Extracorporeal shock waves and bone: can we shock the cells into growth?

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'This (shock waves) causes the expression of bone growth factors...in an amount that is able to activate seemingly 'sleeping' pathways, as with a non-union.'

Extracorporeal shock waves are pressure waves generated outside of the body that can be focused at a target tissue within the body. The shock wave is characterized by positive pressures up to 100 MPa and negative pressures of 5–10 MPa. These transient pressure waves have a rapid rise time (30–120 ns) and a short pulse duration (5 μs) and are propagated three dimensionally through space [1]. They are differentiated from ultrasound by lower frequency, minimal tissue absorption and no thermal effect. They can be reflected by parabolic surfaces and lenses to focus the shock wave within specific tissue. The degree of transmission and reflection is dependent upon the impedance of the tissue. The pressure waves propagate through fluid and soft tissue without releasing large amounts of energy, but upon reaching a greater change in the impedance, high pressure and shear forces occur. Examples where there is a change in impedance are the bone–soft tissue interface and the transition from kidney tissue to calcified kidney stones.

Until now, the most common use for extracorporeal shock waves has been fragmentation and disintegration of kidney and ureter stones – lithotripsy [2,3]. This treatment was invented and clinically administered for the first time in our institute in the late 1970s and early 1980s by Chaussy and coworkers [4]. The indications were extended to gall stones and sialoliths [5]. Subsequently, a broad clinical experience in the handling of extracorporeal shock waves arose in these fields.

Shock waves in orthopedics

Two observations led the way for the use of extracorporeal shock waves in the orthopedic field. Upon observation of the mechanism of breaking up renal calculi, orthopedic patients with calcifying tendinitis of the shoulder were treated in the hope that a similar mechanism and good disintegration rate could be achieved [6]. Other tendinopathies, such as heel spurs with calcifications in the inflamed plantar fascia, or tennis elbow, were the next battle fields in the seemingly triumphal procession of extracorporeal shock waves in orthopedics [7,8]. The second observation was made in urological animal experiments using extracorporeal shock wave therapy. New bone formation was observed on the pelvic bone that was close to the approach path of the shock waves [9]. This led to a number of studies concerning fracture healing, where the outcome was quite controversial [10–12]. Better results could be achieved in the treatment of non-unions of the bone [13,14], thus, the clinical application was reduced to these chronic situations. Recently, some case reports and small series regarding the treatment of osteonecrosis, especially of the femoral head, have been published [15,16]. Due to the diverse development and time course of these pathological bone changes, the results are difficult to interpret.

Treatment of non-unions

In Anglo–American literature, a non-union is defined as a nonhealed fracture or osteotomy 9 months after trauma or surgery. Weber and Czech classified a non-union in hypertrophic and atrophic types as non-union only 6 months after trauma or surgery [17]. The reasons for the development of a non-union may be either mechanical or biological. Mechanical reasons include insufficient stability or a defect exceeding the critical size. The most frequent biological reasons include devastation of the blood supply, either iatrogenic or due to trauma, smoking, diabetes or other vascular diseases that lead to atrophic non-unions. Of course, infection may also lead to a non-union. The gold standard in the treatment of non-unions remains surgery. In a nonstable situation, the osteosynthesis has to be changed. In an atrophic non-union, necrotic tissue has to be removed and spongiosa chips from, for example the iliac crest, are filled in and around the defect. The frequency of successful unions after revision surgery rarely exceeds 70%, and often a second operation is necessary [18].

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These patients have to remain in hospital for a long time and are often not able to return to work within the first 3–6 months after surgery. The need for alternative therapies seems obvious.

In our institution, Delius showed new bone growth in the rabbit femur following shock wave application using high energies, which sometimes led to small cortical fractures [19]. Ikeda also stated that high energy is needed to create bone growth [11]. Although high energies (>0.5 mJ/mm^2) have unfortunate severe side effects, such as partial tendon ruptures, nerve and vessel damage [20,21,22], the next step was to find out whether lower energies could lead to bone growth. Maier, from our group, applied shock waves with an energy flux density of 0.5 mJ/mm^2 to rabbit femora and observed cortical appositions of bone and endostal bone growth [23].

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What Maier could not find were fissures or fractures of the bone. Therefore, the method to promote bone growth is more subtle. As we know from the studies of the Taiwanese group, extracorporeal shock waves with energy flux densities of less than 0.5 mJ/mm^2 induce the production of bone growth factors and the liberation of osteoprogenitor cells [24]. A possible mechanism may be via membrane depolarization and Ras activation. This was also shown by Wang, who treated immortalized bone marrow stromal cells with 0.16 mJ/mm^2 and saw an increase in specific osteogenic transcription factor core binding factor-α (CBFA)-1 expression. He confirmed his results using transfected cells with a dominant negative Ras mutant that did not show CBFA1 activation and bone nodule formation [25]. In our own experiments, we cultivated osteoblasts after collagenase treatment of bone material from patients undergoing hip or knee arthroplasty. Extracorporeal shock wave treatment with an energy flux density of 0.5 mJ/mm^2 and two different numbers of impulses (250 and 500) was applied to the cells and a significant increase of the bone growth factor, basic fibroblast growth factor (bFGF), was found in the supernatant 24 h after treatment using enzyme-linked immunosorbent assay test [26]. There was also a significant correlation between the increase in bFGF concentration and the number of impulses.

In 2003, the Japanese group from Chiba demonstrated that shock waves can induce new bone formation in a similar manner to that following a fracture [27]. They exposed rat femoral shafts to extracorporeal shock waves (0.5 mJ/mm^2 energy flux density) and measured, on the one hand, the bone mineral content (BMC) and bone mineral density (BMD) and, on the other hand, extracellular matrix proteins, such as collagens, osteocalcin and osteopontin using *in situ* hybridization. The increase in BMC was 8.46% and 5.80% in BMD. The expression pattern of the shock wave-induced osteoneogenesis was similar to that of periosteal hard callus formation during fracture healing. However, there are few studies that show no or even negative effect on bone growth. A total of 500 impulses with a relatively low energy (14 kV) were applied to sheep calcaneus and no bony appositions or bone growth could be observed [28]. In another sheep model, a tibial osteotomy stabilized with an external fixator was treated using an electromagnetic shock wave device with 12 or 16 kV at 300, 1000 or 3000 impulses. In this acute fracture model, no radiographic or histological differences were detected compared with the untreated fracture gap control group [29].

Theory of shock wave-mediated bone growth

Why are there such different results in the treatment of bone? Clearly, success is dependent on the energy level and number of impulses, whereas the ideal setting is yet to be found. This is due to the different shock devices, which have different focal sizes, peak pressures, rising times and negative pressure waves. Thus, the comparison of two experiments is difficult and even when there are different animal models used in the same studies, similar results cannot be expected. However, what is the underlying cause of the shock wave-mediated bone growth? It is well known that bone is able to react to external influences, such as pressure and stretching with bone growth or remodeling throughout life. One can see bony apposition in a bunion on the foot with a hallux valgus that experiences constant pressure from the medial inner surface of the shoe. A fibula pro tibia operation, for example in tumor surgery, leads to an impressing growth of the fibula under the new weight. By contrast, even after only 6 weeks a nonweight-bearing leg shows significant osteoporosis due to the lack of mechanical pressure. From *in vitro* experiments we also know that cylic stretching and pressure

chambers force the osteoblastic cells to produce growth factors, increase cell growth and enhance mineralization patterns. In recent studies, the role of mechanoreceptors in the cell membrane has been enlighted and the intracellular pathways are becoming clearer [30,31]. Therefore, we think that the same mechanisms underly shock wave-mediated bone growth. Compared with normal cycles and loads, we have a hyperstimulation concerning pressures and loading times. This causes the expression of bone growth factors, as mentioned previously, in an amount that is able to activate seemingly 'sleeping' pathways, as with a non-union. Once activated (with a single treatment), the whole cascade of cell acquisition, growth and new bone formation starts and may end in a bony union. A totally different situation is presented in an acute fracture model, where the aim of the treatment would not be the bony union alone, as this occurs through nature, but the enhancement of fracture healing leads to shortened fixations and allows a faster return to work. However, this does not work with shock waves, as in all settings the shock waves were applied immediately after the fracture (osteotomy) or within the first 2 weeks. Therefore, new bone formation is already in progress and a fragile cell layer is the base for further bony formation. Extracorporeal shock waves would do nothing other than what a too early mobilization would – lead to a destruction of the already created bone and start over again or, even worse, destroy the mechanism so completely that the bone could not heal any more and end up in a non-union.

Thus, we are convinced that we need more basic research comparing common mechanical influences on osteoblasts with shock wave treatment to understand or even transfer the underlying mechanisms of shock wave-mediated bone growth. From our clinical work, it seems that we should concentrate on treating chronic situations, such as non-unions or osteonecroses, and not try to enhance normal fracture healing. These clinical applications to the bone have to be examined in randomized, multicenter trials to establish extracorporeal shock wave therapy as a tool in the hand of the orthopedic surgeon.

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