Am J Transl Res 2011;3(3):259-268
www.ajtr.org /ISSN:1943-8141/AJTR1103003

Review Article

Study of vascular injuries using endothelial denudation model and the therapeutic application of shock wave: a review

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Received March 13, 2011; accepted April 5, 2011; Epub April 8, 2011; Published May 15, 2011

Abstract: As death toll from cardiovascular diseases has reached historic heights in the developed world, research efforts have been focused on both the understanding of disease progression and also the choice of appropriate treatment strategies. Moreover, to facilitate research, an appropriate animal model is needed to mimic the pathological changes and follow treatment results. This article reviewed the disease mechanisms underlying vascular injuries and also the animal model of endothelial denudation using balloon catheter. On the other hand, the biological effects of shock wave including angiogenesis and the suppression of inflammation were reviewed. Its therapeutic impact on the cardiovascular system and its potential clinical application as well as limitations were also discussed.

Keywords: Shock wave therapy, vascular endothelial damage, cardiovascular diseases, animal model, endothelial denudation, balloon catheter, angiogenesis, review

Key biological changes involved in vascular injuries

Cardiovascular diseases, which initially develop from subtle vascular cell injuries, are one of the most notorious killers in the developed nations. Despite the advance in interventional procedures such as percutaneous coronary intervention and coronary artery bypass grafting for restoring myocardial perfusion, restenosis due to vascular injury is the Achilles' heel that limits therapeutic success [1-4]. As a result, numerous studies have been focused on the mechanisms of vascular injury and its recovery.

A body of evidence has demonstrated that the biological changes related to vascular injuries are complicated and involve a myriad of cellular elements and subcellular signaling pathways. Although the key pathological changes are neointimal hyperplasia [5] and vascular smooth muscle cell (VSMC) proliferation and migration [6-9] that subsequently lead to vascular wall remodeling, the cellular and subcellular events are far more complicated. While neutrophils and monocytes infiltrations [10, 11] as well as intercellular communication between VSMCs through connexin43 [7, 10] are implicated as essential cellular events after vascular injuries, upregulation of platelet-derived growth factor (PDGF) [12, 13] and pro-inflammatory mediators including C-reactive protein (CRP) [14], matrix metalloproteinases (MMPs) [4, 9, 15, 16], nuclear factor (NF)-kappaB [4, 15, 16], tissue-transforming factor (TGF)-beta [3] and its primary signaling protein Smad3 [8], cycloxygenase-2 (COX-2) [1, 17], interleukin-18 [10], plasminogen activator inhibitor-1 (PAI-1) [3] as well as elevated oxidative stress [6] have been shown to be significant molecular participants in the process. On the other hand, nitric oxide [18, 19], interleukin-19 [20], the mitochondrial antioxidant enzyme superoxide dismutase (SOD) -2 [6], and PDGF-receptor-targeting protein-tyrosine-phosphatases [12] have been shown to be beneficial in suppressing neointimal hyper-

Table 1 Anti-inflammatory mechanisms in endothelial cells

External pathway	Intracellular pathway
1. Anti-inflammatory cytokines (1) TGF-β1： *E-selectin, VCAM-1, MCP-1, IL-8, iNOS, Smad, CBP* (2) IL-10： *P-selectin, E-selectin, ICAM-1, VCAM-1, IL-8, IL-6, NF -κB, IκB, superoxide anion, JAK-STAT pathway, ERK1, ERK2, MAPK pathway* (3) IL-1receptor antagonist (4) IL-4 & IL-13： *P-selectin, VCAM-1*	1. NF-κB related pathway *IκB, IKKα, IKKβ, IKKγ(NEMO), NBD, NO, PR39* 2. Protective genes (1) Cytoprotective genes *Bcl-2 family (Bcl-2, Bcl-xL, A1), A20, HO-1* (2) Fas and Fas ligand 3. Nitric Oxide *eNOS, ICAM-1, VCAM-1, M-CSF, MCP-1, IL-6, NF-κB, antioxidant NAC, angiotensin II* 4. PPARs *VCAM-1, AP-1, NF-κB, IκB, n-3 fatty acid*
2. HDL *E-selectin, ICAM-1, VCAM-1, SphK pathway-S1P, ERK, NF -κB,* 3. Angiogenic and growth factors *VEGF, Flt-1, eNOS, VEGFR2, flk-1/KDR, phospholipase Cγ1, IP3, Ca^{2+}, NOS, Ang-1, PECAM-1, FGF-1, FGF-2*	

VCAM-1: Vascular cell adhesion molecule-1; MCP-1: Monocyte chemotactic protein-1; IL: Interleukin; iNOS: Inducible nitric oxide synthase; CBP: cAMP-response-element-binding protein-binding protein; ICAM-1: Inter-cellular adhesion molecule 1; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IκB: Inhibitor of κB; ERK: Extracellular signal-regulated kinase; MAPK: Mitogen-activated protein kinase; HDL: High-density lipoprotein; SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate; VEGF: Vascular endothelial growth factor; Flt-1: Vascular endothelial growth factor receptor-*1;* eNOS: endothelial nitric oxide synthase; VEGFR2: Vascular endothelial growth factor receptor-*2;* KDR: Kinase domain receptor; IP3: Inositol trisphosphate; Ang-1: Angiopoietin-1; PECAM-1: Platelet/endothelial cell adhesion molecule-1; FGF: Fibroblast growth factor; IKK: IκB kinase; NEMO: Nuclear factor- kappa B essential modulator; NBD: NEMO (NF-κB essential modulator) binding domain; NO: Nitric oxide; PR39: Proline-arginine 39 residues; A1: Bcl-2-related protein; A20: Cytoprotective gene; HO-1: Heme oxygenase-1; M-CSF: Macrophage colony-stimulating factor; NAC: N-acetylcysteine; AP-1: Activator protein 1.

plasia and remodeling after vascular insult. Since inflammatory reactions after vascular injury are different in the endothelial and smooth muscle layers of a blood vessel, the anti -inflammatory mechanisms underlying vascular injury can be divided into those in the endothelial cells (**Table 1**) and those in smooth muscle cells (**Table 2**) through both external and intracellular pathways.

Carotid artery injury in the rat as a vascular injury model

To simulate the clinical situation of vascular injury, an animal model has to reproduce similar pathological changes for investigation. In animal studies, endothelial denudation has been widely adapted for this purpose because the procedure produces vascular pathology resembling that of post-angioplasty restenosis [2, 21]. Using this mechanical injury induction model, significant insights have been gained regarding both the pathological responses underlying vascular injury [15, 18, 22, 23] and also the potential therapeutic measures against it [1, 4, 16, 21]. The procedure can be carried out either using small caliber guide-wires for small arteries [24] or balloon catheters for larger arteries such as the femoral artery or carotid artery in the rat [1, 3, 4, 7, 15, 16, 18, 22, 23, 25-28].

The rat carotid artery is usually chosen for the balloon-induced injury model because of the ease of performance and the relatively high quantity of blood and tissue sample that can be harvested for subsequent histologic and molecular analysis. Under flow control using vascular clamps with the rat under satisfactory anesthesia, a small opening over proximal left carotid artery (LCA) can be created with a scalpel after adequate exposure in sterile condition. A coronary angioplasty wire with a diameter of 0.014 inches can be used to pass through the small orifice and advanced into the distal por-

Table 2. Anti-inflammatory mechanisms in smooth muscle cells (SMCs)

External pathway	Intracellular pathway
1. Anti-inflammatory cytokines (1) TGF-β1: *VCAM-1* (2) IL-10: *Inhibition of SMC proliferation, phospholipase A2, JAK-STAT pathway, ERK1, ERK2, MAPK pathway* (3) IL-1 receptor antagonist: (4) IL-4 & IL-13: *IL-8, MCP-1, NOS II,* 2. HDL *COX-2* 3. Angiogenic and growth factors *ambiguous*	1. Protective genes *Serpine proteinase inhibitors 9 (PI-9)* 2. Nitric Oxide *MCP-1, VCAM-1* 3. PPARs *COX-2, IL-6,*

TGF-β1: Transforming growth factor–beta 1; VCAM-1: Vascular cell adhesion molecule-1; IL: Interleukin; JAK-STAT: Janus kinase- signal transducer and activator of transcription; ERK: Extracellular signal-regulated kinase; MCP-1: Monocyte chemotactic protein-1; NOS: Nitric oxide synthase; COX-2: Cyclooxygenase-2

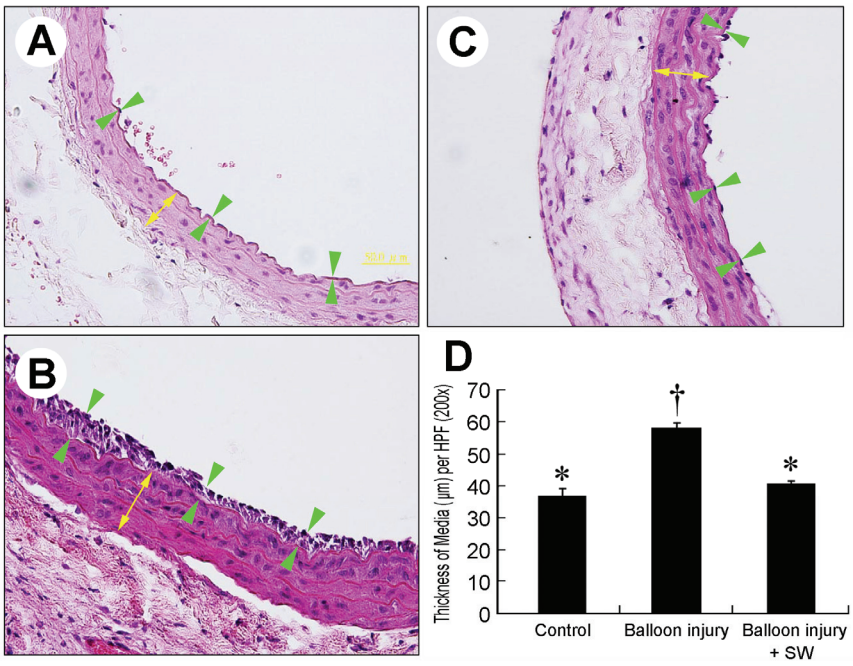

Figure 1. Change in thickness of intimal and medial layers of the carotid artery in the rat after balloon-induced injury. Note the remarkable increase in thickness of the intima (between green arrowheads) and medial layer (yellow arrows) 7 days after balloon injury (B) compared with the normal control (A). Thickness of the intimal and medial layers in animals after balloon injury with shock wave (SW) treatment 7 days after the procedure (C) comparable to the normal controls (D) (Adult male Sprague-Dawley rats, six animals in each group). * vs. †: $p < 0.01$ (Student t test); HPF: High power field.

tion of LCA, followed by insertion of a coronary angioplasty balloon with a diameter of 1.5 mm and length of 20.0 mm to mid-LCA. The balloon is then inflated to a pressure of 6 atmospheres for 10 seconds before full deflation. This method can reliably produce endothelial denudation [10]. Compared with the normal histology of a carotid artery (**Figure 1A**), the typical histologic picture of an injured vessel including neointimal hyperplasia, smooth muscle proliferation, and inflammatory cell infiltration are shown in **Figure 1B**.

Shock wave and its effects on the biological system

Shock wave (SW), which is a longitudinal acoustic wave that can propagate inside soft tissue, is

delivered as a single pulse with a duration of around one micro-second, and a peak pressure of up to one hundred MPa [19]. Since SW was first regarded as a source of injury to the human body, early studies focused on the degree of injuries that it may produce [29-31]. The successful use of the mechanical properties of high -energy SW for extracorporeal renal lithotripsy in a patient series was first reported by Chaussy et al in 1982 [32]. Since then, a number of studies have revealed that not only does SW provide mechanical means of treatment such as in lithotripsy for kidney and ureteral stones, but its low-energy form (0.03 to 0.11 mJ/mm^2) also produces a series of subtle biological changes in the musculoskeletal [33, 34] and cardiovascular system [35-37]. Experimental studies have further shown that SW may serve as a stimulus for stem cell recruitment in the process of tissue repair [38]. The two key effects underlying the potential therapeutic use of SW are its anti-inflammatory and pro-angiogenic properties.

Accumulating evidence in vivo [36, 39] and in vitro [19] has shown that the anti-inflammatory action of SW is at least partly due to its enhancement of endothelial NO synthase (eNOS) activity and the subsequent suppression of NF-kappaB activation [19]. The "bubble cavitation" effect of SW, which resembles shear stress and induces localized stress on cell membrane [40], may at least in part account for the observed upregulation in eNOS expression. Moreover, a non-enzymatic pathway of SW-elicited NO formation in the presence of physiological levels of L-arginine and hydrogen peroxide has also been reported [41]. On the other hand, extracorporeal shock-wave therapy (ESWT) has also been shown to reduce tumor necrosis factor alpha expression [42] and attenuate both polymorphonuclear neutrophil and macrophage infiltration, CC- and CXC-chemokine expression, extracellular matrix proteolytic activity, as well as acute proinflammatory cytokine expression [10, 43, 44] over the wound in animal models. Taken together, these factors may account for the topical anti-inflammatory effects of ESWT.

In addition to upregulating eNOS expression [19], ESWT has also been demonstrated to increase the expressions of vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA) [45]. These may partly explain the enhanced neo-angiogenesis and tissue regeneration after ESWT as reported previously [45], although the actual picture may be more complex. A summary of the mechanisms underlying the anti-inflammatory and pro-angiogenic effects of low-energy shock wave is shown in **Figure 2**.

The effects of shock wave on the cardiovascular system

A number of studies have already demonstrated that low-energy ESWT exerts positive therapeutic effects on ischemic myocardium in different animal models including improvement of ventricular function [37], enhancement of angiogenesis [37, 46], upregulation of VEGF [35, 37, 47], fms-related tyrosine kinase 1 [37], placental growth factor [37], and reduction in brain natriuretic peptide levels [37], thereby attenuating left ventricular remodeling after acute myocardial infarction [47]. We have also recently shown that SW treatment can effectively suppress neointimal proliferation and reduce smooth muscle proliferation in carotid artery after balloon-induced injury (**Figure 1C & D**).

Improved perfusion to ischemic limbs has also been reported in a rodent model following ESWT [36]. Consistently, other studies applying ESWT to skin grafts and flaps have demonstrated enhanced angiogenesis and tissue perfusion compared with the non-treatment groups. The proposed mechanisms included upregulation of eNOS and VEGF expressions [36, 48], thereby enhancing vasodilatation at early postoperative stage and neovascularization at late stage [39]. Through analyzing 84 angiogenesis-specific genes using full-thickness skin isografts after early revascularization in a murine model, another study further demonstrated that the observed ESWT-induced augmentation in early pro -angiogenic and suppression in delayed pro-inflammatory response was associated with enhanced expressions of both skin graft CD31 and angiogenesis pathway-specific genes, including ELR-CXC chemokines (CXCL1, CXCL2, CXCL5), CC chemokines (CCL2, CCL3, CCL4), cytokines (IL-1 beta, IL-6, G-CSF, VEGF-A), MMPs (MMP3, MMP9, MMP13), hypoxia-inducible factors (HIF-1 alpha), and vascular remodeling kinase (Mst1) starting from 6h to 7 days following operation, further highlighting the early pro-angiogenic and anti-inflammatory effects of ESWT [44]. The proposed effects of ESWT on the cardiovascular system have been summa-

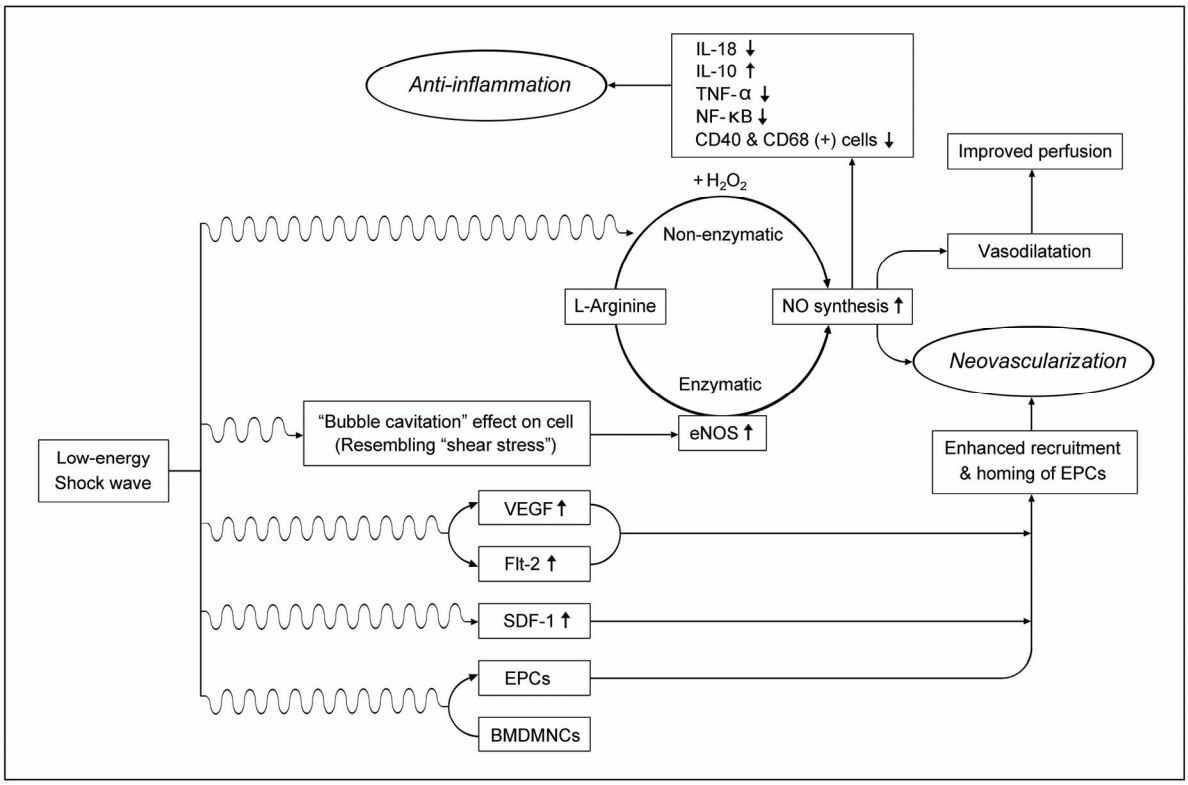

Figure 2. Schematic presentation of the anti-inflammatory and pro-angiogenic effects of low-energy shock wave in the cardiovascular system. Low-energy shock wave causes energy-dependent generation of nitric oxide (NO) in the presence of physiological concentration of L-arginine and hydrogen peroxide through the non-enzymatic pathway. On the other hand, shock wave exerts a cellular "bubble-cavitation" effect resembling shear stress that may lead to the observed up-regulation of endothelial nitric oxide synthase (eNOS) through which NO is synthesized (i.e. enzymatic pathway). The NO thus formed not only contributes to the anti-inflammatory responses [i.e. up-regulation of IL-10, suppression of tumor necrosis factor alpha (TNF-α), nuclear factor kappa B (NF-κB), IL-18, and inflammatory CD40 (+) and CD68 (+) cells], but also causes neovascularization and vasodilatation that improve tissue perfusion. Low-energy shock wave has also been shown to convert bone marrow-derived mononuclear cells (BMDMNCs) into cellular elements with phenotypic characteristics of endothelial progenitor cells (EPCs). This effect, together with shock wave-induced up-regulation of the mRNA expressions of chemoattractant stromal cell-derived factor 1 (SDF-1), vascular endothelial growth factor (VEGF) and Flt-2 (i.e. VEGF receptor) in endothelial cells, leads to enhanced recruitment and homing of EPCs in the process of neovascularization.

rized in **Figure 3**.

On the other hand, recent experimental evidence also revealed that SW not only may improve tissue perfusion via transforming bone marrow-derived mononuclear cells into endothelial progenitor cells (EPCs) [49], but it can also improve recruitment of circulating EPCs in SW-preconditioned ischemic tissue through the upregulation of the expression of chemoattractant factors [50]. We have also shown previously that SW-pretreated bone marrow-derived mononuclear cells can enhance vascularization and cardiomyocyte integrity in a rodent model of dilated cardiomyopathy [51]. Together, it implies that SW may enhance perfusion in ischemic tissue through increasing circulating EPCs and, at the same time, securing EPCs to their ischemic targets.

Potential therapeutic application of shock wave in the cardiovascular system, its consequences, and its limitations

In addition to our taking advantage of the destructive nature of SW in treating urolithiasis, recent studies have opened up a new avenue to its therapeutic application because of our in-

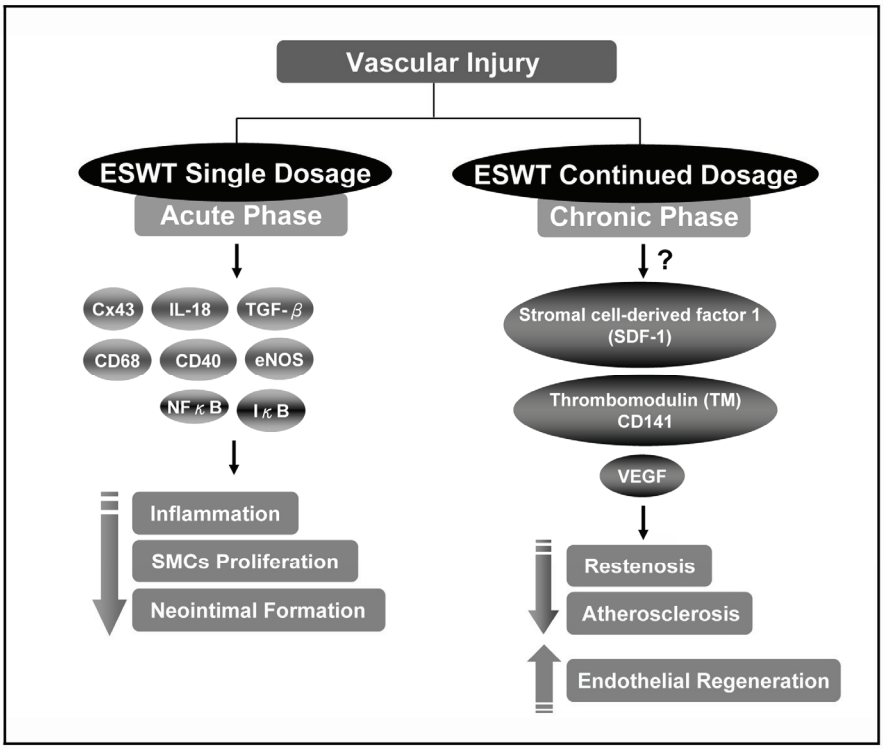

Figure 3. Summary of the proposed effects of extracorporeal shock wave therapy on the injured artery. Cx43: Connexin43; IL-18: Interleukin-18; TGF-β: Transforming growth factor-beta; eNOS: Endothelial nitric oxide synthase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IκB: Inhibitor of κB.

creasing understanding of its pro-angiogenic and anti-inflammatory properties. Indeed, ESWT has been utilized both in veterinary [52-55] and clinical [47, 56, 57] medicine, mainly for treating inflammatory conditions and restoring tissue perfusion in skeletomuscular [57] and cardiac tissue [47] as well as enhancing wound healing [56] with promising results.

Furthermore, although gene therapy seems to be a great step in medicine in the future, a couple of studies comparing the therapeutic effects of SW with gene therapy including VEGF [58] and TGF-beta [59] concluded that SW treatment is more effective than gene therapy in terms of enhancing flap perfusion and survival in animal models [48, 58, 59]. The findings underscore the importance of full utilization of existing treatment modalities while the attempts to develop novel treatment measures are being made.

Potential consequences of therapeutic application of SW on cardiovascular diseases include symptomatic relief for patients with end-stage coronary artery disease without indication for percutaneous coronary intervention or coronary artery bypass grafting [60] and restoration of tissue perfusion for patients with limb ischemia from peripheral arterial disease. Patients with ongoing vascular diseases of inflammatory origin such as atherosclerosis may also benefit from SW treatment, although more tangible clinical evidence is needed to warrant its clinical use.

However, it should be noted that SW is a double-edged sword that also has its downside on therapeutic use. High-energy SW-associated injuries have been documented including vascular damage at both organ [61, 62] and cellular level through impairing endothelial regeneration and altering cytoskeletal functions [63]. Moreover, high-energy SW has been reported to aggravate myelin degeneration in the rat spinal cord [64]. However, ESWT-associated adverse effects may be minimized through suitable adjustments of the voltage and interval of administration [61, 65]. On the other hand, the untoward side-effects of low-energy ESWT is rarely mentioned. Nevertheless, a study of the foot pad of rats has shown that multiple applications of low-energy shock waves might exert a cumulative effect on nerve fibers and cause a longer-lasting antinociceptive effect [66]. Although major adverse effects of applying low-energy SW to

the human body are unlikely according to the clinical evidence to date, potential risks of the widespread clinical use of SW in vital organs such as the heart and major blood vessels remain to be elucidated.

In conclusion, with the advancement of our understanding on the nature of SW from destructive to constructive, revolutionary changes in our concepts of its therapeutic potentials have begun. Although the preliminary results of its clinical application seem promising, further understanding of its nature may be warranted to expand its clinical indications and, in the same breath, minimize the potential untoward complications especially in the cardiovascular system.

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