Extracorporeal shock waves as curative therapy for varicose veins?

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Abstract: In this prospective design study the effects of low-energy partially focused extracorporeal generated shock waves (ESW) onto a subcutaneous located varicose vein – left vena saphena magna (VSM) – are investigated. The treatment consisted of 4 ESW applications within 21 days. The varicose VSM of both sides were removed by surgery, and samples analyzed comparing the treated and untreated by means of histopathology. No damage to the treated varicose vein in particular and no mechanical destruction to the varicose vein's wall could be demonstrated. However, an induction of neo-collagenogenesis was observed. The thickness of the varicose vein's wall increased. Optimization of critical application parameters by investigating a larger number of patients may turn ESW into a non-invasive curative varicose treatment.

Keywords: curative therapy, extra-cellular matrix (ECM), histopathologic changes of varicose veins, extracorporeal shock wave (ESW), progenitor cells

Introduction

Normal veins and varicose veins

From the lumen to the periphery of a normal vein one can recognize (Somers and Knaapen 2006):

(i) tunica intima: endothelium, a thin layer of smooth muscle cells (SMC) embedded in sub-endothelial connective tissue; the elastic fibers tend to be parallel to the inner elastic lamina.

(ii) tunica media: inconspicuous inner layer of longitudinally oriented SMC, and a more prominent outer layer of circular oriented SMC, both embedded in an extracellular matrix (collagen); the elastin pattern formation around individual SMC indicates spiral connection of contractile-elastic units of vein wall; the thickness varies from the proximal to the distal region of the vein according to the number of circumferentially orientated SMC whorls; the outer elastic lamina demarcates the end of the tunica media.

(iii) tunica adventitia: clusters of longitudinally oriented SMC, fibroblasts, capillaries (vasa vasorum), bundles of collagen and elastic fibers interwoven with each other to provide strength and resilience.

Varicose veins are found mainly at the lower extremities of the body, especially on the back of the calf or on the inside of the thighs and may involve saphenous veins, saphenous tributaries, or non-saphenous superficial leg veins and perforators. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. The prevalence of varicose veins is definitely underestimated and affects up to 40% of men and up to 51% of women (Somers and Knaapen 2006).

The vein wall distensibility is controlled by collagen, elastin, and SMC, the content of collagen is 47% and elastin is 7% of the normal venous vessel wall (Somers and

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Knaapen 2006). Dilatation and distensibility of a varicose vein is due to a deficiency in smooth muscle cells (these lose normal fusiform shape and gain marked phagocytic activity) and elastic fibers, and also to a disorganization of the elastin/collagen lattice network and a disproportionate increase in amorphous and fibrous tissue (Wali et al 2003). The lesions are not concentric (hypertrophy with atrophic areas), which explains the bulgings of varicosis.

The amount of collagen increases with senescence, a phenomenon known as phlebosclerosis (Leu et al 1991). Aging is defined as a genetic physiological process associated with morphological and functional changes in cellular and extra-cellular components (Drubaix et al 1998) aggravated by injury throughout life, resulting in a progressive imbalance of the control regulatory systems of the organism, including hormonal, auto-crine, neuro-endocrine, and immune homeostatic mechanisms (King 1988). According to this definition varicose veins could then be regarded more as an aging of the veins than as a disease.

Treatment options of varicose veins

Treatments of varicose veins have the common aim reducing venous recirculation and correcting the venous blood-flow. Table 1 shows the principal therapies.

In all these forms of therapy even fundamental measures are valued differently (eg, the necessity of crossectomy). In addition there is little known about the reason why long-term therapy results are essentially disappointing (predisposition, technical problems, delayed intervention, neoangiogenesis). Minkiewicz stated in 1862: "The plain number of surgically and therapeutically practices being proposed as healing methods against specific diseases is evidence that (i) either these practices are still not enough explored or (ii) that the real healing method is yet to be found. This analysis is very true for varicose veins and their usual surgery methods" (Minkiewicz 1862, 1869).

Table 1 Diverse measures to relieve from venous disease, no curative therapy

- Relieve venous load by elevation and by compression (compression socks, elastic bandage)
- Eliminating veins by surgery (crossectomy, stripping, phlebectomy by Muller, Trivex-process)
- Closing the lumen of veins (sclerotherapy, endovenous LASER and endovenous radio-frequency therapy)
- Correcting and preserving veins (external valvuloplasty, CHIVA-method)

Extracorporeal shock wave therapy (ESWT)

The extracorporeal generated shock wave therapy (ESWT) is the gold standard worldwide to treat urolithiasis. This method is used now for many other indications, eg, of musculoskeletal diseases (such as calcaneal spur, tennis-elbow, golf-arm, lime-shoulder, patella-tip syndrome, ectopic calcification, and pseudarthrosis) (Siebert and Buch 1997; Wang et al 2006) and of soft-tissue diseases (such as cellulite and venous ulcus cruris) as well as burns, and arterial and diabetic ulcus (Siems et al 2005; Sparsa et al 2005; Schaden et al 2006). The general positive response from our patients to ESWT, the observation of tissue strengthening and "regeneration" (Angehrn et al 2007; Kuhn et al 2007), as well as new methods and new results on effects, led us to investigate the effects of ESWT on varicose veins.

Posing the problem

What are the effects of ESWT on the varicose vein? No experimental or clinical data on this issue are available. Can this technique achieve a "*restitutio ad integrum*" of varicose veins? No healing procedures are known for varicose veins. The following hypotheses were tested (using adjustments of ESW device parameters as defined in Table 4) on changes in the varicose vena saphena magna (VSM):

- ESWT does not cause tissue injury.
- ESWT does not cause changes to the luminal wall of veins that would lead to thrombosis or occlusion of the vein.
- ESWT strengthens veins and stabilizes vein walls.
- ESWT improves venous function.

The physics of ESW

Shockwaves are acoustic pressure pulses of some microseconds duration that transmit energy from the place of generation, such as lightning strikes, to distant areas, where they are audibly perceived as loud thunder (as in lightening strikes). Shock waves (Figure 1) are presented by a single, positive pressure pulse arising from ambient pressure within nanoseconds to large amplitude up to more than 100 MPa followed by an exponential descent. Subsequently there is a comparatively small tensile wave component below ambient pressure with negative pressure up to 20% of the value reached by the positive pressure peak and of comparable long duration (2000 nanosec) (Gerdersmeyer et al 2002; Urhahne 2005; Wess 2006).

The bio-medical effects of ESW (Neuland et al 2004) depend on the form and amplitude of the shock wave at the

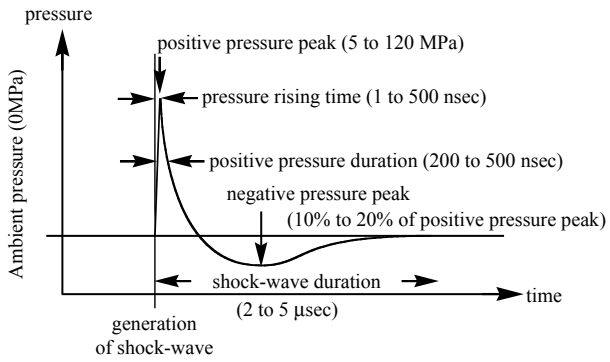

Figure 1 Pressure-time curve of a shock wave.

Table 2 Acoustical impedance values of different human body tissues

Substance tissue	Impedance [10^3 kg/s m^2] (lower and upper limits)
Air	429
Water	1480
Fat	138
Lung	260 —— 460
Brain	1600
Blood	1620
Kidney	1630
Liver	1650
Muscle	1650 —— 1740
Bone	3200 —— 7400
Kidney-stone	5600 —— 14400

place of interest within the tissue. The pressure-time curve at a specific location in the tissue is mainly dependent (i) on how the shock wave is generated (device-specific parameters) and (ii) on the path through the tissue: effects that make the pressure pulse even steeper due to non-linearities in the propagation medium as well as phenomena such as refraction and diffraction at acoustic interfaces have to be taken into consideration. Besides changing the energy flow density and the frequency of shock waves, their focus can be adjusted to generate defocused, partially focused, or focused shock waves. Defocused shock waves distribute radially into the tissue, where the intensity diminishes with the third potency of distance covered ($1/r^3$). A focused shock wave, on the other hand, is generated by an elliptic acoustic mirror where again each component shock wave distributes radially into the tissue, but the sum of all component shock waves add up to a specific focus within the tissue, where the intensity peaks.

The biological effects of ESW

Shock waves traveling through the human body lose mechanical energy, especially at the rear interface between tissues with different acoustical impedance (Table 2). The fragmentation of a kidney stone is a good example of how the shock wave hits the interface kidney/kidney-stone (Hoff and Behrend 1973).

Cavitation bubbles are generated within the propagation medium by the tensile component of the shock wave (Haeussler and Kiefer 1971; Wolfrum et al 2003). These cavitation bubbles collapse after passage of the shock wave, and transform into micro-jets which subsequently may add up to large jet-streams with velocities as high as 800 m/sec.

It has been observed that ESWT applied to bone marrow promotes the generation of progenitor cells (Wang et al 2002; Schmidt et al 2007; Yang et al 2007). Progenitor cells have a great regeneration capacity and, in contrast to stem cells, their future tissue function is predetermined. This behavior is not at all a drawback but is ideal for the regeneration of the specific tissue of an organ. If activation of progenitor cells is conjectured to be a general effect of low energy, partially focused ESW, it may also achieve a curative "*restitutio ad integrum*" in case of varicose veins.

On the other hand a higher energy flow density may achieve total disintegration and thus a destruction of a strongly degenerated vein. Future research on treating varicose veins with ESW will show if a similar reaction takes place as for the sclero-therapy, radio-wave-therapy or as for the endoluminal laser-therapy. If so, ESW could be applied for strongly advanced varicose veins. The great advantage of such a method is its total non-invasiveness and the fact no blood vessel needs to be opened.

Case study: methods, materials, and human resource

Patient

A woman aged 50 had a symptomatic varicose equally on both sides (CEAP-classification: C2EpAs2As3As5Ap17Ap18Pr) and surgery was indicated. She gave informed consent to be treated for the cellulite with ESWT on the left thigh at defined time-intervals 4 times (Table 3) before venous surgery. No other treatment (such as medical stockings, phlebotropic drugs) was carried out during the study period.

Table 3 ESW application regime

Start	1st	ESW application	1\4 length of VSM
7th day	2nd	ESW application	1\2 length of VSM
14th day	3rd	ESW application	3\4 length of VSM
21st day	4th	ESW application	Full length of VSM

The left (sections with 1, 2, 3, and 4 ESW treatments) and right (no treatment) VSM were removed as non-traumatically as possible by non-invaginated stripping (which includes crossectomy, inserting a filament into the lumen of the VSM, and extracting the vein by cutting with a hemispherical blade which was fixed on top of the filament). They were then fixed in 4% buffered formalin and processed for histology by slicing uniformly the whole material and analyzing each slide.

ESW device

The shock waves were produced by electro-hydraulic means with the device ActiVitor-Derma®, the probe ActiVitor Probe D0 (SwiTech Medical AG), with the adjustments shown in Table 4.

LCCT device

Liquid-crystal-contact-thermography (LCCT) can measure minor differences in skin temperature (Hoffmann et al 1989). An increase in the micro-perfusion of the surrounding tissue treated by ESW can be made visible on the skin by this device (Figure 2).

Photoplethysmography (PPG)

Relative changes in blood volume in the dermis of the limb can be determined by measuring with a photo-sensor the backscatter of light emitted from a diode. A PPG probe is placed on the foot with maneuvers to "empty" the foot by calf muscle contraction. The "venous refill time" is the time required to return to 90% of the baseline after cessation of calf contraction. A venous refill time <18 seconds indicates chronic vein insufficiency, a venous refill time >25 seconds suggests normal venous filling.

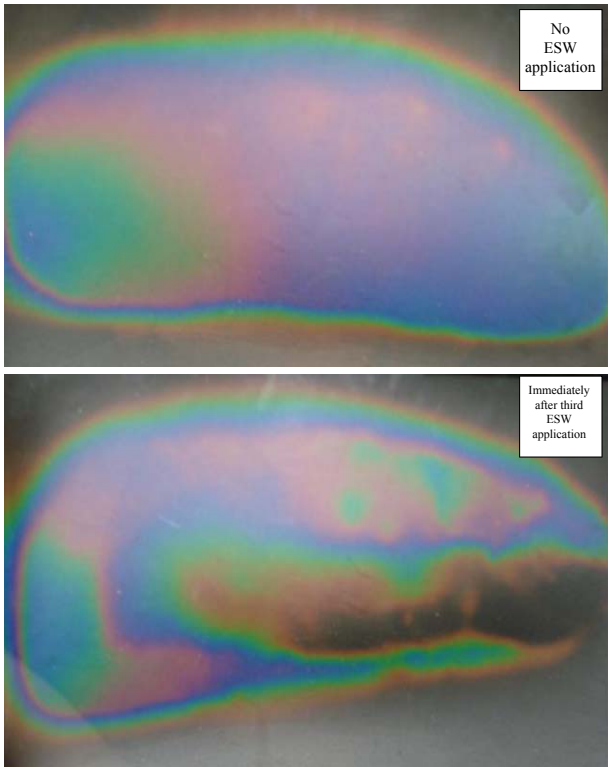

Figure 2 Liquid-crystal-contact-thermography (LCCT) model RW27ST (with colors corresponding to temperature steps of 0.7 °C) of left proximal medial thigh skin taken before (top) and after (bottom) low energy partially focused ESW treatment along trace of vena saphena magna (VSM) showing hyperthermia for several days, implying an increased micro-perfusion of the underlying tissue.

Table 4 Application parameters for ESW treatment of medial thigh

Focus	Partially focused
6 dB (= 50%) isobar	
length (z)	16 mm
diameter (∅, x, y)	23.5 mm
penetration depth	7–8 mm
Pressure rising-time	10–15 nsec
Shock-wave duration	1–2 μsec
Positive pressure peak	21 MPa
Negative pressure peak	1 MPa
Energy flow density per pulse	0.027 mJ/mm^2
Frequency	4 Hz
Number of pulses	40/cm^2
Treated area	4 cm × 50 cm
Total duration	33 min

Duplex sonography

This is part of the routine medical examination.

Results

Dynamic photoplethysmography of the VSM yielded an improvement in the venous filling time (from before to after treatment) from 22 to 29 sec (left side) and from 18 to 19 sec (right side). This result supports the hypothesis of a functional improvement by low-energy partially focused ESW. Additional support is given by color-coded Duplex-sonography measuring a decrease of the VSM's minimal diameter 1 cm below the cross (junction VSM into v. femoralis communis). This decrease was also visible in the histological sample. However, reflux could not be corrected. This single value supports the hypothesis of a restitutio of the vein's wall by low-energy partially focused ESW.

Histopathological results provide evidence that low-energy partially focused ESW increases the scaffolding fabric

of the varicose vein's wall, particularly collagen. The amount of elastic fibers and smooth muscle cells probably increased as well. The thickness of the varicose vein's wall increased (Figure 3). The vein's endothel is seen to be damaged because of stripping, whereas the endothel of the vasa vasorum are seen to be undamaged by ESW.

Discussion

The degenerative changes of varicose veins correlate with those of the patient's skin (Sansilvestri-Morel 2007) and the tissues of other organs (Forster et al 2006). This observation has led to the concept of the "impairment of the connective tissue" and to the interpretation that varicose veins can be seen as a consequence of a hereditary impairment of the connective tissue (Tsukanov and Tsukanov 2004). This hereditary aspect is supported by the evidence of FOXC2 gene-mutation of patients with insufficiency of the vein's valves (Mellor et al 2007) and the changes in the expression of tenascin-C of the varicose patient in comparison to patients with normal veins (Kirsch et al 1999). Research on the extra-cellular matrix of varicose veins by performing immuno-histochemistry has shown that the primary cause of varicose is an increase of expression of metalloproteinase and a decrease of elastic fibers and their fragmentation (Michliels et al 2001; Somers and Knaapen 2006; Jeanneret et al 2007). The insufficiency of the vein's valves is then seen as the consequence of the impairment of the vein's wall. Because the structure of skin's collagen is improved by ESW application (Angehrn et al 2007; Kuhn et al 2007), we considered that similar positive results can be achieved by application of ESW on varicose veins.

Reported effects of ESWT at the cellular level are diverse. Light microscopy or electron microscopy show either no changes within cells, or a complete destruction of cells. Published results show changes in the cell's membrane structure (Seidl et al 1994), edema of the cell, increase of vacuoles within the cytoplasm, dilatation of the endoplasmatic reticulum, peri-nuclear cysternae, enlargement or destruction of mitochondria, or even lethal damage of the cell (Seidl et al 1994). On the human endothel there is evidence of changes in the permeability and even dissection of the endothel's cells (Seidl et al 1994). ESW with energy flow density of more of than 0.3 mJ/mm^2 was found to damage vascular walls (Steinbach et al 1993; Verna et al 2006).

Some evidence of the effects of ESWT on the molecular level is known (positive effect of ESW on the proliferation of endothelial progenitor cells [Aicher et al 2006] or the increased proliferation of osteoprogenitor cells [Wang et al 2002]). These experiments with cells from connective tissue and supporting tissue showed in fibroblasts a decrease in the survival rate proportional to the energy flow density. After a few days there was an increase in the proliferation rate of bone cells (osteoplasts), a sign of regeneration starting. Altogether the clinical studies show an osteoneogenetic effect of ESW application. Correct application of ESW causes no clinically relevant or ongoing damage.

Unwanted side effects on the large venous vessels after ESWT for ureterolithiasis are rare, but these incidences cannot be taken for comparison because of the usage of diverse energy flow densities (deep thrombosis of the femoral vein in case of activated protein C [APC or factor V Leiden] resistance [Brodmann et al 1998], thrombosis of the iliacal vein [Desmet et al 1989], thrombosis of the portal vein in the case of hypofibrinolysis [Abecassis et al 1991]).

The significant result of this study is that in vivo application of low-energy partially focused ESW with an energy flow density of 0.027 mJ/mm^2 increased the scaffolding fabric of the varicose vein's wall, particularly collagen, and probably also the elastic fibers and smooth muscle cells.

Conclusion

Since the apparently encouraging results on neocollagenogenesis and possibly neoelastino-genesis and neogenesis of smooth muscle cells were obtained from a single case, their clinical relevance cannot be deduced conclusively. However, the results suggest that further research with a larger group of patients is essential and worthwhile to show:

(i) the adequate dosage, frequency, and focus attributes of ESW application to generate selectively constituents for recovery of the varicose vein's wall and thereby to open the way for a proper curative and non-invasive therapy for varicose vein (our conception);

(ii) that ESW application leads to even more inclusion of collagen as in terms of phlebosclerosis with an adequate dosage, frequency, and focus attributes to obstruct varicose veins safely and in a controlled way. In doing so, ESW would open a way to therapy that is as effective as other therapies such as sclero-therapy, radiowave-therapy, or endoluminar laser-therapy, but is completely non-invasive.

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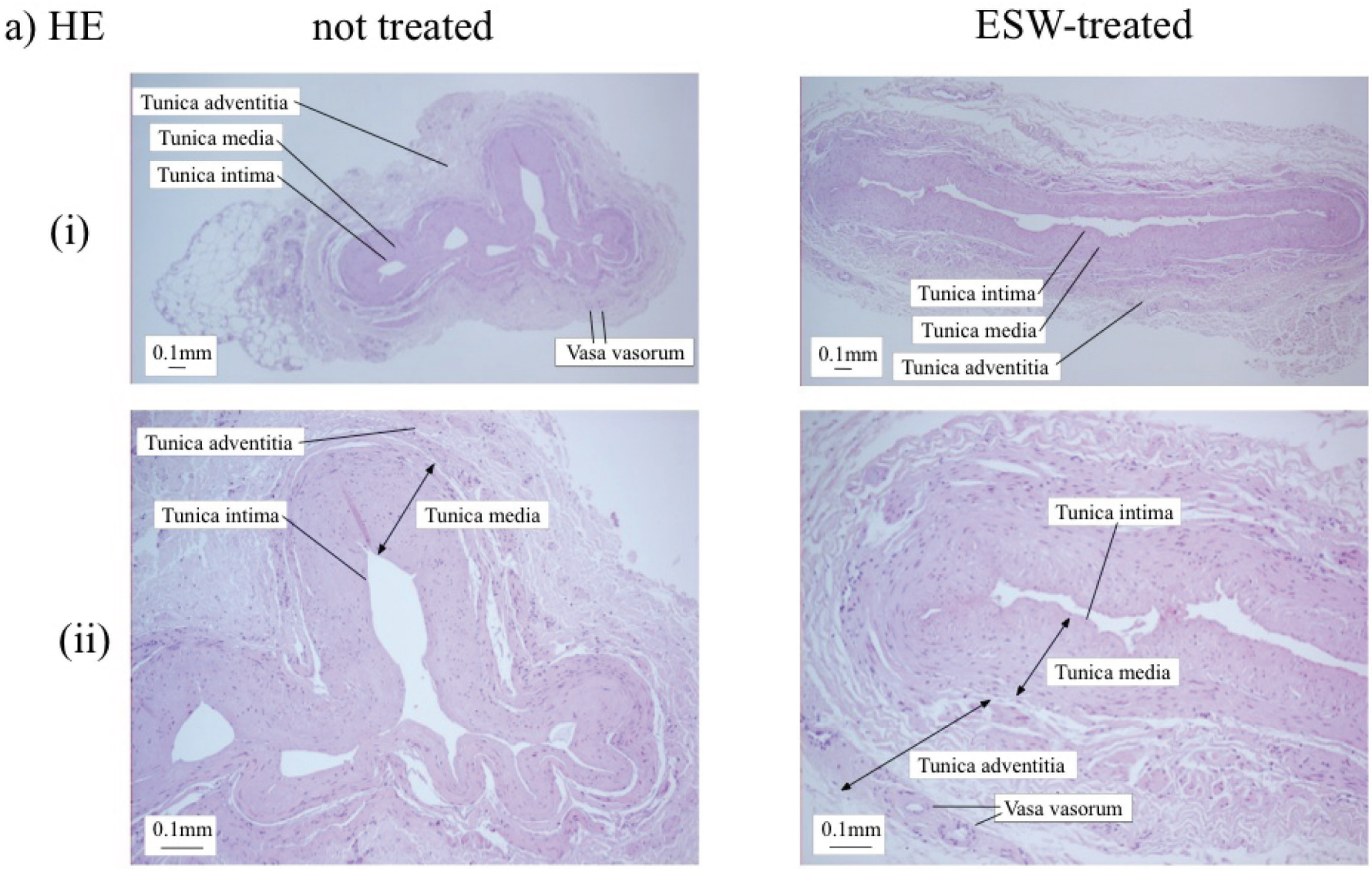
a) HE
not treated
ESW-treated
(i)
Tunica adventitia
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Tunica intima
0.1mm
Vasa vasorum
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Tunica media
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(ii)
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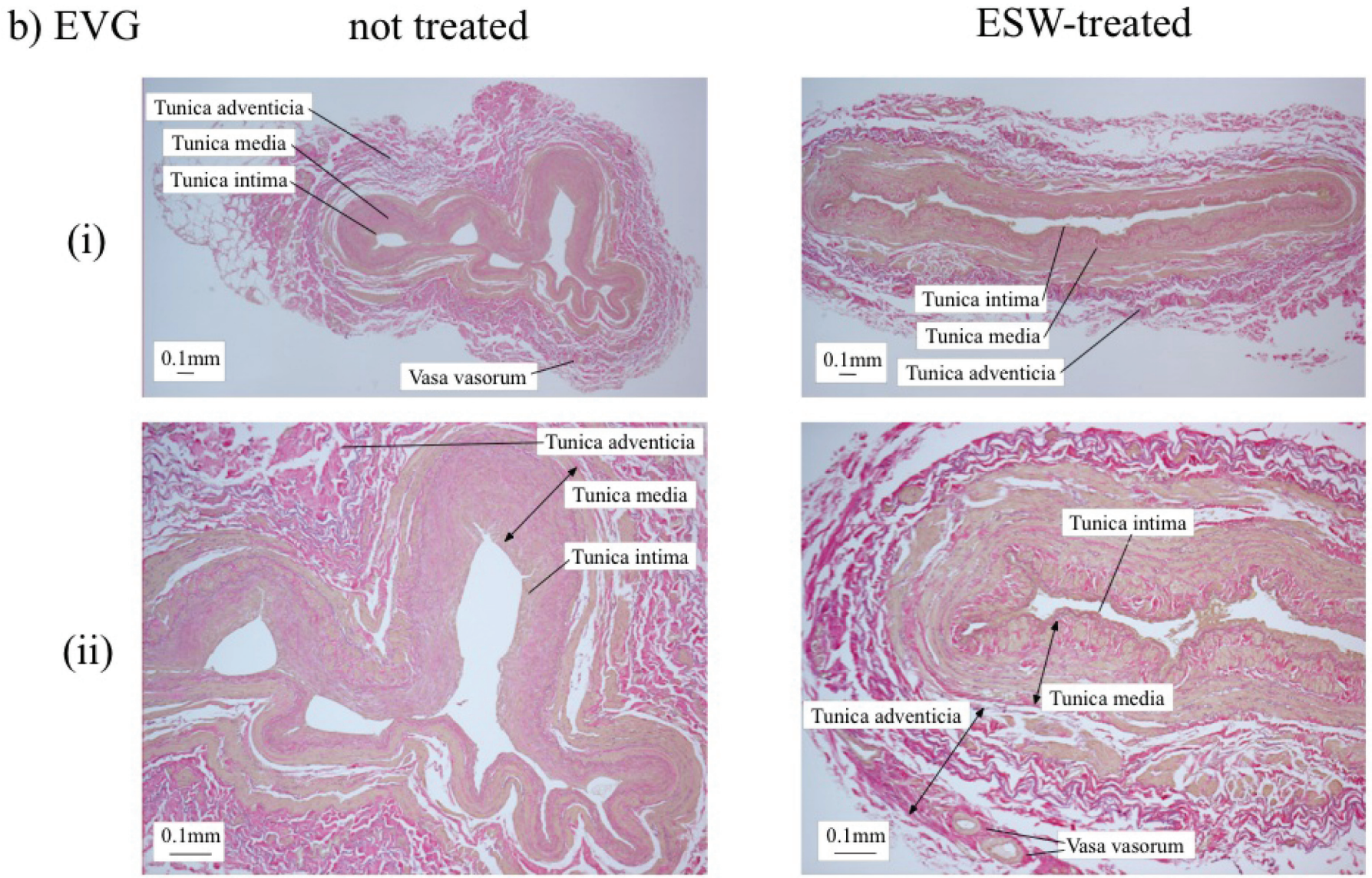

Figure 3 Histopathology of varicose vein: vena saphena magna (VSM). The whole material (the left varicose vein consisting of parts with 1, 2, 3, and 4 ESWT applications and the right varicose vein, not treated) was uniformly sliced and the many slides histologically processed. **a**) hematoxylin eosin (nuclei: blue; cytoplasma and connective tissue: red-pink), **b**) elastin van gieson with resorcin-fuchsin (elastic fibers: black, collagen: red, muscle tissue: yellow). One characteristic and representative slide from the untreated varicose vein (left, note: hypertrophy with atrophic areas explaining bulgings of varicosis) and from the ESW-treated varicose vein (right). No signs of tissue damage are visible. Such signs of a response to an injury would be tissue necrosis, extravasation of erythrocytes, the infiltration of neutrophils lymphocytes and macrophages, and the subsequent scar formation. However, an increase in the vein's connective tissue, the extra-cellular matrix, particularly collagen, was observed resulting in increased thickness of the vein's wall. The amounts of elastin and smooth muscle cells (SMC) are so variable that their apparent increase should be verified through a more quantitative evaluation.

Disclosures

The authors have no conflicts of interest to disclose.

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