

	Nonunions		Delayed Unions	
	No.	%	No.	%
Diagnosis				
Arthrodesis	6	11	1	7
Elective osteotomy	22	39	9	64
Fracture	24	43	4	29
Others	4	7		
Localization				
Long bones	45	80	13	93
Others	11	20	1	7
Type of nonunion				
Hypertrophic	34	61	12	86
Atrophic	22	39	2	14
Time between primary diagnosis and ESWT (mo)				
Mean	19		5	
Maximum	74		5	
Minimum	6		0.2	
SD	15		3	

Review of the Literature

Attention was paid only to peer-reviewed studies of ESWT published in journals listed in the *Index Medicus*. Personal communications, performances, and contributions to books were disregarded in this study. For results of extracorporeal shock wave therapy, a systematic research of the literature was performed via the Internet in the National Center for Biotechnology Information at the National Library of Medicine.

To better understand the natural history of bone union, a search was conducted for studies that showed a long period of observation after the initial trauma. PubMed supplies an immense number of studies containing history of union, almost all of them related to cases after specific operative interventions. Only three studies specified the lapse of time of natural history of bone union (see Results). The *AO: Principles of Fracture Management* had no reply to this problem.[25]

RESULTS

Personal Results

Detailed information of all treated patients can be seen in Table 2. Similar to the literature, union was achieved in 56% of patients with nonunions; better results were achieved for hypertrophic nonunions (62% vs. 50% for atrophic nonunions). Patients treated twice did not show a higher rate of bony union (56%). Mean time between shock wave therapy and bony consolidation was 5.3 months, ranging from 1 to 16.5 months.

In contrast to this, the group of patients with delayed bone healing did show a higher and earlier rate of union (93%; mean time to union, 3.4 months; range, 0.2–4.9

Table 2 Detailed Information of All Patients with Bony Union after Extracorporeal Shock Wave Therapy[a]

	Nonunions		Delayed Unions	
	No.	%	No.	%
Diagnosis				
Arthrodesis	3	50	1	100
Elective osteotomy	13	59	9	90
Fracture	13	54	4	100
Others	3	75	0	0
Localization				
Long bones	25	55	12	92
Others	7	63	1	100
Type of nonunion				
Hypertrophic	21	62	11	92
Atrophic	11	50	0	0
Time to union (mo)				
Mean	5.3		3.4	
Maximum	16.5		4.9	
Minimum	1		0.2	
SD	4		1.4	

[a] Unions quoted in number of patients and percentage of the initial collective (see Table 1), time to union of these patients listed in detail.

months). The survival curve of nonunions is presented in Figure 1, in comparison with the results published by Beutler et al.[11] and Rompe et al.[16] In our study, no precarious side effects and only minor complications such as transient soft tissue swelling or smaller subcutaneous bleedings were observed.

Results in the Literature: Extracorporeal Shock Wave Therapy

Twenty-nine studies were found in the PubMed–National Library of Medicine database within the context of extracorporeal shock wave therapy supporting bone healing. Ten of these studies were clinical studies, but four of these articles, published by the same research group, obviously reported with the same patient material. Results of previously published clinical studies and our study are presented in Table 3.

Localization of nonunions in these studies is heterogeneous, but most of the affected bones are long bones of the lower extremity. The vast majority of these patients had one or more previous operations and were surgically stabilized with a plate or intramedullary nail.

Results in the Literature: Natural History of Union

One hundred consecutive closed fractures of the adult tibial shaft treated by closed methods so that their natural history could be observed were investigated prospectively by Oni et al.[26] Sarmiento et al. treated a total of 780 open and closed tibial fractures with functional bracing.[27]

The time course of the natural history of union in a cast is given the most detailed description by Marsh.[28] Oni et al.[26]

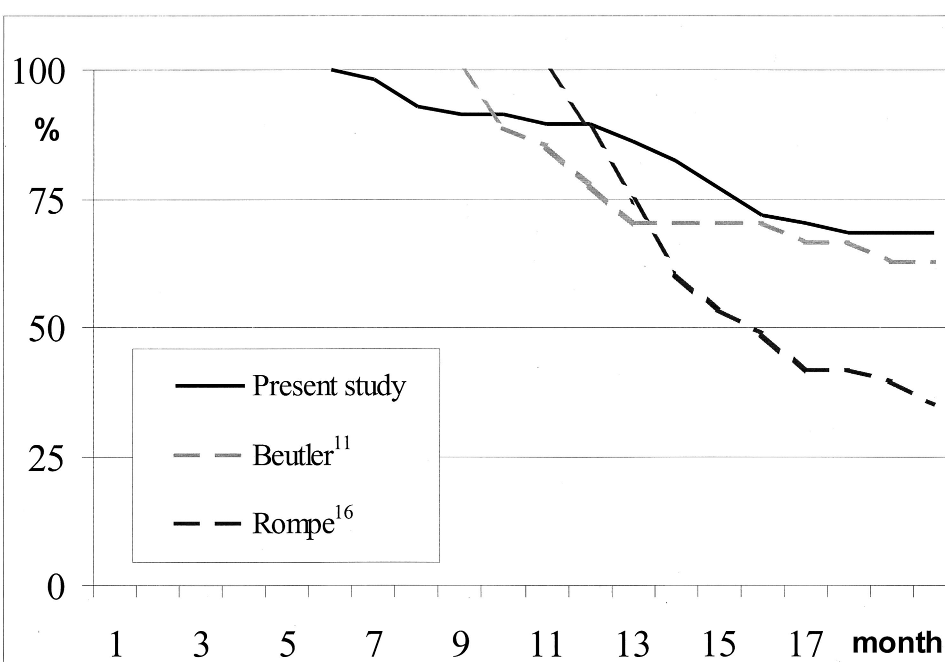

Fig. 1. *Decrease of nonunions with time as presented in three independent studies dealing with extracorporeal shock wave therapy for nonunions. 0–100, persisting nonunions in percent; 1–17, months after the initial trauma. Point of time for the shock wave therapy differs, but was performed after a minimum of 6 months of persistent nonunion. This chart turns extracorporeal shock wave therapy up, to be an effective form of intervention.*

Table 3 Results of All Previous Published Clinical Studies and the Present Study, Treating Nonunions with Extracorporeal Shock Waves[a]

Author	Patients	Before	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)
Valchanou and Michailov, 1991[18]	79	20			85 (time to union not mentioned)			
Schleberger and Senge, 1992[17]	4				Induction of callus in 75% within 6 wk			
Vogel et al., 1997[12,13]	52	13			52			
Rompe et al., 1997[14,15]								
Beutler et al., 1999[11]	27	9			41			41
Rompe et al., 2001[16]	43	11	0	2	19	42	63	67
Wang et al., 2001[19]	72	—			40			61
Schaden et al., 2001[5]	115	—			76 (time to union not mentioned)			
Present study (nonunions)	57	19	13	20	25	29	32	38

[a] Patients = number of patients included; before = mean interval between initial trauma and shock wave therapy; 1–6 = month after shock wave therapy, unions quoted cumulative in %.

and Sarmiento et al.[27] did not consider changes with time to that extent. Results of these three studies at monthly intervals are presented in Table 4, demonstrating that union is a gradual, continuous process that can last 1 year.

DISCUSSION

Experimental and Animal Studies

Although some authors are convinced that shock waves are not able to promote healing in nonunions,[29,30] most of the experimental and animal model studies seem to be very promising.[7–10] Nevertheless, the results of fracture healing studies in animal models based on the relationship of that particular model with bone healing in humans should be questioned.[31] Park et al. have shown different behavior of closed fracture and open osteotomy in animal models.[32] Nunamaker pointed out that the same model in different animal species might produce conflicting results and that only the human experience will determine the clinical value.[31]

Clinical Studies

All clinical studies report positive effects of shock waves on delayed union or nonunion with varying rates of success. In a prospective study of 276 patients, no precarious side effects have been observed within 3 years after shock wave therapy.[33] The authors stated that, in general, lithotripsy has only minor complications when used accurately. Nevertheless, caution must be exercised because of the uncertainty of possible long-term side effects. Only a few authors have mentioned critical aspects for this kind of therapy. Rompe et al. criticized the heterogeneity of patient material in the previous published studies.[14] Heller and Niethard detected a deficiency in the study design of most previous published studies and regarded the operative treatment of nonunion as the "gold standard" and extracorporeal shock wave therapy as a clinical experimental procedure.[34]

When union occurred, we detected suspiciously long intervals between shock wave application and bony union, in some cases even exceeding the definitions of nonunion (6–12 months). Other authors reported on follow-up examinations of 12 months[19] and even up to 4 years[5] after shock wave therapy. In the face of these time intervals, the issue arises as to within which period of time is the incidence of union therapy related.

When analyzing the literature, it becomes evident that the appreciation of nonunion and pseudarthrosis varies. According to the *AO–Principles of Fracture Management*, delayed union describes the situation where there are distinct clinical and radiologic signs of prolonged fracture healing time. Unless there is bone loss, a nonunion is usually declared between 6 and 8 months after fracture. Pseudarthrosis is defined as formation of a false joint where a fibrocartilaginous cavity is lined with synovium producing synovial fluid.[25] Almost all previous published clinical studies followed Wirth's arbitrary definition of pseudarthrosis as absence of union for more than 6 months.[23] However, Oni et al. demonstrated that fractures at this point of time still show osteogenic potential. If a fracture was not united at 20 weeks, the chances of union at the end of 30 weeks were better than 5:1.[26] Hayda et al. stated that delayed union is a clinical diagnosis, reflecting the fact that the restorative process for a specific fracture was not completed within the interval expected for the repair.[35] Other authors have shown that almost

Table 4 Percentage of Bone Healing Over Time under Conservative Treatment[a]

Author	No.	1	2	3	4	5	6	7	8	9	10	11	12
Oni et al., 1988[26]	100					81			96				
Sarmiento et al., 1989[27]	780												98
Marsh, 1998[28]	43			58		91		93			95		98

[a] This table demonstrates that fracture union is a gradual continuous process lasting up to 1 year. 1–12 = month after initial trauma, unions quoted cumulative in %.

all nonunions will heal if left long enough in a cast.[26] After shock wave therapy, immobilization was performed in all published studies. Mechanical stability leads to calcification of the fibrous cartilage, which can only then be penetrated by new vessels, finally allowing bony bridging and remodeling of the nonunion site.[25] Although shock waves produce microfractures, the bone remains stable. Therefore, stabilization is not required as a consequence of shock wave therapy but rather is an additional form of treatment. Resuming application of shock waves in medicine, Thiel clarifies that the stabilization of the fracture after shock wave therapy seems to be an essential condition for the success of the therapy.[36] Among 147 nailed tibial shaft fractures, Böstman and Kyrö found an incidence of delayed unions of the fibulae of 5.4% at 4 months. No further union was detected at the time of removal of the nail—usually after 2 years. When a follow-up examination was performed 5 to 8 years after the original injury, four of eight fractures ultimately healed spontaneously.[37] In consideration of these facts, application of extracorporeal shock waves has taken place at a point of time where, according to the literature, the healing process continues.[38]

The efficacy of shock wave therapy is always presented in a manner of a certain percentage of achieved unions within a period of time (Table 3 and Fig. 1). However, it has to be taken into account that the chosen cases are a selection of worst-case scenarios, representing approximately 2% to 5% of patients with injuries or elective osteotomies.[15,22,27,28]

In Figure 2, the results after extracorporeal shock wave therapy of three independent studies are compared with the natural history of union according to Marsh[28] and Oni et al.[26] and presented as a survival curve of nonunions with time. The percentage of patients with nonunions was determined to be 5% at 6 months. Direct comparison of Figures 1 and 2 clearly demonstrates the problem of retrospective studies without a control group: whereas in Figure 1 the positive effect of shock waves on bone healing seems obvious (up to 50% union of treated patients within the observation period), Figure 2 clearly demonstrates no acceleration of union in the treatment group compared with the natural history of union, although data similar to those in Figure 1 are presented. The impressive steep curves of Figure 1 are reduced to flat curves, presenting a decrease of nonunion of approximately 2.5% within the observation period. Looking at the data of Marsh,[28] the chance for a final union within 3 to 4 months after 6 months of nonunion is approximately 50%, the same as reported after extracorporeal shock wave therapy.[11]

Union is not a scalar, monolithic process but a gradual continuous process lasting sometimes more than 1 year.[28] Indicating further therapeutic steps, a surgeon must be aware that diagnosis of nonunion should not be made just on the basis of a set period of time, because nonunion is a biologic

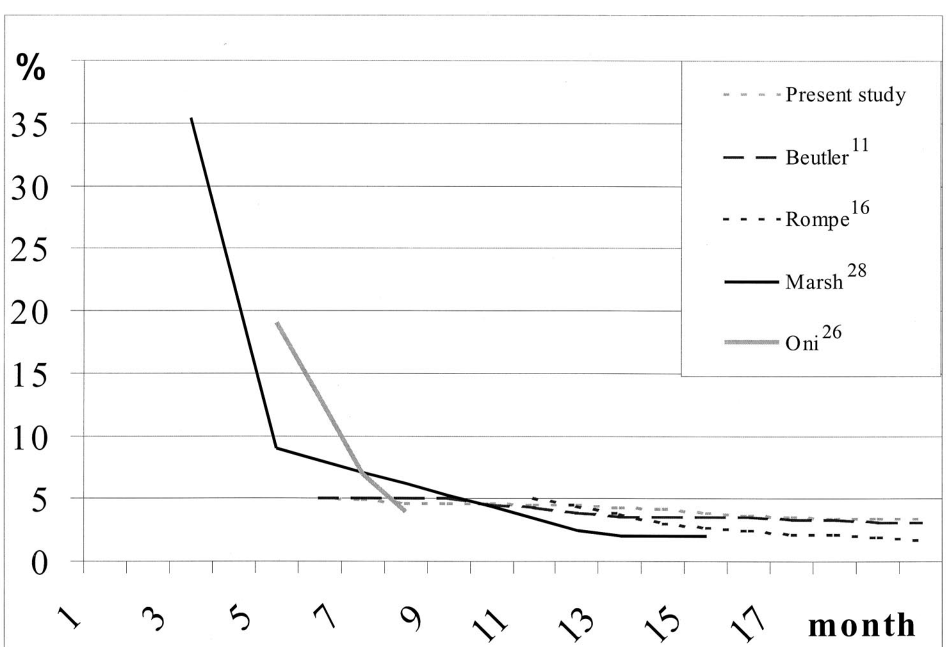

Fig. 2. *Decrease of nonunions with time as presented in three independent studies dealing with extracorporeal shock wave therapy for nonunions* (dotted lines)*.[11,14] According to the literature, the incidence of nonunions at 6 months was ascertained to be 5%. The natural history of bone union as published in two independent studies is presented the same way* (continuous lines)*.[26,28] No acceleration of bone healing after shock wave therapy* (dotted lines) *can be detected in comparison with the natural history of bone union* (continuous lines)*. See also Figure 1.*

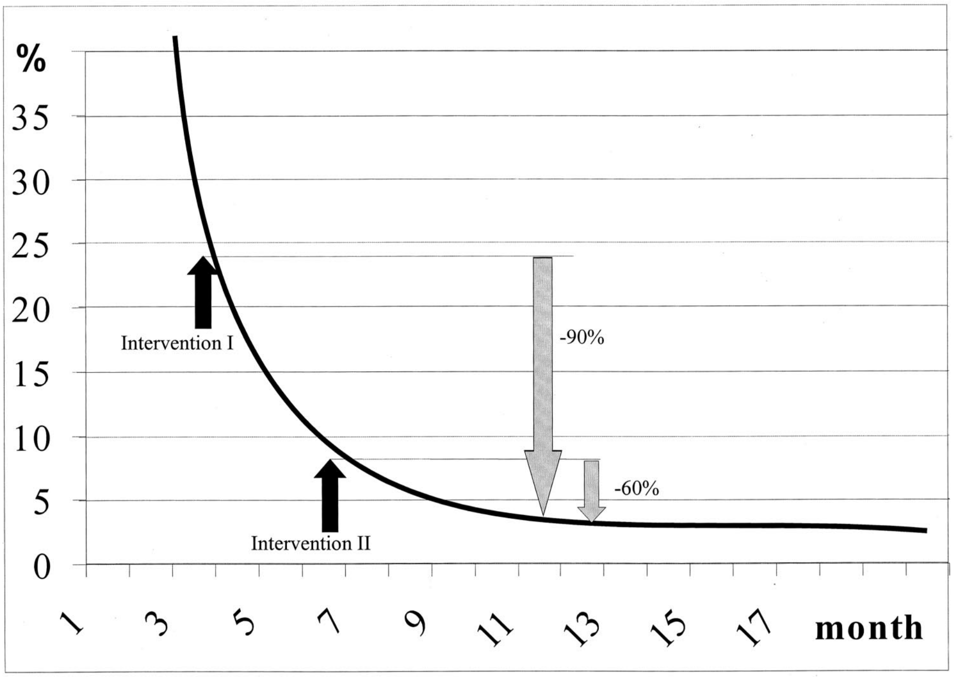

Fig. 3. *Graphic model of the natural history of union according to the data presented in Figure 2 (interpolated curve), presented as a decrease of nonunions in a time flow. All interventions performed on these patients will seem effective unless they hinder progression of union. Intervention I corresponds to extracorporeal shock wave therapy for delayed unions similar to the present study (healing rate, 90%). Intervention II corresponds to shock wave therapy performed at a later date for nonunions as in the present study and published in the literature (healing rate, 60%).*

rather than a chronologic state. Defining nonunion only on the basis of a time period should be abandoned.

The cycle of decreasing nonunions is demonstrated as a chart in Figure 3. This chart demonstrates the present problem in studies dealing with ESWT for nonunion: the natural history of bone healing may be wrongly interpreted as resulting from an intervention. This current problem needs clarification by way of a prospective randomized study. Any form of treatment that would accelerate time for healing and union would be a great benefit to the patient, namely, decreasing the time of disability, financial loss, domestic strife, and other factors.

CONCLUSION

No previous published study could prove the efficacy of extracorporeal shock wave therapy on bone healing. Clinical studies reporting acceleration of union after application of shock waves instead seem to misinterpret the natural history of union. Therefore, no evidence is given for treatment of pseudarthroses with extracorporeal shock waves. A randomized, prospective, clinical trial with a control group is justified and has to be performed before a final decision can be made regarding this indication for extracorporeal shock wave therapy.

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