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Shock Waves (SW) Noninvasive Extracorporeal Thrombolysis Treatment (NISWT)

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ABSTRACT

A group of 24 patients were considered for noninvasive shock waves thrombolysis (NISWT). Of these, 15 patients gave their informed consent. NISWT was attempted in eight patients (while seven patients were randomized for follow-up only). NISWT was possible in six of seven patients. In one patient randomized for NISWT, local inguinal scarring, due to previous surgery, made impossible the visualization of the femoral vein, and therefore focusing of shock waves (SWs). No side effects were reported in the days after SWs administration during the 4-month follow-up. In patients treated with NISWT it was possible to observe just after the SWs session the presence of echolucent "acoustic holes" and flow (by color and power Doppler) within the "holes." All "echolucent holes" produced at the first session were still present at 4 months, and color flow imaging also detected new flow channels in echogenic areas of thrombi previously not visible. In one patient thrombolysis was achieved after the first treatment, but at 3 and 4 months the thrombus was completely avascular. In conclusion, thrombolysis using SWs was obtained in selected cases and it was still persisting at 4 months in six of the seven treated patients. NISWT appears feasible and promising. These results should be confirmed by larger, prospective trials.

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Introduction

Shock waves have been mainly developed and used for noninvasive treatment of kidney and gallbladder stones and for other applications (eg, orthopedics).[1] Experimental and early clinical cardiovascular applications of SWs have recently been reported.[1] A new method, defined as noninvasive shock wave (SW) thrombolysis (NISWT), has been experimentally attempted in in vitro experiments and in a clinical setting using a modified SWs generator prototype (Storz-Minilith).[2]

After initial testing to evaluate in vitro the nondamaging effects of SWs (by high-resolution ultrasound and histology) on the vascular (both arterial and venous) walls at a wide range of SWs intensity and time of exposure to SWs, the first attempt at NISWT was made in May 1998 (using 800 shots of SWs at the intensity conventionally defined as 2 (equivalent to 0.04 mJ/mm^2) in a stable, echogenic thrombus at the common femoral vein.

In the first case[3] a partially echogenic thrombus (common femoral vein thrombosis had been present for more than 3 months), the patient was receiving stable anticoagulant treatment. After SWs treatment in a single session the following ultrasound findings were observed:

1. A marked echolucency (possibly corresponding to localized clot lysis) in several areas within the thrombus
2. The presence of flow (seen by color duplex and power Doppler), which was not visible before NISWT. These observations were still present at the follow-up high-resolution ultrasound, and color flow imaging studies repeated at 1, 2, and 3 months after NISWT. No side effect or pain had been observed after the first case.

After showing the feasibility of noninvasive clot lysis, a pilot study was planned to evaluate the potential clinical applications of NISWT in venous thrombosis. The aim of this pilot study was to evaluate whether the use of NISWT may hasten the spontaneous thrombolysis and recanalization of stable femoral vein thrombi in a randomized study lasting 4 months.

Patients and Methods

NISWT was attempted in a randomized protocol using SWs (1,000 shots at coded intensity 2–3) applied to six different levels of focusing within the femoral thrombus. After high-resolution ultrasound evaluation of the thrombus (using an ATL 5000, with a 10 MHz Broad Band probe), careful aiming and focusing onto the thrombus was obtained by using a Kontron high resolution scanner (Kontron, Switzerland) with a 7.5 MHz probe coupled to the SWs generator. SWs were used to induce local thrombus lysis. Lysis was documented by ultrasound as areas of echolucency in an otherwise partially echogenic thrombus (Figure 1) with the presence of "acoustic holes" within the thrombus and presence of flow at color duplex or power Doppler examinations. Four to six holes were produced at the common femoral vein bifurcation, weakening the structure of the thrombus with the aim of improving recanalization and hastening spontaneous lysis.

The initial study included a group of 15 patients (mean age 48, sd 13 years, range 36–62) randomized into two treatment groups (Table I):

1. Control group: standard treatment with oral anticoagulation and graduated compression (Kendall TED antiembolism stockings) only (seven patients)
2. Same treatment associated with SW treatment (one treatment weekly for 4 weeks) (eight patients)

Patients with the following characteristics were included into the study:

1. Stable, echogenic thrombus
2. Permanent and effective anticoagulation treatment (at least 4 previous weeks of stable treatment)
3. No previous episodes of pulmonary embolism (negative chest radiograph and ventilatory/perfusional scintigraphy)
4. Complete, stable thrombotic occlusion of the iliac veins (abolishing the risk of embolization)
5. Absence of other serious cardiovascular disorder requiring medical treatment (concomitant with anticoagulants)
6. Age range between 35 and 65 years
7. Thrombosis not lasting more than 6 months and not less than 4 weeks.

All patients with coagulation problems were excluded. Patients were included only after giving informed consent. Diagnosis and management of

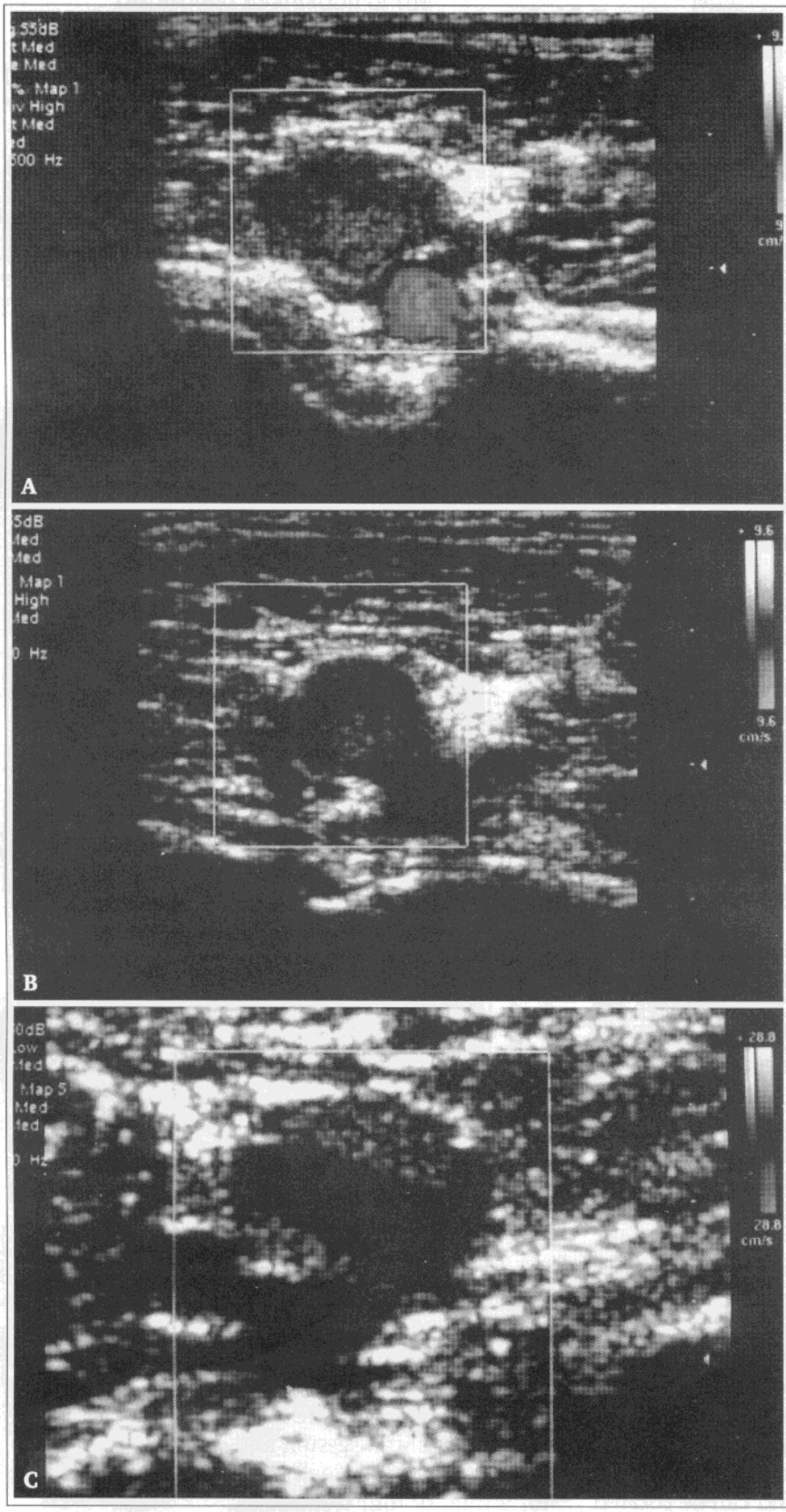


Figure 1.
Ultrasound example of a femoral vein thrombus before (**A**) and after initial thrombolysis and partial dissolution of the thrombus (upper part in **B**) and at the end of the first session. The break in the thrombus in this section is visible as the darker (echolucent) perfused area present after SWs thrombolysis. The thrombized sections and flow areas are distinctly visible (**C**).

Table I

Details of Patients Included into the Study

	No.	Age Years (sd)	Range	Sex M:F
Total	15	48 (13)	36–62	9:6
NISWT	7	47 (11)	36–62	5:3
Control	7	49 (15)	37–62	4:3

venous thrombosis were considered on the basis of the Consensus Document of Venous Thromboembolism[4] and on previous publications[5,6] from our group.

The SWs Generator

The prototype litotriptor (Minilith SWs generator, Storz, Kreuzlingen, Switzerland) was considered on the basis of previous safety evaluation and an in vitro study performed using the same instrumentation to be used in the NISWT study (Figure 2). The apparatus was originally designed for orthopedic applications. The Minilith SL1 (Storz, Medical, Switzerland), had been modified for thrombolysis applications.

Mounted on an articulated arm the SWs source is coupled to the patient's target area to treat with a soft, silicon water cushion. SWs are produced electromagnetically by a cylindrical coil surrounded by a metallic membrane. A parabolic reflector focuses the cylindrical waves to the target area. The focal pressure can be adjusted between 6 and 70 Mpa in eight steps. The energy flux density is variable from 0.03 to 0.5 mJ/mm^2. Focal diameter (FWHM) is 3 mm: Focal distance is fixed relative to the reflector rim and is adjusted to the patient by inflating or deflating the coupling water cushion, giving a depth of target area within the patient of about 70 mm. Shock waves are released with up to four shots per second. The target area can be monitored on-line during the procedure by a 7.5 MHz ultrasound system (B-mode) coupled with the generator. The mechanical sector transducer is mounted coaxially to the cylindrical opening of the coil and can be rotated according to the need. The SWs focus is marked on the ultrasound screen by an electronic viewfinder (cross-hair).

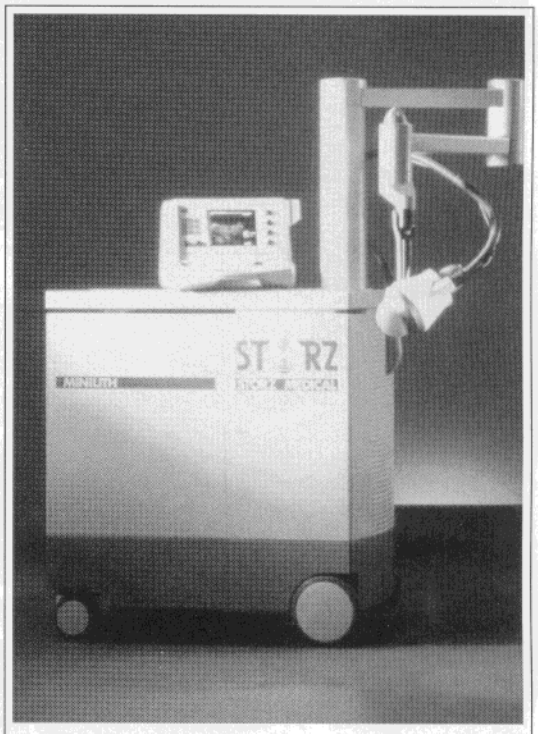


Figure 2. The shock waves generator.

All treatments were attempted and performed in a single initial session and repeated in one single session every week in the following 3 weeks for a total of four treatments.

Ultrasound Evaluation of the Thrombus and Follow-up

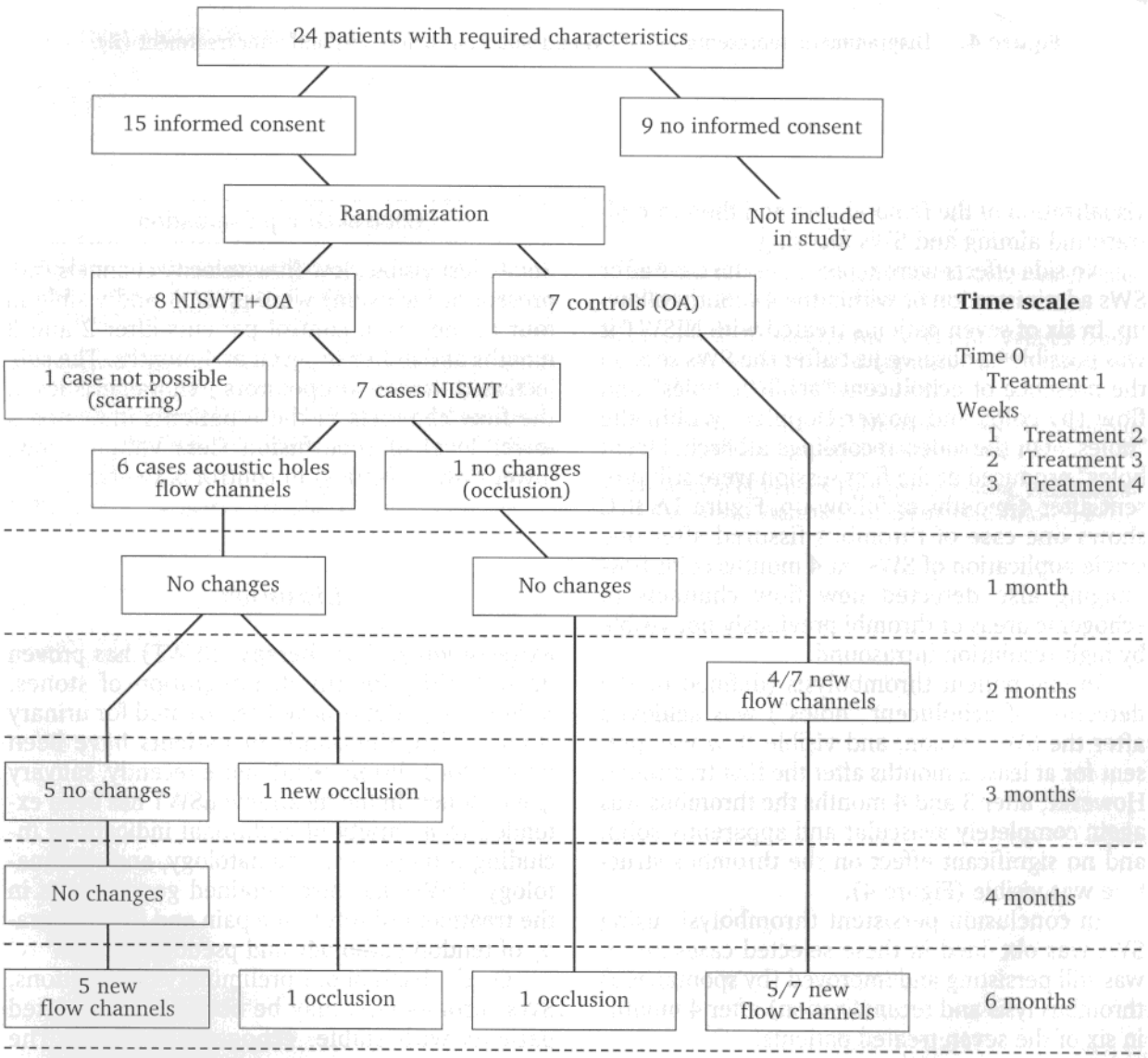
Inclusion data and results were evaluated with high-resolution ultrasound (B-mode, color, and power Doppler) by use of an ATL 5000 with a 10 MHz, high-resolution, Broad-Band probe). Ultrasound was repeated after inclusion (at 2, 3, and 4 months after the SWs treatment). The final result was evaluated in terms of thrombus echogenicity and vein patency after 4 months of follow-up after NISWT.

Results

A group of 24 patients with the needed characteristics were considered for randomization. However, only 15 gave their informed consent. Therefore NISWT was attempted in eight randomized patients (while the remaining seven were randomized for follow-up only) (Figure 3).

NISW treatment was possible according to the protocol in seven patients. In one patient randomized for NISWT, local inguinal scarring, due to previous surgery, made impossible the correct

Figure 3. The patients' flow chart. OA = oral anticoagulants.



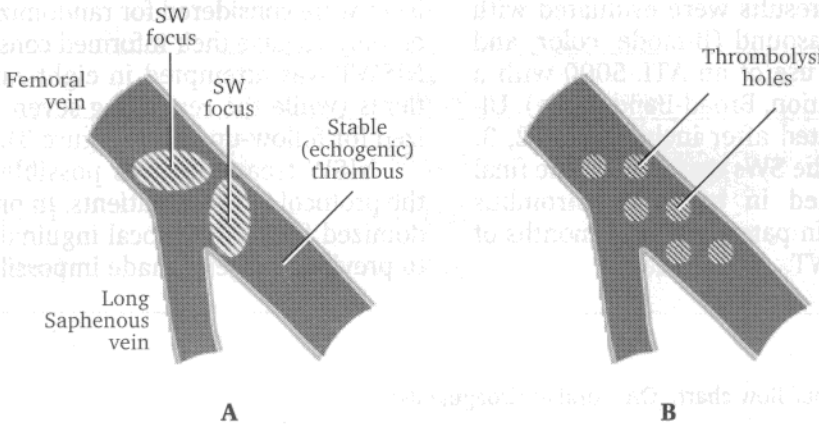


Figure 4. Diagrammatic representation of SWs thrombolysis before (**A**) and after treatment (**B**).

visualization of the femoral vein and therefore ultrasound aiming and SWs focusing.

No side effects were reported in the days after SWs administration or within the 4-month follow-up. In six of seven patients treated with NISWT it was possible to observe just after the SWs session the presence of echolucent "acoustic holes" and flow (by color and power Doppler) within the "holes." On the video recordings all "echolucent holes" produced at the first session were still present after 4 months of follow-up. Figure 1A, B, C shows one case of thrombus fissured after one single application of SWs. At 4 months color flow imaging also detected new flow channels in echogenic areas of thrombi previously not visible by high-resolution ultrasound.

In one patient thrombolysis (defined by the detection of echolucent "holes") was achieved after the SWs session, and visible flow was present for at least 2 months after the first treatment. However, after 3 and 4 months the thrombus was again completely avascular and apparently solid, and no significant effect on the thrombus structure was visible (Figure 4).

In conclusion persistent thrombolysis using SWs was obtained in these selected cases and it was still persisting and improved (by spontaneous thrombus lysis and recanalization) after 4 months in six of the seven treated patients.

Control Group Evaluation

Small, just visible, low-flow velocity channels (not present at inclusion) were present and visible in four of the seven control patients after 2 and 3 months and in five of seven at 4 months. The subjective (ultrasound operators') characteristics of the flow channels in these patients indicated a lower level of reperfusion (less volume flow, lower flow velocities) in control patients.

Discussion

Extracorporeal SWs therapy (ESWT) has proven its suitability for the disintegration of stones. Millions of patients have been treated for urinary stones. Also, thousands of patients have been treated for gallstones and, more recently, salivary gland stones. In the meantime ESWT has been extended to a variety of additional indications including orthopedics, traumatology, and rheumatology. ESWT has also obtained good results in the treatment of soft tissue pain and in the therapy of tendon pathology and pseudoarthrosis.

On the basis of our preliminary observations, SWs thrombolysis may be obtained in selected patients with stable, echogenic thrombi. The

method appears to be effective and without side effects and/or significant risk for the patients. NISWT induces a faster recanalization of femoral thrombi by breaking the thrombus and producing new flow channels, which may be useful to enhance and speed up spontaneous thrombolysis and which may require months. The technique of NISWT is presently still experimental, but these promising findings may help in planning a larger and more prolonged clinical trial in this field.

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