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WHAT'S NEW IN THE LITERATURE ABOUT SHOCKWAVE MEDICINE

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Shockwave therapy (SWT) is gaining increasing acceptance and application in many areas of medicine, including "Regenerative Medicine", by virtue of its recognized therapeutic effects, based on numerous basic science researches, which seek to shed light on the intimate mechanisms at the base of the biological SW effects, derived from mechanical stimulation (mechanotransduction).

The musculoskeletal and osteoarticular fields have undoubtedly always represented the area of main interest and application of shock waves and, since also in this sector, in recent years, research efforts have turned to validate new techniques of regenerative medicine, it emerges naturally the intent of comparison of the different methodologies, that is between the shock waves and both all therapies that they have supplanted, both those with which they are emerging.

This is a very important process, that requires particular rigor and scientific methodology, because only in this way it will be possible (hopefully soon) to define some therapeutic protocols that, depending on the pathology (differentiated by type and stage of disease)), together with the local and systemic characteristics of the patient and possible concomitant therapies, will allow to optimize the treatment process, in terms of cost – benefit, both for the patient and the health system as a whole.

Hence the importance of clinical studies, comparing the effects of different therapeutic procedures of the present (and the future), in order to evaluate possible synergies and integrated treatment programs.

An example of this purpose has been recently published in the international literature: if on one hand it further confirms the efficacy and safety of SWT, on the other one it also offers an interesting starting point to guide the clinician towards the best therapeutic option.

In 2018, Ioppolo and co-authors published a study on: "Comparison Between Extracorporeal Shock Wave Therapy and Intra-articular Hyaluronic Acid Injections in the Treatment of First Carpometacarpal Joint Osteoarthritis" *(Ann Rehabil Med 2018;42(1):92-100 pISSN: 2234-0645 • eISSN: 2234-0653 https://doi.org/10.5535/arm.2018.42.1.92).*

As illustrated by the Authors, conservative procedure is the first step for the treatment of Trapezio - Metacarpal (TM) joint OsteoArthritis (OA). Commonly prescribed treatments would include rest, anti-inflammatory drugs, occupational therapy, night splinting, and intra-articular (IA) steroid or hyaluronic acid (HA) injections. Nevertheless, there is not consensus on which procedure can offer the best results with minimal complications. From this point of view, new therapeutic strategies for the management of TM OA are very hoped for.

Based on the very well known effects of shockwaves in clinical practice, its safety and preliminary tests in vitro and in the animal of the possible efficacy on cartilage diseases, together with a substantial lack of clinical studies in humans on this topic (except one), the Authors performed a study, in order to compare the effects of extracorporeal shockwave therapy (ESWT) with hyaluronic acid (HA) intra-articular injections in terms of pain relief, improvement in hand function, and strength in subjects with TM joint osteoarthritis.

Patients were randomly assigned to receive either focused ESWT or HA injection, based on strict clinical inclusion and exclusion criteria. Fifty-eight patients received either focused ESWT or HA injection once a week for 3 consecutive weeks.

In the ESWT group, patients received 2400 consecutive pulses during each treatment session, using a frequency of 4 Hz and an energy flux density (EFD) of 0.09 mJ/mm2 (focused shock waves were generated electromagnetically with a shock wave device equipped with an in-line ultrasound positioning system).

Patients of the HA group underwent one cycle of three injections of 0.5 cm^3 HA, once a week for 3 consecutive weeks; the injection was carried out under ultrasound guidance using a 10-MHz probe). To avoid bias from different treatment techniques, all injections were done by the same investigator, as stated in the randomization list. Patients were controlled at the beginning of the study (T0), at the end of the therapies (T1) and at the follow – up of 3 months (T2) and 6 months (T3).

Primary endpoints were pain and hand function, measured by the Visual Analogue Scale (VAS) and Duruoz Hand Index (DHI), respectively. The secondary endpoints were grip and pinch strength. Each assessment was performed at baseline, at the end of treatment, and at 3- and 6-month follow-up visits.

According to VAS and DHI scores, a significant change in test performance was observed over time in both groups ($p<0.001$), with a greater average improvement in painful symptomatology at the 6-month follow-up in the ESWT group. A significant improvement in strength was observed in both groups, but the ESWT group showed better results on the pinch test starting immediately at the end of treatment.

All the treatments were well tolerated without side effects.

The Authors were able to demonstrate that the application of ESWT in patients affected by OA of the TM joint, is efficacious in reducing pain, as well as in improving the “pinch test performance”, whose results persisted for at least 6 months, with a decrease in hand disability up to the 6-month follow-up visit.

As TM osteoathritis is a very common finding in orthopedic practice, and a not negligible cause of hand disability both for work and daily activities, this study makes us glimpse how ESWT could represent the first therapeutic conservative approach for this condition, with the undoubted advantage of effectiveness and non-invasiveness, with the possibility of delaying time for surgery.

Another great advantage of ESWT is its interesting versatility, being able to be effective both in simple pathologies of inflammatory and degenerative nature, and in diseases of more complex nature, in which the regenerative aspect properly said is fundamental, like in myocardium for example. For this reason, the main efforts in basic research are increasingly focused on the definition and characterization of the biological mechanisms, that are the basis of the beneficial mechanical action transduced in the clinical practice. Right in this field, once again, thanks to the rigorous and tireless experimental research work of Johannes Holfeld and his team, we have got further confirm about the angiogenic action of shock waves, but, above all, the further biochemical pathway through which this effect is translated to the cellular level. This further scientific data will certainly open new therapeutic possibilities not only in the field of cardiac regeneration, which has been investigated for many years, but also in soome other areas of regenerative medicine, of which shockwave therapy can nowadays be said officially considered part of it.

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Shock Wave Therapy Improves Cardiac Function in a Model of Chronic Ischemic Heart Failure: Evidence for a Mechanism Involving VEGF Signaling and the Extracellular Matrix

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The effect of improved cardiac function by ESWT is nowadays demonstrated and related to the induction of angiogenesis. Hower, the possible effects of ESWT in chronic heart failure remains still poorly known. The Authors aimed to study whether SWT improves heart function in chronic ischemic heart failure as well, by induction of angiogenesis and postnatal vasculogenesis and to understand the mechanisms of action.

In details, they hypothesized that, besides angiogenesis, mechanical stimulation of heart muscls is able to induce also the recruitment of bone marrow–derived endothelial cells (BMECs) to chronically ischemic myocardium, supposing the involvement of heparan sulfate proteoglycan (HSPG)–bound growth factors in the extracellular matrix after the physical stimulus of SWT, as a possible responsible for the beneficial effects.

The Authors applied SWT in a mouse model of chronic myocardial ischemia, based of ligation of the left anterior descending artery (LAD); after 3 week from the ligation, animals received SWT with a manual applicator and electrohydraulic source, according to this protocol: 300 impulses on the ischemic area with an energy flux density of 0.38 mJ/mm^2 at a frequency of 4 Hz. Some of the experiments were conducted also in vitro, with 250 impulses with an energy flux density of 0.1 mJ/mm^2

at a frequency of 3 Hz, according to the results of some previous studies and using a specifically designed “water bath” for standardization of the treatments.
In order to explore the potential effects of SWT on postnatal vasculogenesis, wild-type mice received bone marrow transplantation from green fluorescence protein donor mice. Echocardiography and pressure/volume measurements demonstrated improved left ventricular ejection fraction, myocardial contractility, and diastolic function and decreased myocardial fibrosis after mechenical stimulation. Moreover, increased numbers of capillaries and arterioles were detected, together with enhanced expression of the chemoattractant stromal cell–derived factor 1 in ischemic myocardium and serum, after SWT, thus suggesting the induction of angiogenesis and arteriogenesis in the ischemic border zone of chronically ischemic myocardium..
A very interesting finding was the recruitment of BMECs (bone marrow–derived endothelial cells) to the site of injury, induced by SWT, while in vitro studies revealed (after SWT) endothelial cell proliferation, enhanced survival and capillary sprouting, whose effects were vascular endothelial growth factor receptor 2 and heparan sulfate proteoglycan dependent.
General conclusions were that SWT positively affects heart function in chronic ischemic heart failure by induction of angiogenesis and postnatal vasculogenesis; moreover mechanical stimulation upregulated pivotal angiogenic and vasculogenic factors in the myocardium in vivo and induced proliferative and anti-apoptotic effects on endothelial cells in vitro. Mechanistically, these effects depend on vascular endothelial growth factor signaling and heparan sulfate proteoglycans. General results were improved cardiac function after SWT stimulation in a model of chronic ischemic heart failure as measured by echocardiography and invasively by catheter, together with reduction of fibrotic scar tissue, and improved neovascularization via angiogenesis and postnatal vasculogenesis. The Authors were able to describe how the mechanical impulse of SWT translates to a HSPG and VEGF-dependent stimulation of intracellular signal transduction pathways, leading to increased proliferation and inhibition of apoptosis in vitro and stimulation of capillary sprouting ex vivo in aortic rings. Inhibition of these effects by heparinase

and by blocking of VEGF and VEGFR2 indicates a pivotal role of VEGFR2 stimulated by ECM-stored VEGF in SWT-induced angiogenesis.

If increased angiogenesis and subsequent improvement of heart function in a model of acute myocardial ischemia had been already described in the literature, in this study they were able to show for the first time improved vascularization in chronically ischemic myocardium, related to concomitant improvement of cardiac function. This is an undoubted significant result, as regenerative therapies for improving heart function are limited, in spite of the increasing number of patients with chronic ischemic heart disease.

Some important scientific considerations are related to this study, as underlined by the Authors themselves:

• SWT can improve cardiac function in a murine model of chronic ischemic cardiomyopathy by induction of angiogenesis and vasculogenesis and reduction of myocardial fibrosis.

• As underlying mechanism, responsible for this regenerative effect of SWT is Vascular endothelial growth factor release from heparan sulfate proteoglycans, resulting in enhanced endothelial cell proliferation and survival, together with capillary sprouting.

• Shock wave therapy induces enhanced expression of the chemoattractant stromal cell–derived factor 1 in ischemic myocardium and serum and results in higher numbers of bone marrow–derived endothelial cells at the site of injury.

Some important considerations seems to derive from this interesting study, in particular the possibility to apply SWT as "endogenous cell therapy", thus avoiding the disadvantages and risks related to cell harvesting for conventional cell therapy. Moreover, it has to be considered that longterm effects of SWT are well known since a long time (3 decades), during which it has been applied in medicine, without any severe side effects. It is so hopefully that SWT for regeneration of ischemic myocardium could be translated into a clinical setting in the near future.