



Review

Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction

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H I G H L I G H T S

- SW represents a revolutionary form of mechanotherapy (acoustic stimulation).
- Unlike urological lithotripsy (mechanical model), on living tissues, SW exert an anti-inflammatory action and pro-angiogenic and regenerative effects as well (biological model).
- Mechanotransduction pathways sustain their clinical and experimental results.
- We present a summary of current knowledge of SW mechanisms of action, according to main recent data (mechanobiology).
- Better comprehension of SW mechanobiology could led to new therapeutical perspectives.

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A B S T R A C T

Extracorporeal Shock Wave Therapy (ESWT) is a form of “mechanotherapy”, that, from its original applications as urological lithotripsy, gained the field of musculo-skeletal diseases as Orthotripsy (mainly tendinopathies and bone regenerative disorders) and Regenerative Medicine as well.

The mechanisms of action of Shock Waves (SW), when applied in non-urological indications, are not related to the direct mechanical effect, but to the different pathways of biological reactions, that derive from that acoustic stimulations, through “mechano-transduction”. So, the “mechanical model” of urological lithotripsy has been substituted by a “biological model”, also supported by current knowledge in “mechanobiology”, the emerging multidisciplinary field of science that investigates how physical forces and changes in cell/tissue mechanics can influence the tissue development, physiology and diseases.

Although some details are still under study, it is known that SW are able to relief pain, as well to positively regulate inflammation (probably as immunomodulator), to induce neoangiogenesis and stem cells activities, thus improving tissue regeneration and healing.

ESWT can be nowadays considered an effective, safe, versatile, repeatable, noninvasive therapy for the treatment of many musculo-skeletal diseases, and for some pathological conditions where regenerative effects are desirable, especially when some other noninvasive/conservative therapies have failed.

Moreover, based on the current knowledge in SW mechanobiology, it seems possible to foresee new interesting and promising applications in the fields of Regenerative Medicine, tissue engineering and cell therapies.

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1. Introduction

Shock Waves (SW) were originally introduced in medicine as Extracorporeal Shock Waves Lithotripsy (ESWL) in the early 1980s for kidney stones treatment and these clinical applications

widespread all over the world until today. After its original introduction in medicine as *urological lithotripsy*, this technology indeed has been increasingly applied also to a broad range of musculoskeletal diseases, up to present day, when it represents an interesting therapeutic tool in the field of Regenerative Medicine [1–4].

Nowadays in fact, Extracorporeal Shock Wave Therapy (ESWT) is currently applied to a wide range of pathologies of different origins

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and localization, both in orthopedics and rehabilitative medicine (tendon pathologies, bone healing disturbances, vascular bone diseases) [1–3,5–8], dermatology/vulnology (wound healing disturbances, ulcers, painful scars) [9–12] and neurology (spastic hypertonia and related syndromes) [13–15]. More recently, the positive effects of ESWT on soft tissues and the local vasculature allowed its application, in clinical practice, also for some andrologic disturbances (*induratio penis plastica* and erectile dysfunctions) [16–18]. Regenerative and trophic effects have also been demonstrated for ischemic heart diseases, although, at present, SW application in this field has still to be considered as an experimental one [19].

In general, ESWT, in virtue of its noninvasive approach, absence of main side effects, repeatability, good tolerability and compliance by the patients (if properly applied, on the basis of a correct diagnosis), seems to offer new therapeutical perspectives in *Orthopaedic and Regenerative Medicine* [1–3]. In particular, it may represent a very useful tool, especially when all other noninvasive treatments were ineffective or surgery failed, especially in the field of orthopedics and rehabilitation [20], better if in synergistic action with some other therapeutical options (as, for example, rehabilitation programs) [21].

2. Shock waves as mechanotherapy: from fisics to mechanobiology and mechanotransduction

SW are “mechanical” waves, whose shape is characterized by an initial positive very rapid phase, of high amplitude, followed, after very few microseconds, by a sudden phase of mild negative pressure, afterwards returning to the ambient (basic) values. Medical SW are generated, through a fluid medium (water), by a *source* (electrohydraulic, piezoelectric or electromagnetic type generator). They are sonic pulses characterized by: high peak pressure, up to 100 mpa (500 bar) or even more, rapid rise in pressure (<10 ns), short duration (<10 μ s) and a broad range of frequency [22,23] (Fig. 1).

Independently of the type of generator (source) mounted in the lithotripter, SW are produced as consequence of a rapid increase in pressure (like a “micro-explosion”) into the water, and sooner they are “focused” on the *target* (that is the anatomical area to be treated). Focusing is possible for a parabolic lens, which concentrates the front of SW, as soon as they are produced from the source. These *focused* Extracorporeal SW (fesw) are well defined in their characteristics, that differentiate them from the *radial waves* [23,24]. Radial Waves are mechanical stimulations (acoustic waves) as well, but differ from fsw according to their shape, and act

through a *ballistic* mechanism. Technically, in the applicator (a barrel handpiece), a metallic bullet is accelerated at very high speed by compressed air (pneumatic source) or by an electromagnetic mechanism. Due to the high kinetic energy produced, it impacts against the tip of the applicator itself, which is directly applied on the body surface: as a consequence, the kinetic energy, forfeited during running, is directly transferred to the skin on the area of treatment. Differently than SW, this *pressure waves* propagate into the body as a spherical or ball-shaped waves, that is in a radial fashion, that gives them the descriptive term of “*radial waves*”. They are not focused in the deeper layers, and, at some extent, join the more superficial layers in the area of treatment. From the physical point of view, both fsw and radial waves are mechanical waves, but differ relatively to the shape of the wave itself; nevertheless, they share, as *mechanotherapies*, some useful clinical applications in some soft tissue disorders [23–25].

The importance of mechanical stimuli on living beings, as well as the influence that biomechanical deformations can exert on cellular biology and physiology, in health and diseases, have been recently seen a renewed interest in scientific literature, especially with the purpose of possible therapeutical applications [4,26,27].

Mechanical stimulation usually brings to mind the obsolete concept of “physical therapies”, especially in the fields of orthopedics and rehabilitation: for a long time, studies and researches for exploring the applications of “physical” stimulations have been generally limited to describe and quantify the final general outcomes of these therapies, without analyzing in details the pathways of actions, at biological level, that these “physical means” may produce on the treated tissues and cells [4].

Only in more recent years, due to the developing of the new branch of science named *Mechanobiology*, researchers began to analyze in details the effects of the physical stimulus and, most of all, to correlate the interactions of physical energies with the various tissues and cell elements [28,29].

It can be considered a field of science at the “cross-road” between biology and engineering of mechanics, whose main goal is to describe *mechanotransduction*, that is all the molecular mechanisms, by which cells can sense mechanical stimulations and adapt their behavior to mechanical signals [30,31].

“Mechanotransduction” is a *biological pathway* to which many cell types are sensible: after sensing and processing the mechanical informations from the extracellular environment, these biomechanical forces are converted in biochemical responses, thus influencing some fundamental cell functions as migration, proliferation, differentiation, and apoptosis [31].

Originally studied in “adhesion biology”, where *integrins* have been described to convey force transmission between the extracellular matrix and the intracellular actin cytoskeleton, it has been described that the phenomenon of *mechanosensing* is correlated with the laterally rearrangement of proteins within the membrane, thus inducing some changes in their tridimensional structure and modifying their activity, according to the different and changing biomechanical conditions [32].

Many cells structures have been described to contribute to mechanotransduction: stretch-activated ion channels, caveolae, integrins, cadherins, growth factor receptors, myosin motors, cytoskeletal filaments, nuclei, extracellular matrix, intercellular “gap junctions”, “hemi channels” among membrane proteins, “primary cilia” among cell organelles (capable of perceiving possible mechanical, physical or other “perturbations”), “transient receptor potential channels” intracellular mechanical-signaling “pathways” and numerous other molecular structures and signaling molecules. Moreover, endogenous cell-generated traction forces significantly contribute to these responses by modulating

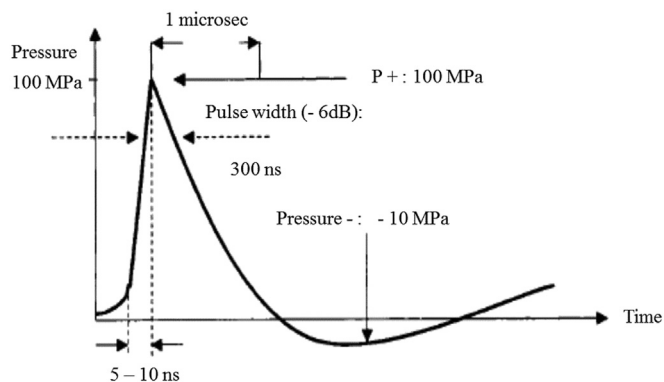


Fig. 1. Typical “biphasic” form of the therapeutical extracorporeal shock waves. (from: Odgen JA, Toth-Kischkat A, Schulteiss R. Principles of Shock Wave Therapy. Clinical Orthopaedic and Related Research, 2001; 387: 8 – 17).

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