

Pain relief by extracorporeal shock wave therapy: an update on the current understanding

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(Nyon [Switzerland] / Dallas [TX, USA]: March 10, 2009): In a recent article published in the journal "Urological Research"* a hypothesis was developed as to how pain relief could be achieved by extracorporeal shock wave therapy (ESWT) [1]. We would like to express our concerns about the content and concept of the hypothesis article by Dr. Wess [1]. Of particular importance is that Dr. Wess' [1] article seems to be contradictory to the content of the last newsletter of the International Society for Medical Shockwave Treatment (ISMST) published in May 2008 (Volume 4, Issue 1).

We believe, a clear warning should be expressed. On page 328 of his article Dr. Wess [1] states "This treatment regime or a similar one is used for chronic pelvic pain as well as shoulder pain, heel spur and angina pectoris for example." This statement is made without any reference and might imply to the readers that ESWT is an equally accepted treatment modality for these very different indications. However, this is not the case. Neither is this view in line with the "Consensus statement: recommendations for the use of extracorporeal shockwave technology in medical indications" published by ISMST in 2008 [2].

ESWT has become a well-established treatment opportunity for several painful diseases of the musculoskeletal system such as chronic plantar fasciitis [3-5], chronic Achilles tendinopathy [6-9], chronic lateral epicondylitis ("tennis elbow"; [10-12]), calcifying tendinitis of the shoulder [13-15] and non-unions [16-18]. On the other hand, experience with ESWT as a treatment regime for chronic pelvic pain syndrome or angina pectoris can be regarded only experimentally to date [19,20], or for that matter anecdotally. The casual use of ESWT in the treatment of angina pectoris could result in unwanted side effects such as arterial embolisms or even severe damage of the lung.

Our major concern however is linked to Section "Associative memory model for establishing reflex functions" of Dr. Wess' article [1]. This section outlines in one and half pages, a hypothesis of so-called "associative pain memory", without so much as a reference to the literature. An essential part of this model is the idea of separating pain from pathology, as expressed in the following sentences by Dr. Wess [1]:

- "Chronic pain, for example, without underlying anatomical disorders is considered a pathological control function" (p. 328, right column, lines 12 ff);
- "In cases of chronic pain without organic reasons [...]" (p. 329, right column, line 24); and
- "Therapeutic treatment modalities are no more focused on specific organs under pain but on pain memory" (p. 329, right column, lines 33 ff).

Further, in Section "Hypothetic mechanism of shock wave therapy" Dr. Wess writes [1]:

- "The problem seems to be too complex for a simple answer since the location of the pathology is considered not in the painful organ itself anymore but is diffusely spread over extended areas as well as over several levels of the PNS/CNS." [peripheral nervous system / central nervous system] (p. 331, right column, lines 7 ff).

In this regard the following questions arise:

1. Is this really the field of ESWT, i.e., are users of ESWT really treating "pain without underlying anatomical disorders", and are they "no more focused on specific organs under pain but on pain memory"?
2. Are molecular and cellular mechanisms known as to how extracorporeal shock waves might mediate their pain-relieving action on anatomically defined disorders of the musculoskeletal system?
3. If users of ESWT are treating anatomically defined disorders and the potential underlying molecular and cellular mechanisms are known, what might have been Dr. Wess' [1] motivation to publish his hypothesis without reference to this knowledge?

It is beyond the scope of the present article to provide comprehensive answers to these questions. However, the following appears essential:

1. ESWT is not used in the international peer-reviewed literature to treat "pain without underlying anatomical disorders", and ESWT cannot be regarded "no more focused on specific organs under pain but on pain memory". This can be deduced easily from the titles of recent prospective, randomized, controlled clinical trials using ESWT published in the international peer-reviewed literature, such as:
 - "Radial extracorporeal shock wave therapy is safe and effective in the treatment of chronic recalcitrant plantar fasciitis: results of a confirmatory randomized placebo-controlled multicenter study." [5];
 - "Eccentric loading, shock-wave treatment, or a wait-and-see policy for tendinopathy of the main body of tendo Achillis: a randomized controlled trial." [7]; and
 - "A randomized controlled trial of extracorporeal shock wave therapy for lateral epicondylitis (tennis elbow)." [12]Note that these indications are anatomically defined diseases of attachment sites ("entheses") where tendons and ligaments meet bone, i.e., regions with a very specific pathology and pathophysiology [21]. The "Consensus statement: recommendations for the use of extracorporeal shockwave technology in medical indications" published by ISMST in 2008 [2] also lists only anatomically defined diseases.
2. Several molecular and cellular mechanisms were reported recently on how extracorporeal shock waves might mediate their pain-relieving action (again, reference was made to specific titles of studies published in the international peer-reviewed literature, and readers of the ISMST Newsletter will remember these mechanisms from Dr. Rompe's comprehensive review in ISMST Newsletter 4 (1) 2008 [6]):
 - "Substance P and prostaglandin E2 release after shock wave application to the rabbit femur." [22];
 - "Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5." [23];

- “Application of shock waves to rat skin decreases calcitonin gene-related peptide immunoreactivity in dorsal root ganglion neurons.” [24]; and
- “Selective loss of unmyelinated nerve fibers after extracorporeal shockwave application to the musculoskeletal system.” [25]

Substance P is concentrated in unmyelinated C-fibers and a subpopulation of slowly conducting, lightly myelinated A- δ nerve fibers, and is released at central and peripheral terminals of sensory nociceptive neurons after stimulation [26-28]. Calcitonin gene-related peptide (CGRP) is a marker of sensory neurons typically involved with pain perception and was immunohistochemically co-localized with substance P in capsaicin-sensitive axons [29]. Activation of peripheral small diameter sensory neurons by local depolarization, axonal reflexes, or dorsal root reflexes releases substance P and CGRP. Both substances then act on target cells in the periphery such as mast cells, immune cells and vascular smooth muscle cells, thus producing inflammation. This phenomenon is called neurogenic inflammation, and is, an inflammatory symptom that results from the release of substances from primary sensory nerve terminals [30,31]. Evidence has emerged that chronic inflammation contributes to the etiology of pain in tennis elbow and chronic plantar fasciitis [32-36]. Furthermore, a recent study revealed the contribution of substance P (as well as interleukin 1 alpha and transforming growth factor beta1) in the pathogenesis of tennis elbow, without apparent infiltration of inflammatory cells [37]. Moreover, depletion of substance P was shown repeatedly to reduce experimentally induced inflammation of paws and joints in laboratory animals [38-40]. It is therefore reasonable to hypothesize that (i) neurogenic inflammation plays an important role in the pathogenesis of tennis elbow and chronic plantar fasciitis, and (ii) reduction of substance P in the target tissue [22] in conjunction with reduced synthesis of this molecule in dorsal root ganglia cells [23] plays an important role in ESWT-mediated long-term analgesia in the treatment of these diseases. Selective destruction of unmyelinated nerve fibers within the focal zone of the shock waves [25] might also contribute to this analgesia. Also important to mention is that unmyelinated C-fibers are known to be responsible for throbbing, chronic pain [41].

3. One can only speculate as to Dr. Wess’ motivation to publish his hypothesis [1] without any reference to the detailed knowledge existing in the international peer-reviewed literature and the ISMST Newsletter outlined above. An interesting indication in this regard might emerge from the fact that Dr. Wess is affiliated with Storz Medical AG (Tägerwillen, Switzerland), the manufacturer of several extracorporeal shock wave systems (among them the D-ACTOR 200, marketed in the USA [42]). The U.S. Food and Drug Administration (FDA) classifies extracorporeal shock wave therapy devices as Class III, “highest” risk devices. According to FDA, the risk this type of device poses to the patient or the user is a major factor in the class it is assigned [43]. Approval of a Class III device requires demonstration of clinical efficacy and safety in a so-called “investigational device exemption” (IDE) study. Based on the results of this study, FDA then grants “pre-market approval” (PMA) to the manufacturer to market the device in the U.S. marketplace.

To date (February 25, 2009), the following extracorporeal shock wave devices have been granted PMA by FDA:

- OssaTron (HealthTronics, Inc., Marietta, GA, USA); PMA no. P990086 issued on October 12, 2000 to treat chronic heel pain [44];
- Dornier Epos Ultra (Dornier Medical Systems, Inc., Kennesaw, GA, USA); PMA no. P000048 issued on January 15, 2001 for treatment of chronic plantar fasciitis

for patients with symptoms of plantar fasciitis for 6 months or more and a history of unsuccessful conservative therapy [45];

- Siemens SONOCUR Basic (Siemens Medical Solutions, Inc., Iselin, NJ, USA); PMA no. P010039 issued on July 19, 2002 for treatment for pain due to tennis elbow [46];
- Orthospec Extracorporeal Shock Wave Therapy (Medispec, Ltd; Germantown, MD, USA); PMA no. P040026 issued April 1, 2005 for treatment of proximal plantar fasciitis with or without heel spur in patients 18 years of age or older [47];
- Orbasone Pain Relief System (Orthometrix, Inc., White Plains, NY, USA); PMA no. P040039 issued on August 10, 2005 to relieve heel pain (proximal plantar fasciitis) [48]; and
- EMS Swiss DolorClast (EMS Electro Medical Systems, Nyon, Switzerland); PMA no. P050004 issued on May 8, 2007 to treat heel pain associated with chronic proximal plantar fasciitis [49].

In contrast, the extracorporeal shock wave system D-ACTOR 200 has been presented to the FDA as Class I medical device, predicated on a similar function and purpose to “Therapeutic Massagers” (Regulation Number 890.5660 within Title 21 of the Code of Federal Regulations (CFR) [50]. As a result, the D-ACTOR 200 has been granted 510[k] Premarket Notification by FDA as a Class I “Massager, Therapeutic, Electric” (510[k] no. K072809; decision date June 27, 2008) [51]. It remains unknown whether clinical efficacy and safety of ESWT treatment with the D-ACTOR 200 has been demonstrated in an IDE study; corresponding data has not been published in the international peer-reviewed literature. Note that 510[k] Premarket Notification of Class I devices usually does not require a medical device manufacturer to perform an IDE study and present the results to FDA. The reason for this is that FDA considers Class I submissions as “lowest risk” devices that may bypass the lengthy and costly trials needed to enter the U.S. marketplace. Examples of Class I medical devices include: tongue depressors, elastic bandages, reading glasses and forceps [43].

Appendix G of the 510(k) Premarket Notification of the D-ACTOR 200 indicates that this medical device is intended for the following: (i) to relieve minor muscle aches and pains, and (ii) for the temporary increase in local blood circulation [51]. This is in striking contrast to all other extracorporeal shock wave devices listed above whose use is clearly intended for treating pain associated with anatomically defined disorders. The latter, however, is not the purpose of Therapeutic Massagers regulated by FDA under Regulation Number 890.5660 within CFR Title 21 [50]. In other words, FDA has not specified that Therapeutic Massagers may be used for the treatment of the anatomically defined diseases as discussed in the present article, and is not listed in ISMST’s consensus statement on recommendations for the use of extracorporeal shockwave technology in medical indications [2]. This is also in line with the fact that no evidence exists in the international peer-reviewed literature that Therapeutic Massagers exert their biomedical actions on the musculoskeletal system by the molecular and cellular mechanisms outlined above. Rather, anatomically defined diseases such as chronic plantar fasciitis and chronic Achilles tendinopathy are discussed in the current international peer-reviewed literature as potential indications for treatment with extracorporeal shock waves but not with Therapeutic Massagers [52,53].

In summary, the modern concept of extracorporeal shock wave treatment for various indications of the musculoskeletal system is based on the principles of molecular cell biology and clinical

evidence based medicine, witnessed by numerous publications in the international peer-reviewed literature and fully supported by ISMST. Dr. Wess' hypothesis [1] does not refer to this knowledge and should be evaluated cautiously against the fact that the extracorporeal shock wave system D-ACTOR 200 manufactured by Storz Medical AG (Dr. Wess' affiliation) has not been presented to FDA as a Class III extracorporeal shock wave device but rather as Class I device, being similar in function and purpose to Therapeutic Massagers.

Finally we would like to clarify an important issue that has caused some confusion: ballistic extracorporeal shock wave sources, such as the D-ACTOR (Storz Medical AG) and the EMS Swiss DolorClast (EMS), as well as piezoelectric and electromechanical extracorporeal shock wave sources operated at low settings, miss one element of shock waves in a strict physical sense, because the rise time of the leading positive phase of the acoustic waves produced by these devices (in the amount of microseconds) is longer than would be expected for a shock wave (in the amount of nanoseconds) [54]. Whether this is simply an issue of semantics, or whether there is something specific about the shock front that is necessary for effective shock wave treatment, cannot be ascertained until the mechanisms are better understood [54]. The rise time of the leading positive phase of acoustic waves does not seem to have substantial impact on the biomedical effects in clinical applications of extracorporeal shock waves. This view has never been postulated in the international peer-reviewed literature, and the part(s) of acoustic waves that actually mediate their biomedical effects on the musculoskeletal system remain unknown [1,55]. The international standard IEC-61846:1998 [56] does not define a specific limit, for the rise time of the pressure waves generated by a device, that must be exceeded in order to recognize the device as a Pressure Pulse Lithotripter. Noteworthy is that cavitation following the negative phase of the wave propagation has been proposed to mediate significant tissue effects [57]. The experiments performed by Cleveland et al. [54] demonstrate that the acoustic waves generated by the Swiss DolorClast comprise a substantial negative phase of the wave propagation. This is believed to be a major reason why the Swiss Dolorclast has been proven to be effective in the treatment of chronic proximal plantar fasciitis [5], chronic mid-body Achilles tendinopathy [7,9] and chronic insertional Achilles tendinopathy [8] according to Level I criteria of evidence based medicine.

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