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Editorial

How can we Better Know, Understand and Utilize Extracorporeal Shock Wave Therapy?

Pietro Romeo*

Galeazzi Orthopedic Institute, Via Riccardo Galeazzi, Milan, Italy

***Corresponding Author**: Pietro Romeo, Galeazzi Orthopedic Institute, Via Riccardo Galeazzi, Milan, Italy.

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From the first disruptive intent in the treatment of the kidney stones, a mistaken idea of similar effects in muscle-skeletal diseases has trapped Extracorporeal Shock Wave Therapy (ESWT) in a mechanistic limbo for many years. In spite of this, and thanks to the efforts and the determination of the researchers in the scientific community of shock waves, new perspectives overlooking the horizon have progressively overcome the old biases.

Although ESWT is a form of mechanotherapy, for our current data their distinctive character is the activation of extracellular mechano-sensors and intracellular pathways able to trigger biological responses characterized by the production of growth factors and signalling molecules. According to the principles of mechanobiology, mechano-sensitivity is different for each tissue and, for this reason, we should aspect different responses from the mechano-transduction of the acoustic signal [1]. Therefore, approaching to this therapy each practitioner should consider that SWs belong to Biophysics and so, the possibility to induce in the treated tissues metabolic responses has to be in tune to the physical features of the energy, frequency and duration of the exogenous pulse. This means that the effective distribution of the signal in the treated area has to be considered the cornerstone to ensuring the specificity of the biological response, from its part regulated by the stress and strain induced in the extracellular matrix (ECM) and cell membrane level, rather than the absolute values of the energy of the acoustic pulse.

Biomechanics teach us that a great part of the body tissues lives of mechanical stimuli, bone and tendon are a fitting example of this. Bone remodelling is a scholastic adaptive model to external loading forces while, thanks to mechano-transduction, tendons can regulate the homeostasis of the ECM. A substantial number of scientific papers demonstrate the positive effects of shock waves in modulating bone remodelling and enforcing its own trabecular structure [2]. For their part, tendons cells produce collagen and re-arrange its assembly [3]. In this perspective, the hypothesis that the shock waves impulse reactivate physiological processes in stimulated tissues is to be regarded as a conceivable scenario.

It has been also observed that the specificity of the biological response to SWs applies, at the cellular level, both to differentiated cells and Mesenchymal Stem Cells (MSC). Quite characteristic is the observation that Adipose-Derived Stem Cells (ADSCs), according to the nature of the culture medium, i.e. tenogenic or osteogenic, differentiate respectively in the tendinous and osseous series foreshadowing important perspectives in the field of tissue engineering, as for example in the field of bio-scaffold [4,5]. Shock waves are not only capable to activate and differentiate stem cells in their environment, but they are able to recall and activate stem cells in ischemic areas as detailed for some time in experimental studies [6].

In the course of the time, thanks to these and other experiences moreover supported by the evidence of a significant neo-angiogenic effect combined with the production of growth factors, it has been possible to bring out the strength of shock waves in regenerative medicine. Nevertheless, this connotation of the therapy remains in some ways still potential, at least from a conceptual point of view, when

the dogma "damage to reactivate" instantly prompts as regards for bone and tendons treatments. It is less so, even if with some perplexity when the regenerative effect of ESWT becomes visible as for the treatment of burns, difficult wounds and ulcers [7]; as if it should prevail a common-sense of "seeing to believe".

In spite of these shadows of scepticism, great signs of progress derive from the applications of ESWT in other medical fields such as dentistry, urology and cardiology.

If dental applications of SWs are still restricted at the experimental and speculative levels and [8], urologic practice gained a constant and progressive diffusion in the treatment of erectile dysfunction [9] Undoubtedly, very intriguing are the current advances in cardiology that are giving a strong impulse in the individuation of the complex and profound mechanisms at the basis of the biological effect of shock waves.

Cardiologic applications of shock waves are a relative novelty. The first experimental applications started in the early 2000s but only in the second part of the present decade, we were able to learn more about the mechanism of action and the efficacy of Cardiac Shock Waves Therapy (CSWT) as in refractory angina. Experimental proofs disclose a series of effects which consist in the reduction of myoblast apoptosis (P13K- AKT pathway), suppression of fibrosis, anti-inflammatory response (TL3) and angiogenesis (VEGF) mediated by the HIF 1α/SDF-1 system [10]. A series of protective mechanism in response to ischemia would involve the homing of endothelial progenitor cells (EPCs) and former experimental models have shown how shock waves trigger this activity [6]. Exosomes have been proposed also as cardioprotective substances. In the post-ischaemic heart model, shock waves treatment induced the release of extracellular vesicles (EVs) from endothelial cells (EC) identified by specific morphology, size and markers (CD9, CD81, CD63). One of the miRNA species contained in such exosome cargoes (miR-19a-3p) would be of particular importance in mediating the angiogenic and proliferative effects of shock waves [11] and their extracellular release leads us to consider a possible paracrine effect of extracorporeal shock waves as a model of nearby amplification of their biological effect.

Angiogenesis is crucial for tissue regeneration and its full accomplishment needs a preliminary inflammatory reaction. Previous reports had shown that SWs induce the release of mRNA (not in a damaging way) and then the activation of toll-like receptor 3 (TLR3) with a consequential angiogenic response [12]. As part of the evolutionary innate immune, but also of adaptative systems, TLRs are expressed on the membranes of leukocytes, dendritic cells, macrophages, natural killer cells, and non - immune cells (endothelial cells and fibroblasts). In particular, TLR3 would rule the production of cytokines and chemokines which, in turn, modulate a macrophage-mediated inflammatory response, prerequisite for the angiogenesis promoted by VEGF. A peculiar mechanism of angiogenic induction has been also observed in animal models of acute spinal cord ischemia. Here, along with a neuroprotective effect (lower number of degenerate neurons) attributed to the prevailing expression of TLR3 versus TLR4 not-protective proteins, shock waves induced a self-limiting inflammation marked by the meaningful increase of the cytokines IL 6 and TGF- β [13]. IL6 production has been associated with the recruitment of macrophages and, in turns, macrophages produce TGF- β. This synergy would justify the neuroprotective effect of the acoustic pulse through the preservation of the microglial cells, known as the macrophages of the spinal cord. Furthermore, in this study, evident capillary sprouting via pro-angiogenic molecules HIF α and VEGF, always due to the expression of TLR3, has been demonstrated.

Macrophages are sensitive two-faced cells behaving as pro-inflammatory defensive cells (M1) or anti-inflammatory regenerative cells (M2) and utilize the recognition system of TLRs. ESWT, unlike for resting macrophages, in polarized M1 macrophages inhibits the expression of marker genes (CD80, COX2, CCL5) and their ability to secrete the pro-inflammatory cytokine IL-1b. On the contrarily, M2 polarized macrophages react to shock waves by means the expression of marker genes (ALOX15, MRC1, CCL18) and induce significant production of the anti-inflammatory IL-10 cytokine [14]. Further studies may investigate the role of macrophages in the mechanisms underlying the biologic effect of the SWs, especially with regard to the intriguing correlation between the immune system - self-limiting inflammation and tissue regeneration.

Recent advances in basic research have shown that several factors secreted by stem cells in the nearby medium (conditioned medium) induce tissue repair and are referred to as secretome. Secretome includes extracellular matrix proteases, hormones, genetic material, growth factors, cytokines, chemokines, angiogenic factors. These molecules are released by stem cells through classical and non-classical mechanisms including protein translocation, exocytosis, and vesicle or exosome encapsulation. Various secreted substances may act directly by mediating intracellular pathways or, indirectly, by inducing the secretion of functionally active products from adjacent tissues [15]. It is interesting to recall, on this purpose, the above-reported experiences demonstrating, post-shock waves treatment, the release of exosomes carriers for genetic material in ischemic muscle [11]. Furthermore, in a model of murine ischemic heart failure, neo-angiogenesis and postnatal vasculogenesis has been related to the expression of VEGF and FGF families bound to Heparan Sulphate Proteoglycans (HSPGs) of the ECM [16]. In this report, in addition to a direct neo-vascularization, a significant effect has been observed when the supernatant from SW treated Bone Marrow-Derived Endothelial Cells was added in aortas cultures. The result of this *ex vivo* experience showed the improvement of the capillary sprouting in a cultured aortic ring that could be attributed to a complex orchestrated effect given by signal-dependent recruitment of stem cells and a post -exocytosis effect induced by shock waves.

The complex mechanism of action of ESWT is not entirely known and the mechanical pulse would have the role of starter. A great part of our knowledge derives from cultured cells or laboratory animal studies but the energy levels are different for the treatments in the human body and they can vary across the tissues according to the speed of the impulse and the acoustic impedance. Consequently, reflection, diffusion and absorption of the shock wave, as well as its attenuation and variations of the rise time can occur [17,18]. Computational 3D models, shown that cells would react to SWs according to the engineered type. Isolated cells embedded in a tissue-mimicking phantom, would respond to the to stress and strain induced by the acoustic pulse with different morphological changes respect to the cells organised in a surrounding multilayer set-up [19]. This configuration has been applied to early tumour growth model given by neoplastic cells surrounded by multilayers of healthy cells. SWs affected the rupture strain threshold of cancer cells respect to healthy ones due to different profiles of the tensile pressure values. In these conditions, the mechanical effect seems to prevail, but this model lacks the demonstration of any corresponding biologic consequences to the mechanical deformation of the cell membrane. Anyway, about cancer, an interesting series of researches have demonstrated over time the possibility to employ successfully shock waves in enforcing the tumour cytotoxic effect of antineoplastic drugs as well as their delivery in neoplastic cells trough nanobubbles [20,21]. In practical applications, this means the possibility to increase the efficacy as well as to limit the side effects, like cardiotoxicity, of this kind of drugs.

Repair or regeneration of damaged tissues is based on the activation, homing, differentiation of a ubiquitous population of stem cells, able to develop into different cell types. In regenerative therapies, Stem Cells of various type and source, alone or embedded in scaffold or engineered structures have been employed. Furthermore, the exploitation of active growth factors is another strategy. These methodologies demonstrated to be effective but the procedures can be invasive, require a certain number of passages in the laboratory, costly modalities and potential risks of infections have to be considered. For many years now, ESWT has demonstrated to be effective, safe and low cost, easy in the practice while increasing evidence shows a direct or paracrine stimulating effect on cells at various stages. More recently a correlation with that part of immunity-system active in tissue repair has been considered. We shall not need any further demonstration on these potentialities. Nonetheless, respect to this huge translational possibility ESWT is struggling to take off in terms of regenerative therapy, even in combination with the above-mentioned procedures. In this regard, in a series of non-union of long bones, the combined treatment by autologous bone marrow mesenchymal stem cells (BMSCs) transplantation plus ESWT demonstrated a higher healing rate respect to ESWT treatment alone [22]. This would be a feasible way and it has been proposed also as effective hypothesis [23].

Mechanical energies like extracorporeal shock waves and low-intensity pulsed ultrasound (LIPU) as well as electrochemical interactions with the cells given by low intensity pulsed electromagnetic fields (LI-PEMF) and more recently (HI-PEMF) [24], are currently the most descriptive aspects of the Biophysics application suitable for therapeutic purposes. In particular, ESWT and PEMF have proven to interact, powerfully, with several of the more representative and currently known pathways that rule the mechanical and electrochemical

activities in cell membranes, like for MSC [25]. In this scenario, PEMF and SWs would interact with specific receptors of the cell membrane, respectively the adenosine A2A receptors and integrinβ for PEMF, submembrane redox reactions activated by integrins and elicited by early O2 production for tyrosine kinase-mediated ERK pathway for SWs. These effects, at the basis of many responses of the cells to external forces, in combined mode or arranged in the same device, would become an exciting future perspective to implement these kinds of Biophysical activation.

The scepticism, sometimes exceeding the scientific evidence, about the possibility to induce exogenous repair and regeneration of degenerated or damaged tissues from Biophysics energies still exist. Is this, probably a cultural issue that requires time, economic resources for high-quality studies and, at the same time, more visibility in regenerative medicine conferences, as well as in medical school learning.

Basically, it's only a way to replicate physiological adaptative mechanisms and self-repair systems.

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