Ultrasound in Med. & Biol., Vol. 42, No. 12, pp. 2975–2982, 2016

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2016.08.010

● *Original Contribution*

IMMEDIATE DOSE–RESPONSE EFFECT OF HIGH-ENERGY VERSUS LOW-ENERGY EXTRACORPOREAL SHOCK WAVE THERAPY ON CUTANEOUS MICROCIRCULATION

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(*Received* 15 *December* 2015; *revised* 5 *August* 2016; *in final form* 8 *August* 2016)

Abstract—Elucidation of the precise mechanisms and therapeutic options of extracorporeal shock wave therapy (ESWT) is only at the beginning. Although immediate real-time effects of ESWT on cutaneous hemodynamics have recently been described, the dose response to different ESWT energies in cutaneous microcirculation has never been examined. Thirty-nine Sprague–Dawley rats were randomly assigned to three groups that received either focused high-energy shock waves (group A: total of 1000 impulses, 10 J) to the lower leg of the hind limb, focused low-energy shock waves (group B: total of 300 impulses, 1 J) or placebo shock wave treatment (group C: 0 impulses, 0 J) using a multimodality shock wave delivery system (Duolith SD-1 T-Top, Storz Medical, Tägerwilen, Switzerland). Immediate microcirculatory effects were assessed with the O2C (oxygen to see) system (LEA Medizintechnik, Giessen, Germany) before and for 20 min after application of ESWT. Cutaneous tissue oxygen saturation increased significantly higher after high-energy ESWT than after low-energy and placebo ESWT (A: 29.4% vs. B: 17.3% vs. C: 3.3%; $p = 0.003$). Capillary blood velocity was significantly higher after high-energy ESWT and lower after low-energy ESWT versus placebo ESWT (group A: 17.8% vs. group B: −22.1% vs. group C: −5.0%, $p = 0.045$). Post-capillary venous filling pressure was significantly enhanced in the high-energy ESWT group in contrast to the low-energy ESWT and placebo groups (group A: 25% vs. group B: 2% vs. group C: −4%, $p = 0.001$). Both high-energy and low-energy ESWT affect cutaneous hemodynamics in a standard rat model. High-energy ESWT significantly increases parameters of cutaneous microcirculation immediately after application, resulting in higher tissue oxygen saturation, venous filling pressure and blood velocity, which suggests higher tissue perfusion with enhanced oxygen saturation, in contrast to low-energy as well as placebo ESWT. Low-energy ESWT also increased tissue oxygen saturation, albeit to a lower extent, and decreases both blood velocity and venous filling pressure. Low-energy ESWT reduced tissue perfusion, but improved oxygen saturation immediately after the application. (E-mail: robert.kraemer@uksh.de)

Key Words: **Extracorporeal shock wave therapy, Cutaneous microcirculation, Dose dependency.**

INTRODUCTION

Extracorporeal shock wave therapy (ESWT) was initially established in the 1980s for urologic lithotripsy. It requires a repetitive sequence of single sonic pulses defined by a high peak pressure of 100 MPascal and a rapid rise in pressure under 10 ns with a short life cycle of approximately 10 μs. These pulses are conveyed by a generator using electrohydraulics and applied to a specific target area with a radius between 2 and 5 mm at a distinct energy density (Perez et al. 2013; Wang et al. 2007). Different protocols of ESWT have since been used in several fields of medicine, including orthopedic diseases such as fractures, non-union fractures, osteonecrosis of the femoral head, tendinopathy, calcarea of the shoulder, epicondylitis, plantar fasciitis and several inflammatory tendon diseases (Elster et al. 2010; Kuo et al. 2009a; Schaden et al. 2001; Wang et al. 2001, 2002, 2005).

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Conflict of interest disclosure: None of the authors has a financial interest in any of the products, devices or drugs mentioned in this article.

Furthermore, ESWT has been applied in limb or myocardial ischemia and recently in the field of plastic reconstructive surgery for the treatment of acute and chronic wounds, skin flaps and burns (Kisch et al. 2015b; Omar et al. 2014; Ottomann et al. 2010, 2012; Reichenberger et al. 2012). Shock wave pre- and post-conditioning treatment has been reported to improve skin flap survival through neovascularization and early upregulation of angiogenesis-related growth factors (Mittermayr et al. 2011; Nacak et al. 2014). In the current scientific literature, there is a consensus that shock waves influence a complex spectrum of cellular and biomolecular functions. In particular, recent studies reported increased blood perfusion and microvessel number, vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase upregulation, proliferating cell nuclear antigen expression and decreased pro-inflammatory activity (Ha et al. 2013; Kisch et al. 2015a, 2016; Kuo et al. 2009a; Mittermayr et al. 2011; Yeh et al. 2012). Nevertheless, the physical and biochemical mechanisms remain unclear. There exist only a few studies that have investigated hemodynamics after shock wave treatment, including the evaluation of clinical parameters as skin flap survival, invasive measurements as *in vivo* microscopy or laboratory parameters as biomolecular proteins (Kuo et al. 2009a; Mittermayr et al. 2011; Reichenberger et al. 2012). Current trials on short-term and long-term cutaneous microcirculatory changes after the application of ESWT using different energy levels are missing. Therefore, the aim of this preliminary study was to determine the immediate effects of high-energy versus low-energy shock wave therapy on the cutaneous microcirculation in a real-time and non-invasive setting, using a rat standardized model.

METHODS

Animal model and experimental protocol

The study included 39 male Sprague–Dawley rats (250–350 g body weight, Charles River Laboratories, Sulzfeld, Germany), housed two/cage at 21°C on a natural light/dark cycle, as well as water and standard laboratory chow *ad libitum*. The experiments were conducted in accordance with the German legislation on protection of animals and the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, National Research Council). Rats were randomly assigned to three groups. Group A received focused high-energy ESWT (shock waves at 0.3 mJ/mm^2 and 4 impulses/s for a total of 1000 impulses totaling 10 J). Group B received focused low-energy ESWT (shock waves at 0.1 mJ/mm^2 and 5 impulses/s for a total of 300 impulses totaling 1 J). Group C received placebo ESWT without energy application (0 impulses totaling 0 J). The hair of the left lower leg of each rat was removed with an electrical shaver. Rats were fixated with tape on a platform. The ESWT device (Duolith SD-1 T-Top, Storz Medical, Tägerwilen, Switzerland) was applied to the lower leg of the left hind limb. The device allows generation of both focused and radial shock waves. In this study, focused extracorporeal shock wave therapy was used. Applications were performed by the same experienced physician using contact gel without relevant pressure to the tissue. During the experiments, the rats were under sufficient pentobarbital sodium anesthesia (55 mg/kg body weight ip, Narcoren, Merial, Hallbergmoos, Germany) controlled by stable heart rate and breathing frequency to minimize microcirculatory affection caused by pain reaction. Body temperature was maintained at 36°C–37°C using a heating pad.

Microcirculatory analysis

After anesthesia delivery, the cutaneous microcirculation of each rat was allowed to stabilize for 10 min before investigating the cutaneous microcirculation using a non-invasive combined laser Doppler and photospectrometry system (O2C [oxygen to see], LEA Medizintechnik, Giessen, Germany). Before and continuously over 20 min after application of ESWT, the microcirculation was assessed in real time at the treated body area.

A fixation apparatus was used for placing the probe at the same location as the ESWT device, to minimize measurement artifacts caused by vibration (Fig. 1). Baseline measurements were carried out for 1 min before application of focused ESWT. After application of ESWT, microcirculation was assessed continuously in real time for 20 min.

The determination of hemoglobin and the principle of blood flow measurement are combined in the O2C system. The optical method for measuring both blood flow velocity with the laser Doppler technique and hemoglobin oxygenation and hemoglobin concentration in tissue with spectrometric techniques has been described in detail elsewhere (Frank et al. 1989; Rothenberger et al. 2014). Local oxygen supply parameters, blood flow velocity, oxygen saturation of haemoglobin and relative post-capillary venous filling pressures were recorded with an optical fiber probe. The fiber probe incorporates both the laser Doppler method and the broadband light spectrometry technique. The probe used assessed data at a 2-mm depth with respect to: cutaneous capillary blood flow velocity (arbitrary units [AU]), cutaneous tissue oxygen saturation (%) and cutaneous venous filling pressure (AU).

We recently described the use of the O2C system in evaluation of cutaneous effects of remote ischemic preconditioning and the correlation of free flap skin temperature to free flap microcirculation (Kraemer et al. 2011a, 2011b). A 5% intra-subject variability was determined

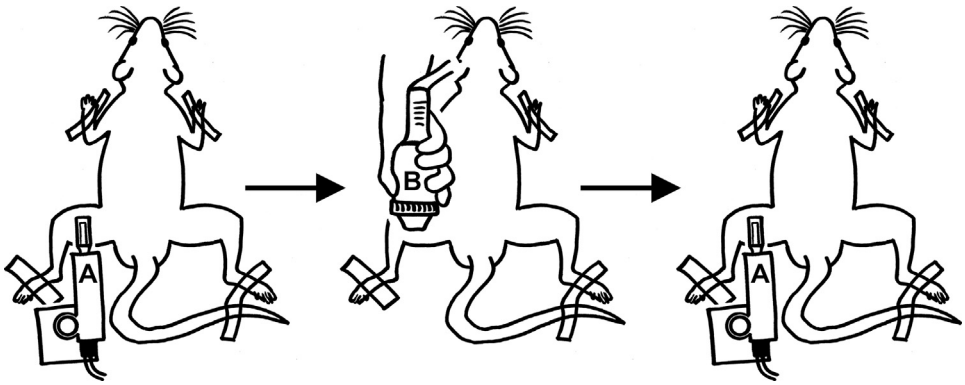

Fig. 1. Apparatus for fixing the laser Doppler system at the dorsal lower leg of the hind limb of the rat to minimize measurement artifacts caused by vibration.

for the O2C system indicating that the laser Doppler and spectrophotometry method is reliable under standardized testing conditions (Ghazanfari et al. 2002).

Statistical analysis

Repeated-measures analysis of variance with a Bonferroni–Holm *post hoc* test was used to compare baseline pre-application versus post-application microcirculatory changes with respect to treatment. A p-value < 0.05 was considered to indicate statistical significance. The SPSS statistical software package Version 16.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Cutaneous tissue oxygen saturation

Baseline cutaneous tissue oxygen saturation was similar in both experimental groups (group A: 55.6 ± 9.0%, group B: 55.6 ± 10.2%, group C: 63.9 ± 13.0%, n.s.). Cutaneous tissue oxygen saturation increased 41.2% more in group A than in group B immediately after ESWT ($p = 0.003$). Compared with baseline, cutaneous tissue oxygen saturation increased by 29.4% in group A ($p = 0.001$), by 17.3% in group B ($p = 0.008$) and by 3.3% (n.s.) in group C. Cutaneous tissue oxygen saturation remained on a significantly higher level in group A versus group B over the 20-min observation period. Oxygen saturation decreased to 60.4 ± 15.4% in group A and 49.2 ± 11.5% in group B, respectively after 20 minutes suggesting an equivalent level of oxygen saturation versus baseline in group A and a significantly decreased level (by 18.3%) in group B ($p = 0.047$). Cutaneous tissue oxygen saturation in the group C remained non-significantly changed from baseline (Fig. 2).

Cutaneous blood velocity

Baseline cutaneous capillary blood velocity in the high-energy ESWT group A was 16.1 ± 3.6 AU versus 19.7 ± 9.9 AU in the low-energy ESWT group B and 15.5 ± 2.2 AU in group C. Directly after ESWT application, capillary blood velocity increased by a mean of 17.8% at the treated area of the rodents in group A, whereas it decreased by means of 22.1% and 5% in groups B and C (difference $p = 0.045$). Cutaneous capillary blood velocity of group A remained elevated both above baseline and above group B until the end of the 20-min observation period (group A: 19.8 ± 8.4 AU vs. group B: 16.1 ± 6.5 AU, $p = 0.024$ vs. baseline). In contrast, cutaneous capillary blood velocity in group C remained below baseline over the 20-min observation period ($p > 0.05$ vs. baseline) (Fig. 3).

Cutaneous relative post-capillary venous filling pressure

Baseline cutaneous post-capillary venous filling pressure was 23.2 ± 3.2 AU in group A versus 25.0 ± 4.3 AU in group B versus 27.6 ± 7.5 AU in group C. Immediately after ESWT, post-capillary venous filling pressure increased 23% more in group A relative to group B ($p = 0.014$). Compared with baseline, cutaneous post-capillary venous filling pressure increased by 25% in group A ($p = 0.001$), and 2% ($p = 0.373$) in group B immediately after ESWT, whereas it decreased by 4% in group C ($p > 0.05$). Post-capillary venous filling pressure continued to decrease after 5 min post-ESWT until the end of the experiment to the lowest level versus baseline in group B. These levels were significantly lower than what was observed for groups A and C for all time points assessed (group A: 27.3 ± 6.4 AU vs. group B: 22.8 ± 3.9 AU, $p = 0.014$; group C: 25.0 ± 7.6 AU, $p > 0.05$). Post-capillary venous filling pressure in group A remained at a significantly higher level versus baseline measurements until the end of the 20-min observation period (group A: 27.3 ± 6.4 AU vs. 23.2 ± 3.2 AU, $p = 0.043$) (Fig. 4).

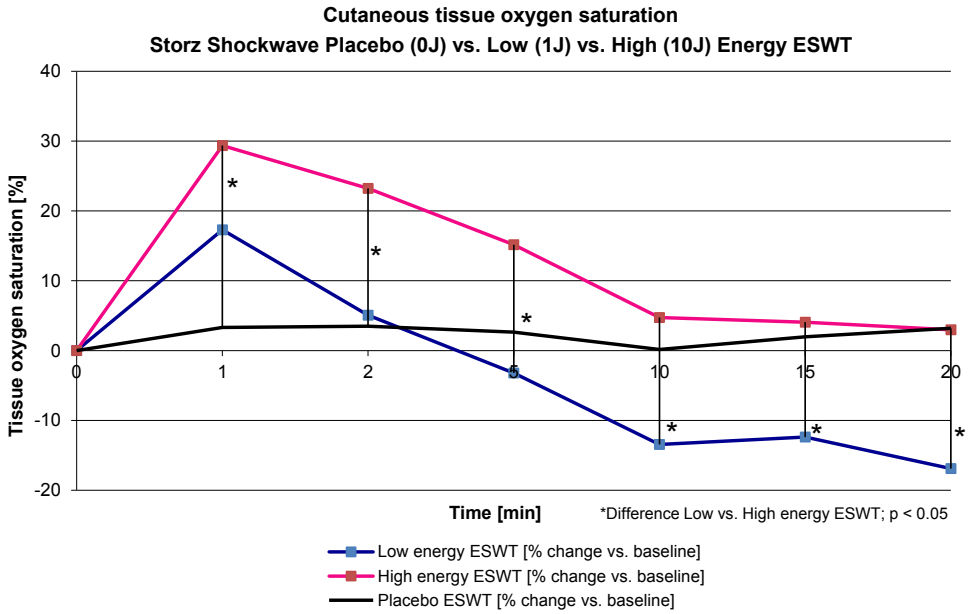

Fig. 2. Microcirculatory effects of high-energy (10 J) versus low-energy (1 J) versus placebo (0 J) extracorporeal shock wave therapy (ESWT) on cutaneous tissue oxygen saturation. One minute after ESWT application, cutaneous tissue oxygen saturation increased 41.2% more in the high-energy ESWT group than in the low-energy ESWT group ($p = 0.003$). Compared with baseline, cutaneous tissue oxygen saturation in the high-energy ESWT group increased by 29.4% ($p = 0.001$), that in the low-energy ESWT group by 17.3% ($p = 0.008$) and that in the placebo group by 3.3% (n.s.). Cutaneous tissue oxygen saturation remained at a significantly higher level in the high-energy ESWT group versus the low-energy ESWT group over the 20-min observation period. Twenty minutes after the application, oxygen saturation parameters decreased in the high-energy ESWT group to baseline and those in the low-energy ESWT group to a significantly decreased (by 18.3%) level ($p = 0.047$). Cutaneous tissue oxygen saturation in the placebo group remained non-significantly changed from baseline. *$p < 0.05$.

DISCUSSION

During the last few decades, ESWT has been successfully employed in the medical fields of orthopedics and urology (Elster et al. 2010; Perez et al. 2013; Schaden et al. 2001; Wang et al. 2001, 2002, 2005, 2007). Of late, additional fields, for example, dermatology, esthetics, plastic surgery, hand surgery and internal medicine, have begun to investigate ESWT as a useful and effective therapy (Kisch et al. 2015a, 2016; Kuo et al. 2009b; Mittermayr et al. 2011; Reichenberger et al. 2012). Regardless of the medical speciality, the underlying mechanisms of the physical force and corresponding biological changes that result from ESWT are not entirely clear. Thus, we aimed to determine the acute hemodynamic effects of this therapy on cutaneous microcirculation, in addition to the dose–response relationship between different ESWT energies and the target tissue. Furthermore, we hypothesized differential effects over time on the cutaneous microcirculation of rats receiving either high or low ESWT. Indeed, as reported above, both high-energy and low-energy ESWT had an impact on the cutaneous circulation of the rat's lower hind limb. Interestingly, the effects were profoundly different (Figs. 2–4). High-energy ESWT significantly increased cutaneous capillary blood flow velocity with enhanced tissue oxygen saturation. On the other hand, low-energy ESWT significantly decreased cutaneous capillary blood flow velocity and post-capillary venous filling pressure.

The shock waves used in this therapy can be generated by electrohydraulics emitting biphasic high-energy acoustic waves that rapidly decline with high peak pressures (Wang 2003). The energy of the shock wave is absorbed by the target tissue as it propagates over a specific distance. Parabolic reflectors can modulate the degree of wave focus to administer a certain concentration of energy leading to transient micromechanical forces (Mariotto et al. 2005; Yan et al. 2008). One proposed mechanism of action is mechanotransduction initiated through cell surface receptor response to extracellular matrix and fluid changes (Ha et al. 2013). Resultant changes in biological activity occur because of perturbations to the cytoskeleton (Kuo et al. 2009b; Sonden et al. 2006). This may explain why ESWT exhibits not only destructive effects on solid materials like bone and urolithiasis, but also healing effects on tendinous,

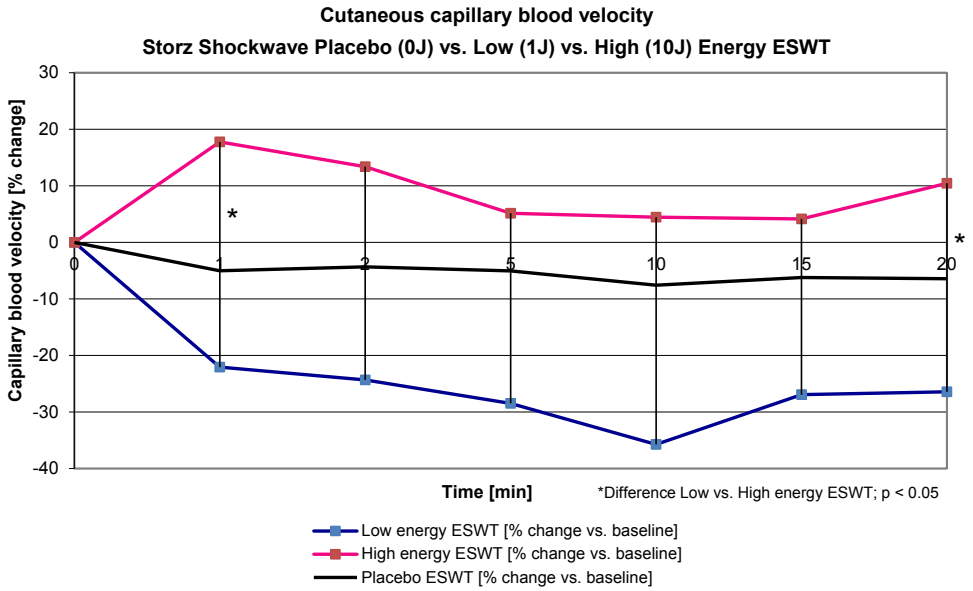

Fig. 3. Microcirculatory effects of high-energy (10 J) versus low-energy (1 J) versus placebo (0 J) extracorporeal shock wave therapy (ESWT) on cutaneous capillary blood velocity. Directly after ESWT application, capillary blood velocity increased by a mean of 17.8% and remained elevated both above baseline and above the low-energy ESWT group until the end of the 20-min observation period. In contrast, it decreased by a mean of 22.1% in the low-energy ESWT group and 5% in the placebo group. Cutaneous capillary blood velocity in the low-energy ESWT group and placebo group remained below baseline over the 20-min observation period. $*p < 0.05$.

muscular, subcutaneous and cutaneous tissue. In particular, ESWT used in the treatment of tendon and muscle tissues improved tissue regeneration long term and, in addition, had a more immediate analgesic and anti-inflammatory effect (Lee et al. 2012). Recently, shock wave administration has been reported to consistently suppress an early pro-inflammatory immune response after traumatization (Davis et al. 2009; Kuo et al. 2007; Mariotto et al. 2005). ESWT was also found to improve survival of ischemic skin flaps through enhanced tissue revascularization and repair in animal models (Kuo et al. 2007, 2009b; Mittermayr et al. 2011). Yan et al. (2008) applied ESWT with 750 impulses at 0.09 mJ/mm^2 to the mid- and distal portions of a cranial random pattern flap model in rats and observed increased blood perfusion and increased nitric oxide and vascular endothelial growth factor expression. The authors reported increased vasodilation of pre-existing vessels in the early post-operative period with neovascularization on post-operative days 3 and 10. In our study, we found significantly increased higher tissue oxygen saturation, venous filling pressure and blood velocity of the cutaneous microcirculation immediately after the application of high-energy ESWT. Our data support previous findings that ESWT can lead to alterations in the microcirculation, specifically tissue oxygen saturation, which may explain the enhanced tissue survival in the standardized flap models. This is in line with the findings of Kuo et al. (2007), who observed an increase in vascular endothelial growth factor and proliferating cell nuclear antigen expression, reduced leukocyte infiltration and decreased tumor necrosis factor expression in ischemic zones of the flap, after administering focused shock waves (500 impulses at 0.15 mJ/mm^2) to certain areas of a random dorsal skin flap model in rodents. The authors proposed that ESWT had an ameliorating effect on the inflammatory response in the ischemic tissue.

Another aim of our study was investigation of a probable dose–response relationship between different ESWT energies on tissue, as no study to date has investigated a real-time dose dependent effect immediately after ESWT on the cutaneous microcirculation. Kamelger et al. (2010) recently assessed a clinical dose-dependent effect of shock wave therapy in a murine epigastric skin flap model by varying impulses (200, 500, 1500, 2500, 5000) at 0.11 mJ/mm^2. An enhancement of skin flap survival was observed at 500 impulses without a further beneficial effect at 1500 and 2500 impulses. Increased necrosis of the skin flap was even observed at 5000 impulses. Accordingly, we chose a maximum energy of 10 J, equivalent to 1000 impulses of shock waves at 0.3 mJ/mm^2 with 4 impulses/s for our study. Mittermayr et al. (2011) administered shock waves at 0.1 mJ/mm^2 with 5 impulses/s and a total of 300 impulses in an epigastric flap ischemic region at various times before, immediately after and 24 h after ischemia in an animal model and found that flap perfusion, microvessel number and flap survival in the treated groups were significantly enhanced compared with controls

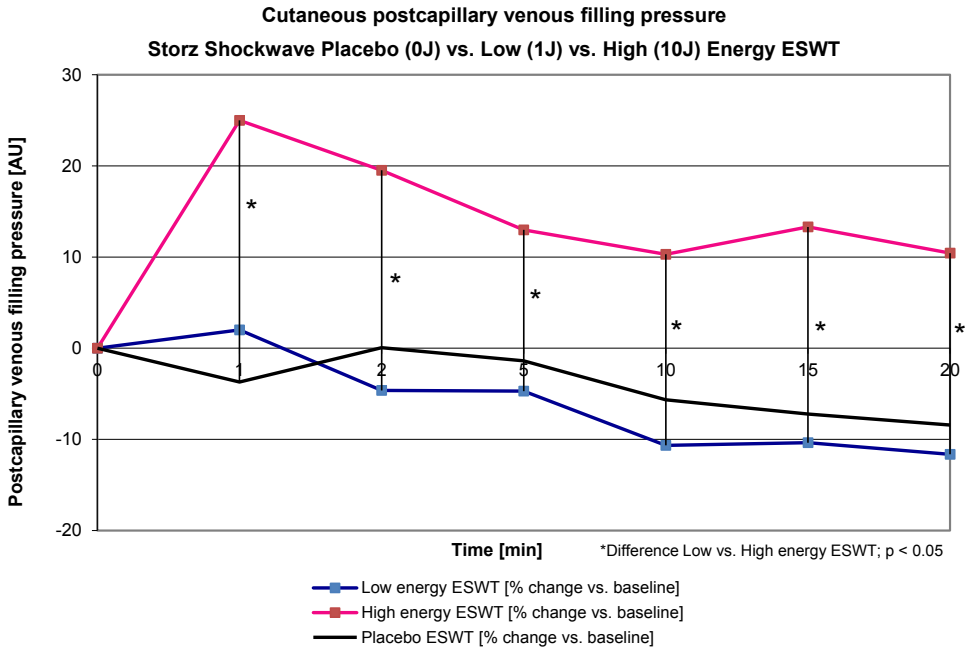

Fig. 4. Microcirculatory effects of high-energy (10 J) versus low-energy (1 J) versus placebo (0 J) extracorporeal shock wave therapy (ESWT) on cutaneous post-capillary venous filling pressure. Immediately after ESWT, post-capillary venous filling pressure increased 23% more in the high-energy ESWT group relative to the low-energy ESWT group ($p = 0.014$). Compared with baseline, cutaneous post-capillary venous filling pressure increased by 25% ($p = 0.001$) in the high-energy and 2% in the low-energy ESWT group ($p = 0.373$) immediately after ESWT, whereas it decreased in the placebo group by 4% ($p > 0.05$). Post-capillary venous filling pressure continued to decrease after 5 min post-ESWT until the end of the experiment to the lowest level versus baseline in the low-energy ESWT group. These levels were significantly lower than what was observed for the high-energy ESWT and placebo groups for all time points assessed. Post-capillary venous filling pressure in the high-energy ESWT group remained at a significantly higher level versus baseline measurements until the end of the 20-min observation period ($p = 0.043$). *$p < 0.05$.

(Mittermayr et al. 2011). Both studies suggest that flap perfusion was improved after extracorporeal shock wave treatment using high and low energy. However, immediate effects on microcirculation that might influence vessel growth in the flaps, for example, by shear stress (Galie et al. 2014), have never been elucidated. Therefore, we compared high-energy ESWT at 10 J with low-energy ESWT at a minimum dosage of 1 J at 0.1 mJ/mm^2, 5 impulses/s and a total of 300 impulses, in line with Mittermayr et al. Microcirculation is an important parameter of tissue nutrition. Here, we used a non-invasive combined laser Doppler and photospectrometry system to measure cutaneous capillary blood flow velocity, cutaneous tissue oxygen saturation and cutaneous venous filling pressure. Tissue oxygen saturation and venous filling pressure are measured by simultaneous photospectrometry, and blood flow in the small vessels is measured by the laser Doppler system, which estimates the sum of the product of erythrocyte number and velocity. We found that blood flow velocity increased in the high-energy ESWT group, whereas it decreased in the low-energy ESWT and placebo groups. Because blood flow is a measure of erythrocytes that move in the tissue and no systemic differences in heart rate or blood flow were documented in our experiment, it might have been reduced by local vasoconstriction of the small vessels. However, this phenomenon might be a part of future studies.

Limitations

Although we found immediate effects of high-energy and low-energy ESWT on cutaneous microcirculation, our study is not able to support any findings of the current literature with respect to tissue neovascularization, cellular gene expression or clinical consequences. However, as clinical data on this issue are pending, our study clearly indicates immediate changes in the cutaneous microcirculation after both high- and low-dose ESWT in a standard rodent model. Albeit, caution is warranted when extrapolating these data to a clinical situation, as the precise response on the tissue microcirculation in humans is yet to be determined.

CONCLUSIONS

Both high-energy and low-energy ESWT cause changes in cutaneous hemodynamics in a standard rodent

model in comparison to placebo. High-energy ESWT significantly increases parameters of microcirculation immediately after application in the treated cutaneous lower hind limb—higher tissue oxygen saturation, venous filling pressure and blood velocity—suggesting enhanced tissue perfusion with improved oxygen saturation in contrast to low energy as well as placebo ESWT. On the other hand, low-energy ESWT also increases tissue oxygen saturation, albeit to a lower extent, with a decrease after 5 min. Both blood velocity and venous filling pressure decrease directly after the application, indicating that oxygen saturation depends on the saturated hemoglobin and, to a lower extent, on blood flow. The reason for the reduction in oxygen saturation 5 min after the application might be due to its indirect dependency on tissue perfusion. Oxygen saturation is measured with the O2C system mainly in the venules. Consequently, a lower blood inflow might lead to lower oxygen saturation in the venules because of the relatively increased utilization of oxygen by the tissue during reduced blood flow. Our findings support the indication of high-energy ESWT to induce or re-establish inflammatory status in a tissue that is inert and/or does not heal, for example, chronic wounds, pseudarthrosis, non-union fractures and osteonecrosis of the femoral head. Low-energy ESWT may be a therapeutic option for reduction of inflammation in abacterial inflammatory processes of the skin or the musculoskeletal system, such as acute tendinopathy or tendinosis calcarea of the shoulder, epicondylitis and/or plantar fasciitis. However, the effects of repetitive use of low-energy ESWT should be a part of future studies.

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