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Shock Wave Therapy (Orthotripsy®) in Musculoskeletal Disorders

John A. Ogden, MD; Richard G. Alvarez, MD**; Richard Levitt, MD†; and Marie Marlow, RN‡*

Extracorporeal shock wave therapy, which now is used routinely for urolithiasis, has gained increasing acceptance in Europe for some musculoskeletal problems and has led to the inception of clinical studies in the United States. The authors have reviewed the available literature to assess the biologic effects of shock waves on human musculoskeletal tissues, the credibility of published studies on therapeutic applications, and the potential for more widespread application of this modality to various skeletal and near-skeletal disorders. The primary advantage of extracorporeal shock wave therapy is its noninvasive nature and seemingly minimal complications when applied to musculoskeletal tissues.

Since the initial therapeutic introduction of shock waves to the human body to noninvasively treat kidney stones (lithotripsy), this technology has evolved to be considered the procedure of primary choice for urolithiasis.[5,25,62,105,152] In contrast, surgery to extricate urinary calculi now is reserved for those few patients who do not respond to treatment with extracorporeal shock waves, or those patients who, because of certain medical disorders, are not appropriate candidates for the technology. Other types of stones (biliary, salivary) also have been addressed with shock waves.[73]

In some of the experimental studies to assess the effects of extracorporeal shock waves on various animal tissues, it became evident that if the ilium was in the wave propagation pathway a demonstrable effect was initial, focal osteocyte death followed by significant recruitment of osteoblasts within 72 hours.[15,37,40,41,61] Because of these observations and other analyses of the effects of extracorporeal shock waves on urinary stones of differing hardness and composition, many studies were undertaken to assess the effects of shock waves on similar hard tissues such as bone and contiguous, near bone tissues (cartilage, tendon, fascia).[2,3,25,37,55,60,61,72,85,89,92,120,135,166,170,175,176,185,186]

Valchanou et al[185,186] showed that high extracorporeal shock wave energy actually would fracture rat bones, whereas lower applied energy levels stimulated osteogenesis, especially the elaboration of callus. A subsequent study confirmed the osteogenic potential of shock waves and the possibility of reactivating osteogenesis in fracture nonunions that could lead to healing by noninvasive methods.[25] Ekkernkamp and coworkers[53–55] were able to show dose-dependent osteoblast recruitment and osteogenesis and the production of callus in a fracture

From the *Atlanta Medical Center and the Skeletal Educational Association, Atlanta GA; the **Memorial Hospital, Chattanooga TN; †HealthSouth Doctor's Hospital, Coral Gables FL; and ‡HealthTronics, Marietta GA.

Reprint requests to John A. Ogden, MD, Skeletal Educational Association, Inc, 3435 Habersham Road, Northwest, Atlanta, GA 30305.

pseudarthrosis model. This led to early clinical applications for patients with delayed union and nonunion. These studies showed a positive effect of extracorporeal shock waves on initiating fracture healing in patients in whom the natural biologic fracture healing process had failed.

It became evident that lithotripsy technology had to be modified for appropriate use on musculoskeletal tissues. The energy characteristics and delivery systems applicable to urologic applications have limitations, if not possible contraindications, when used on musculoskeletal tissues. Accordingly, numerous manufacturers have developed devices specifically for bone and contiguous soft tissue applications. Three such devices, OssaTron® (High Medical Technologies, Lengwil, Switzerland), Epos (Dornier, Germering, Germany) and Sonocur (Siemens, Erlangen, Germany), have instituted United States Food and Drug Administration-approved, randomized, double-blind studies. To date the Food and Drug Administration has approved only the OssaTron for the treatment of chronic proximal plantar fasciitis.

The aforementioned devices rely on different methods to generate the shock waves. The OssaTron produces shock waves electrohydraulically, whereas the Epos and Sonocur generate shock waves electromagnetically. These methods produce different volumes and amounts of energy, and different depths of penetration into human tissue. Whether treatment efficacy differences will be evident still needs to be determined from the ongoing studies being conducted under Food and Drug Administration sanction and through future studies comparing machines in a randomized study with each other. At least one other generational mechanism, piezoelectricity, is available, but is not currently undergoing Food and Drug Administration-approved testing.

The increasing potential and importance of extracorporeal shock waves to the treatment of musculoskeletal disorders has led to not only an increasing number of publications, but also to the formation of the International Society for Musculoskeletal Shock Wave Therapy. This organization particularly is concerned with encouraging the conduct of credible efficacy studies and standards of application of the technology, while recognizing the need for interaction with medical practice regulations specific to each country or region.

To prove that extracorporeal shock wave treatment is clinically equal to or even more effective than treatment modalities that currently are used, appropriate efficacy analyses must be conducted.[124,125,134,161] Unfortunately, for many of the potential applications similar studies have not been conducted even for currently accepted nonoperative treatment preferences. For example, there are no documented studies comparing the relative benefits of oral drugs (nonsteroidal antiinflammatory agents) compared with injection of cortisone, and, in turn, compared with placebo treatment, for a disorder such as plantar fasciitis. Additionally, endoscopic or open surgical release of the plantar fascia also lacks such comparison and placebo studies. Surgery and cortisone injections have significant complication risks, delayed healing, and recurrence.

Extracorporeal shock wave therapy for musculoskeletal use is an emerging technology that has been used principally in Europe for less than a decade. The emphasis has been on clinical application, without a great deal of experimental evaluation of the mechanisms of action on different musculoskeletal tissues or contiguous neurovascular structures. Many of the published clinical studies lack significant data generating parameters that would allow credible outcome analysis.

Because of the proliferation of articles dealing with the application of extracorporeal shock waves to musculoskeletal tissues, Heller and Niethard[82] did a metaanalysis of those studies published as of early 1997. They classified articles based on the methodology of the study and thought that only a limited number of studies warranted comparison for analysis of extracorporeal shock waves effectiveness. Only approximately 20% of the published treatment cases fit such selective criteria. They thought the results of treatment for plantar fasciitis were credible, whereas all other indications war-

ranted additional study. Haist et al[65] and Haupt[73] also presented an overview of emerging musculosketal applications of extracorporeal shock waves as of 1997.

Because the literature proliferated after 1997, and with the publication of proceedings of focused meetings (such as the annual meeting of the International Society for Musculoskeletal Shock Wave Therapy), the authors have upgraded and reassessed the data of Heller and Niethard to additionally evaluate the potential clinical use and efficacy of extracorporeal shock waves as applied to musculoskeletal disorders. The authors also have revised the study classification system to reflect differences between ongoing and completed Food and Drug Administration-approved extracorporeal shock waves studies and types of studies previously reported in the literature.

MATERIALS AND METHODS

Because the current metaanalysis is an update of additional material published after the review article of Heller and Niethard,[82] and a reassessment of data in their article, the authors have used a similar classification scheme to that proposed by the American Association for Spine Surgery.[183] In this previous classification, Type A studies were prospective studies including control groups and having adequate followup data, whereas Type B studies also were prospective, but lacked control groups. However, neither the Type A or Type B category fits the specific criteria required of a randomized, double-blind crossover study, as have been and are being conducted under Food and Drug Administration scrutiny to assess the efficacy of extracorporeal shock waves for musculoskeletal applications. Such studies blind the treating and evaluating physicians and the patients, and include validated outcome assessments.[13,24] The authors have classified such randomized, double-blind studies as Type A, and reassigned designations to the previous classification. In addition, the authors have added another classification (Type F) that would include studies using retrospective data, with or without recall of patients for up to date clinical assessment. Finally, the last classification, abstracts, has been broken down to discern abstracts published in proceedings of meetings from verbal presentations not accompanied by written proceedings. The last two categories (Types G, H) reflect the number of podium presentations that eventually may or may not be published in peer-reviewed journals. Publication rates vary considerably among societies, with rates of 20% or less occurring in some societies. As an additional example, the papers presented at the London meeting of the International Musculoskeletal Shockwave Therapy Society in 1999 were published in book form.[29] The papers varied considerably in their format and often presented minimal study details, results, or statistical analyses. This book, and abstracts, often lack peer-review and have inaccessability to Medline retrieval. This makes Types G and H studies the least credible for citation, even though they may be excellently conducted studies. Realistically, Types G and H studies should not be compiled numerically for metaanalysis, but certainly may be cited for new ideas or trends pending their eventual peer-reviewed publication.

Accordingly, the quality of published clinical outcome studies is as follows: (A) prospective study with randomized, double-blind crossover, statistically validated differences between patients who are treated and patients who receive a placebo and followup studies of sufficient scope and duration, with all patients being treated by exactly the same protocol; (B) prospective study with appropriate control group (nonrandomized), adequate analysis and followups of sufficient scope and duration in which neither study subjects nor treating and evaluating physicians are blinded to actual treatment and the treating and evaluating physician may be the same individual; (C) prospective study without a control group, but with adequate analysis and followup of sufficient scope and duration; (D) prospective study with a control group, but with a followup of insufficient duration or inadequate followup protocol; (E) all other published prospective studies, with the exception of abstracts, with such studies having a hard-to-understand study protocol with inadequate followup of the patient cohort; (F) retrospective data analysis studies that may include patients treated by one or more physicians, and often have variations in treatment that the patient receives, which may or may not involve an attempt to actually assess the patients to obtain accurate, up to date outcome data, and may include metaanalyses and evidence-based medicine reviews; (G) published abstract (in the meeting proceedings or a society journal) of an invited presentation to a recognized scientific society; and (H) unpublished

presentation (in the meeting proceedings) to a recognized scientific society or group.

Under this reclassification only the currently approved Food and Drug Administration study on plantar fasciitis,[126] and the currently ongoing studies of extracorporeal shock wave treatment of plantar fasciitis, lateral epicondylitis, and delayed union or nonunion of tibial fractures conform to the Type A category. All other studies fit the Types B to H classifications.

Because the published material covers a wide-spectrum of musculoskeletal conditions, the published data will be analyzed by specific topic: (1) heel spur or plantar fasciitis; (2) lateral epicondylitis; (3) delayed union or nonunion of fractures; (4) calcific tendinitis of the shoulder; (5) other enthesopathies; and (6) additional skeletal applications. Articles that only relate to the basic science of shock waves will be reviewed in the Discussion section.

RESULTS

More than 8000 cases of musculoskeletal problems treated with extracorporeal shock wave therapy have been documented. Patients with a wide variety of musculoskeletal indications have been treated, with considerable variation in the validity of the studies. Although the total number of reported cases seems to be large, the actual number decreases when the quality and scientific rigidity of the published studies are ranked by the aforementioned study classification system. If only studies fitting the criteria of Types A to C are analyzed, the number of cases is at least 2723, which represents approximately 34% of the published cases.

For plantar fasciitis or heel pain, the first musculoskeletal indication of extracorporeal shock waves approved by the Food and Drug Administration, there are published and abstracted studies involving at least 1131 patients.[18,25,29,95,110,126,144,146–148,160,182] Of these studies, one of which is included in this symposium,[126] 736 patients fit the category of Types A to C studies, with approximately 300 being the only patients in a published Type A study. The data in these studies strongly support a positive response to extracorporeal shock wave treatment, and that such response usually lasted to at least 1 year. The results certainly were comparable with those attained by surgery, but did not have the expected morbidity and delayed healing associated with surgery. Success rates from 34% to 88% were achieved in these studies. The Type A study included in this symposium[126] used one treatment in approximately 80% of the patients, and two treatments in approximately 20% of the patients to achieve a successful result. In contrast to the studies with an electrohydraulic extracorporeal shock wave device, the other reported studies used multiple treatments (usually three or more) with electromagnetic or piezoelectric devices.

For lateral epicondylitis, which is under active study, using approved Food and Drug Administration protocols for at least two extracorporeal shock wave devices, there are published and abstracted studies involving at least 1672 patients.[18,69,70,78,88,94,96,97,114,133,140,142,143] There are no published Type A studies. Eleven of the studies involving 763 patients are Types B and C studies. The success rates range from 48% to 73%. All of these reported studies have involved electromagnetic or piezoelectric extracorporeal shock wave devices, which invariably have involved multiple treatments (several days apart) to achieve final success.

Delayed union and nonunion of fractures in long bones and the smaller bones of the hand and foot involve studies involving at least 1737 patients.[8,18,20–23,25,32–34,50–52,63–67,76–78,81,98,134,135,151,156,157,162–164,189–192,198] These studies are easier to document as far as an end point of successful treatment, which is established by fracture healing by radiographic studies, rather than the soft tissue disorders (enthesopathies) that rely on more subjective analytical data. Types B and C studies report at least 714 patients with well documented healing success rates of 62% to 83%. Poor results were achieved with electromagnetic devices. The electrohydraulic (high energy device) appears requisite to achieve single treatment union of fracture nonunions.

The presence of implanted hardware (rod,

plate) does not seem to interfere with the likelihood of a successful response. Hypertrophic nonunion is more likely to be treated successfully than an atrophic nonunion. A nonunion gap greater than 5 mm has a less likely chance of success than a gap less than 5 mm. These studies have involved long bones and small bones in the hand (scaphoid) and foot. At least one Type A study (Food and Drug Administration approved) has been started.

Calcific tendinitis of the rotator cuff is also relatively easy to document radiographically relative to presence of the lesion before treatment and its diminution in size or disappearance after treatment. As with other enthesopathies, there is a subjective aspect (lessening or disappearance of pain) that also factors into the end result. There are published studies involving at least 916 patients.[19,31,52,69,78,88,90,106–109,115–117,137,149–154,169,180,193,194] More than 510 of these patients are in Types B or C studies, in which the success rates range from 47% to 70%. Approximately all the studies equated success with either diminution in the size or complete disappearance of the calcific deposit, and subjective symptomatic improvement. These studies support the positive effect on the pathologic calcification, but should not be extrapolated to patients with shoulder pain (impingement syndrome, rotator cuff disease without a tear) who do not have radiographic evidence of calcification.

Maier et al[116] studied the outcome of extracorporeal shock waves for calcific tendinitis of the shoulder by magnetic resonance imaging (MRI). They used pretreatment contrast enhanced MRI to document the size and morphologic features of calcifications and the presence of inflammation (positive contrast reaction) around the lesion. Lesion size did not affect outcome. However, patients with more chronic tendinitis, as evident by the absence of contrast uptake around the calcific deposit, had the best outcome.

Other enthesopathies that have been treated include medial epicondylitis, patellar tendinitis, trochanteric bursitis, Achilles tendinitis, and noncalcific shoulder problems.[25,29] Dahmen et al [4] reported treatment of patients with back pain, although this is the only reported study of spinal column application. Until the effect of extracorporeal shock waves on large nerves and spinal cord tissue has been documented, this indication probably is contraindicated. Other skeletal applications include treatment of osteochondritis dissecans, osteonecrosis of the femoral head, and reversal of heterotopic bone formation in patients with spinal cord injury or head injury.[23,25,29,139,184] These other indications only have been explored recently, and statistically valid results are not yet available. These studies are Types D, E, G and H categories. In many cases, the patients were treated with lithotripsy devices, rather than the aforementioned devices modified for orthopaedic applications.

DISCUSSION

Heller and Niethard[82] undertook a metaanalysis of 105 articles. The study included articles written up to 1997, although some were not published until 1998, that assessed the outcome of extracorporeal shock wave therapy for musculoskeletal disorders. They specifically evaluated 4825 patients who were reported in 55 published articles and abstracts. However, only 24 articles describing 1585 patients (33%) satisfied their standards of an adequate scientific evaluation and only 978 (20%) involved their Type A or Type B study classification. From the current review of more recent studies, the number of reported cases has approximately doubled. More importantly, the percentage of high level studies (Types A to C) has increased from 20% to 34%. This reflects the realization of the current need for valid study design and outcome analysis. Heller and Niethard[82] thought that only the data concerning treatment of plantar fasciitis supported its unequivocal clinical use to avoid the recognized risks and complications of heel surgery. The Food and Drug Administration-approved study reported elsewhere in this symposium[126] corroborates the efficacy of extracorporeal shock waves for chronic proximal plantar fasciitis. All other disorders (lateral epicondylitis, calcific tendinitis

of the shoulder, Achilles tendinitis, and osseous delayed union and nonunion) were documented insufficiently relative to their evaluation criteria, although they thought that the data suggested at least the equivalency of treatment effect without potential surgical morbidity. They stressed the need for continuing evaluation of all musculoskeletal indications, and particularly emphasized the need for more studies. The authors agree conceptually, but suggest that the current Type A category (double blind with placebo control or alternate treatment) should be the goal of future clinical prospective studies.

Since the initially sporadic application of shock waves to musculoskeletal conditions in the 1980s, there has been a rapid and widespread application in the last ½ of the 1990s, especially throughout Europe. The rapid application has not been accompanied by an acceptable number of well-conceived and promulgated studies, which has led to some skepticism regarding the actual efficacy of extracorporeal shock waves for musculoskeletal disorders. As an example, in 1996, more than 30,000 patients were sent to European (principally German and Italian) health insurance providers to request coverage of such treatments.[18] In turn, the health authorities expressed the need to justify such coverage (reimbursement) by conducting studies to statistically corroborate the efficacy of such treatments compared with nonoperative and operative treatments that currently are considered acceptable treatments for any given musculoskeletal condition. Such considerations currently involve the cost-benefit aspects of a treatment when applied to a specific need. For example, should extracorporeal shock wave treatment of heel pain or plantar fasciitis at 3 months of symptoms that traditionally has been treated to that point with heel cord stretching, orthotics, and nonsteroidal antiinflammatory drugs be applied before cortisone injections, which have a serious recognized risk of rupture of the plantar fascia, to restore a patient to normal work or recreational activities.

Perhaps the most variable areas in the published studies have been the type of applied energy (low versus high energy), the number of treatments (one versus multiple), the need for anesthesia or sedation, and the total number of applied shocks. Particularly for fracture nonunions, the number of recommended or shocks that are used has increased substantially.[157] Because of differing devices, differing energy outputs and inputs at the first focal point and the second focal point, and differing energy generation, it is difficult to compare treatments for the same musculoskeletal indication. Attempts are being made to standardize the analysis of energy per shock and total treatment energy to create some type of standard.

Rompe and coworkers[145] attempted to define the concepts of low-, medium-, and high-energy shock waves. According to their criteria, low energy waves had an energy density of 0.08 mJ/mm^2 at the second focal $point_2$, whereas an energy density up to 0.28 mJ/mm^2 constituted medium energy, and an energy density exceeding 0.6 mJ/mm^2 was high energy.

Additional differences among the available devices in the United States under Food and Drug Administration approval study and additional devices being used in Europe and the Pacific Rim relate to the size of the actual energy toroid and whether effective treatment can result from one treatment or requires multiple sessions. Patient preference would seem to favor one treatment, although the energy effect on human tissues usually necessitates some type of anesthesia (local, regional block, or general), especially at the energy levels most effective to accomplish osseous healing. In fact, of the three machines currently under Food and Drug Administration study only the OssaTron is capable of producing the high energy necessary for fracture healing (and possibly for the more severe tendinopathies).

When considering the applicability of extracorporeal shock waves to musculoskeletal conditions, early concepts were to alleviate pain using the low energy levels, and to use the medium and high levels to either disintegrate or crush calcific deposits or to cause osteoinduction. The definition of what constitutes low, medium, and high energy has been the subject of intense discussion. As presented

elsewhere in this symposium,[126] measurement of energy and energy flux density to allow device comparisons is not easy. This procedure requires specialized devices termed hydrophones.[173] Without interdevice comparison criteria for energy applied per dose (per shock wave) and total energy applied per treatment, effective comparisons of devices cannot be done. Additionally, the appropriate dosage (number of shocks, kV or the mJ/mm^2 setting) cannot be effectively determined statistically. Attempts to cross-quantify and compare energy outputs of devices have been made by groups such as the German and International Study Group for Extracorporeal Shock Wave Therapy[59] and the International Society for Musculoskeletal Shockwave Therapy.[87] Both organizations have web sites that document completed comparison studies of energy outputs by numerous devices including those participating in Food and Drug Administration-approved studies and additional devices used outside of the United States.

An additional comparison relates to the direct and indirect effects of shock waves. The direct effect is caused by the conversion of shock waves into kinetic energy at impedance interfaces. The impedance differences (muscle or fat versus bone) further alters energy through reflection and transmission. The bone or implanted rod may redirect the wave (echogenic effect), which may amplify the effect by a double hit to the target tissue. The shock wave indirect effect is achieved by cavitations within the target tissues.

Another important, if not essential aspect, of extracorporeal shock was treatment relates to the transmission of the shock waves through the generation device into the target tissue. Because shock waves transmit poorly in air (lose their potential therapeutic effect), the generating device must be coupled acoustically to the target tissue. This can be accomplished easily with readily available ultrasound gel, although other substances have been evaluated.[7,117]

The actual biologic mechanism of action of clinically applied shock waves within human and animal tissue has received a paucity of attention. Studies to date have assessed basic biologic tissue effects and more germane topics such as the potential for neurovascular injury.[38,146] There is no question that lung tissue is highly susceptible to disruption by shock waves, minimizing the applicability to thoracic disorders (stress fractures of the first rib). Such susceptibility also necessitates specific targeting of shock waves to avoid lung tissue when treating shoulder disorders.

Cavitation is the generation and movement of bubbles in a fluid or tissue caused by changing gases normally dissolved in fluids back into their gaseous phase.[1,27,28,36,39,46,56,79,101,118,155,197,205–208] Such phase conversion is a very powerful process that may be a factor, even in hard materials.[36] Such a mechanism may induce surface erosion in ship propellers or turbine blades.[181] A comparable cavitation in bone or relatively hard tissue (cartilage, tendon) also may occur consequent to extracorporeal shock wave application.[181]

Cavitation is a very fast process with crucial events occurring in the microsecond range. A moving cavity generated near a solid surface collapses asymmetrically under formation of a water jet at the impedance surface. This surface impairs the flow of water in the direction of the bubble center.[30] A surface pit (microdisruption) generated by such collapse has the same diameter as the water jet and is considered the primary damaging event. Cell damage may occur from the production of free radicals.[177] The process of cavitation produces free radicals that may affect the cellular antioxidative defense status. When a shock wave hits an already present stable gas bubble within a fluid, it also induces a strong jet in this bubble. This interaction between a shock wave and a preexisting bubble is an even stronger mechanism of microdamage formation.[39,41]

Although initial studies showed no damaging effects of shock waves on organs and tissues, Brümmer and coworkers[15] gathered numerous reports that documented severe acute effects and chronic complications after shock wave treatments in humans and experimental

animals.[129,132] This study was published in 1990, before the advent of musculoskeletal applications of shock waves. Lung tissue especially is susceptible to profound damage if extracorporeal shock waves are directed toward the chest.[26,42] Whether similar or other complications will surface in musculoskeletal tissues remains to be seen.[171,203]

Petechial bleeding may be observed in approximately 10% of patients being treated for renal stones.[123] This complication has been observed in patients who were treated for fracture nonunions, and certainly occurred in all the patients in a Food and Drug Administration feasibility study of 21 patients treated for fracture nonunions (Unpublished data, Ogden JA: The use of shock waves in musculoskeletal disorders. Presented at the American Orthopaedic Association, West Palm Beach, FL 1998). In contrast, in the treatment of more than 200 patients for chronic plantar fasciitis, [26] petechial hemorrhage virtually was nonexistent. The differences undoubtedly related to the number of shocks applied and the finite energy per shock.[120]

Neural damage is of concern with the use of applied energy forms.[35,121,136] Miller et al[122] showed that heating, rather than cavitation, was responsible for mouse hindlimb paralysis by ultrasound. Similar tissue heating does not occur during shock wave therapy. Schelling et al[158] showed that shock waves stimulated frog sciatic nerves in a manner similar to electrically-induced compound action potentials. They thought cavitation was the causal excitatory factor, and that such cavitation was the underlying mechanism of shock wave related pain in clinical medicine. They also reported that shock waves do not directly stimulate nerves, despite high pressure and short rise times. Another effect of the shock waves seems to be a distortion of axonal contents, straining of the cell membrane, and a resulting increase in permeability, leading to depolarization, factors that effect mechanosensibility. Lohse-Busch and coworkers[111,112] assessed neuromuscular dysfunction disorders (cerebral palsy); however, the results were not dramatic. Obviously, additional animal and clinical studies are essential.

Another aspect of shock wave treatment is pain.[160] In lithotripsy, there are two general patterns: superficial discomfort at the skin surface and deep pain within the kidney. Similar problems occur with high-energy shock waves for musculoskeletal applications. The skin delivery site, when coupled with gel, is painful to most patients. Some patients will feel pain or discomfort in the underlying bone when plantar fasciitis or lateral epicondylitis is being treated. Generally deep bone pain is more likely when 20 kV or greater is used. The low-energy machines (electromagnetic generation are reported to cause no pain[141]; however, some patients experience pain even when these devices are used. Local anesthesia, conscious sedation, or a nerve block are ways of alleviating treatment pain or discomfort. In seeming contrast, extracorporeal shock waves have been used for the alleviation of musculoskeletal pain in high performance athletes.[68,141,200] This effect may be similar to transcutaneous neuromuscular stimulation.[121] The initial analgesic effect that many patients have may be attributable to altered or increased cell membrane permeability. The nocioceptors lose their ability for generation potential, which is necessary to elicit a pain signal response (the gate control mechanism).

Brümmer et al[15] tabulated the reported complications of shock waves, including those that could occur by direct exposure of organs and tissues to shock waves. Kidney and liver damage and heart arrhythmia may occur.[43–45,131] Certain chemical markers (S100aO protein, C-reactive protein) may be used as tissue markers for abdominal organ damage.[71,201] However, these are unlikely with distant musculoskeletal extracorporeal shock wave applications.

In the hamster and mouse there was microhemorrhage and leakage of macromolecules within muscle.[15,172] In immature rat bone and rabbit bone, there was evidence of local physeal dysplasia in approximately 50% of the animals. Mature bone (rat) may have dose-dependent hemorrhagic lesions. Brümmer et al[15]

additionally showed that extracorporeal shock wave application to multicellular spheroid suspensions caused considerable cellular agitation.[16] This probably is the result of cavitation and jet streams, which occur as a consequence of local acceleration of fluid in the shock wave focus. These rapid accelerations expose cells to shear forces and cause collisions that may be responsible for cellular damage. Placement of the cellular spheroid suspensions in gelatin, effectively duplicating solid organ structure, essentially protected the cells, which showed no detectable cellular damage in this experimental construct.

Seidl et al[167,168] and Steinbach et al[174,175] determined the energy-dependent extent of vascular damage caused by high-energy (electromagnetic) shock waves on vascular tissues. Other researchers also have assessed the effects of extracorporeal shock waves on blood vessels.[14] During treatment (using umbilical cords) macroscopically visible hematomata and superficial holes appeared. In some areas, there was separation of normally adherent endothelial cells. A local energy density of 0.3 mJ/mm^2 appeared to be the lower threshold for occurrence of severe vascular damage in their model. In other studies, umbilical cords from humans were exposed to focal energy densities of 0.4 and 0.6 mJ/mm^2.[2,167] The degree of tissue change ranged from the induction of stress fibers and intercellular gaps to complete detachment of endothelial cells combined with basement membrane damage. The increased number of stress fibers seemed to correlate with increased vessel wall permeability.[14,49,84] Gaps in the vessels might promote the diffusion of cytokine molecules through the vessel wall. Such a mechanism may be active in the symptom relief experienced after extracorporeal shock wave therapy for plantar fasciitis or epicondylitis.

There are some contraindications to the use of extracorporeal shock waves. Because of microvascular disruption that leads to transient cutaneous petechiae (especially with high energy and large numbers of shocks for fracture treatment) patients with any type of disease-related (hemophilia) or physician-induced coagulopathy should be excluded. The effect of shock waves on infected tissue and bacteria are unknown. Lung tissue is particularly sensitive, and must be avoided from being in the beam pathway. Thus, treatment of rib and clavicular fractures is excluded. The effect of energy on distant coronary stents or implanted heart valves is unknown. Malignancy is a relative contraindication, although some research suggests a tumor may be more receptive to chemotherapy or radiation therapy when initially subjected to extracorporeal shock wave therapy.[130,131] The growth plate is an unknown; experimental studies suggest possible physeal damage, but the studies have involved lithotripsy devices, and not the newer orthopaedic machines.[113,185,187] Heterotopic bone, once mature, probably will not respond (by resorption) to extracorporeal shock wave therapy. However, there is a suggestion that extracorporeal shock wave therapy in the early phases of development (often detectable by bone scan) may reverse the process, not unlike current treatments with drugs or low-dose radiation.[29]

Extracorporeal shock waves have been delivered to tumor cells in vitro and tumors in vivo to study the possibility of enhanced tumor treatment.[12,16,17,47,48,127,128,130,131,152,176,196,202] Combining extracorporeal shock waves with biologic response modifiers, such as tumor necrosis factor alpha, led to complete tumor regression in bone xenograft models. The reason for the synergistic effect is unknown, although vascular damage is thought to be a factor especially contributing to tumor necrosis.[48] Most studies have involved soft tissue tumors. Whether musculoskeletal primary or metastatic tumors would respond has yet to be studied. Genetic manipulation also has explored the potential benefits of extracorporeal shock waves.[6,103]

Haupt and Chvapil[74] studied the effect of shock waves on the healing of partial-thickness wounds in piglets. They found that wounds treated with 100 shock waves at 14 kV and 10 shock waves at 18 kV had similar rates

of reepithelialization as nontreated control wounds. With increased numbers of shock waves (500–1000 at 14 kV; 100 at 18 kV) healing was inhibited significantly. In contrast, low-dose treatment (10 shock waves at 14 kV) led to significant enhancement of reepithelialization. Histologically, the upper dermis in the animals that received low-dose treatment had increased numbers of dilated microvessels and increased macrophages in the perivascular spaces. They thought their observations could be applied more broadly to activation of cellular healing (fracture healing) by promoting the repair process and changing cell kinetics.

At the beginning of the 1990s, the musculoskeletal applications of extracorporeal shock waves attracted significant interest. Valchanou and Michailov[185] showed high energy could fracture rat (rabbit) bones, but that lower applied energy levels stimulated osteogenesis, and, in particular, elaboration of callus. A subsequent study confirmed the osteogenic potential of shock waves but also the possibility of stimulating an osteogenic response in fracture nonunions that could lead to healing by noninvasive nonsurgical methods.[186] Ekkernkamp and coworkers[55] were able to show dose-dependent (high versus low extracorporeal shock waves) osteoblast recruitment and osteogenesis and elaboration of bridging and solidifying callus in a fracture pseudarthrosis model (sheep) using standard fluorescent histologic methods. This subsequently led to early clinical applications for patients with delayed union and nonunion. These studies definitely showed a positive effect of extracorporeal shock waves on initiating fracture healing in patients. Many investigators also have evaluated the effect of extracorporeal shock waves on the stimulation of bone function.[4,11,40,57,58,60,61,63–67,75,89,99,100,138,158–164,178,179,181,182,184,199]

Haupt and coworkers[76] used multiple (five) treatments of 100 shocks generated by an experimental early lithotripter (XL-1). Their assessment, based on radiographic, histologic, and biochemical evaluations, showed that fracture healing was initiated. Graff et al[61] concomitantly assessed the effects of shock waves on the various tissues through which they traversed to reach a urethral or renal stone. These experiments used bone from rabbits, pigs, and dogs. Hematomas and petechial bleeding were evident; such findings are comparable with those of blunt trauma. No obvious fractures were found. However, there were no magnetic resonance imaging studies for bone bruising or selective histologic stains that would elucidate intertrabecular hemorrhage. Short-term effects were bleeding and necrosis with the effect being related to the energy imparted. Early changes were aseptic necrosis within the marrow tissue and osteocyte damage and, in some cases, death (although the latter process was not all-enveloping in the shock wave pathway). Subsequently, there was evidence of new bone formation, de novo, and against existing trabeculae. This observation was confirmed by Johannes et al[89] in a canine model.

Ikeda and coworkers[86] applied extracorporeal shock waves to canine bone. Their extracorporeal shock wave generator produced shock waves by explosion of a silver azide pellet at the first focal point, a generational method not being explored clinically in the United States. Their first group of animals were sacrificed immediately after shock wave application. The relevant findings were periosteal detachment and microfractures on the inner surface of the cortex. In a second group, the femurs were studied 2 months after extracorporeal shock wave treatment. There was marked callus formation under the displaced periosteum. They also treated six patients with delayed union or nonunion of fractures, achieving union in four. Of the two patients who did not achieve union, one patient with humeral nonunion with a 1-cm fracture gap and no internal stabilization did not achieve union, whereas the other patient had avascular necrosis of a vascularized fibular graft. In retrospect, they thought neither patient was an appropriate candidate for extracorporeal shock wave treatment.

In a previous study, Ikeda and coworkers[85] applied extracorporeal shock waves to rabbit

bone. This led to cortical fracture and saucerization of the inner surface of the opposite cortex. However, similar opposite cortex saucerization was not observed in the canine bones.[86] This may have occurred because of size differences in the overall bone and the thickness of the cortex. The extracorporeal shock waves caused gross fractures in rabbit femurs, but only microfailures in the canine femur. They also found a transient increase in creatinine kinase, probably attributable to damage to muscles in the extracorporeal shock wave path. These values returned to normal within a week.

Other investigators have found osteogenesis may be stimulated by extracorporeal shock wave treatment.[83] Saisu and coworkers[153] reported local increase in bone mineral content and overgrowth of immature rabbit bone. Kusnierczak and others[99,100] studied the effect of extracorporeal shock waves on osteocyte cell cultures. They observed that although there was a short-time effect of cell destruction, the subsequent effect, 3 to 8 days later, was cell stimulation. These studies suggest additional evaluation should be done to assess the possibility of focal bone augmentation (in the osteoporotic femoral neck or radius) or the stimulation of longitudinal bone growth in a congenitally or posttraumatically shortened long bone. Interestingly, the longitudinal growth stimulation in the study by Saisu et al[153] applied extracorporeal shock waves to the middiaphysis of the femur, rather than near the physis (that may be affected adversely by extracorporeal shock waves).

Additional osseous applications have included osteochondroses (femoral and talar osteochondritis dissecans) and early stages of osteonecrosis.[29] Currently, insufficient data are available, although preliminary results are promising.

The effects of extracorporeal shock waves on the physis must be explored in much more detail.[113,187] One study showed no overt damage to the rabbit physis.[185] However, the shock waves were not focused specifically on the physis. In another study, 44% of the animals (rats) had moderate to severe dysplastic changes in the physis.[204] Again, specific studies must be done to evaluate application of extracorporeal shock waves to large physes reasonably similar to human physes. Because the local volume of the second focal point is well controlled, the use of extracorporeal shock waves for a lesion such as a bone cyst (instead of grafting or cortisone injection) might be feasible as long as the energy was directed at least 1 to 2 cm away from the physis within the metaphysis.

Extracorporeal shock wave treatments have been applied experimentally to the distal femurs in rabbits.[188] There were no pathologic changes in the articular cartilage. In a small clinical study, extracorporeal shock waves were applied to osteochondritis dissecans lesions to accomplish healing of the lesion to the underlying bone.[29]

Given the difficulty in the removal of cemented prosthetic implants, several researchers have assessed whether the preoperative or intraoperative use of extracorporeal shock waves could disrupt the cement-bone interface to allow easier removal of the prosthesis and the cement mantle during revision surgery.[9,10,91,104,119,165,195] The results suggest extracorporeal shock waves may loosen the cement-bone and cement-prosthesis interfaces, making extraction of prosthesis and cement easier. Another prosthesis-related potential application is the loosened noncemented prosthesis. Because extracorporeal shock waves have been shown to cause new bone formation, there is a potential for its use to the bone surrounding an unstable (clinically symptomatic or painful) implant. Coombs et al[29] and Vogel et al[192] have shown elaboration of new bone and symptomatic relief in a small number of patients. Both applications, easier removal of cemented implants and encouragement of osseous ingrowth to stabilize a press-fit implant, deserve well-designed clinical studies. The stimulation of osseous ingrowth and incorporation of a noncemented prosthesis even may benefit from early extracorporeal shock wave application.

After the fracture applications the problem of calcific tendinitis was addressed, with the specific aim of disrupting the calcific intra-

tendinous deposit to encourage resorption, which was reasonably well documented as an outcome phenomenon.[32–36, 105–109] Low-energy and high-energy treatments were studied. The responsiveness of shoulder pathologic disorders gradually led to applications in other tendinopathies not usually characterized by grossly evident calcification (lateral epicondylitis, plantar fasciitis). These include medial and lateral epicondylitis, patellar tendinitis, Achilles tendinitis, and plantar fasciitis.

One of the important aspects of treating soft tissue impairments is the basic concept of etiology. The prevailing concept of disorders such as plantar fasciitis and lateral epicondylitis is that they are inflammatory disorders. The fact that many patients do not, accordingly, respond to treatment with antiinflammatory medications has led to suggestions that other pathologic processes may play a role in the patient's disorder.[80,102] Detailed evaluation in these aforementioned disorders suggests inflammation may be a concomitant, rather than the primary, aspect of the painful condition.[116]

The application of extracorporeal shock waves to the rabbit Achilles tendon causes dose-dependent changes in the tendon and paratenon.[145] The application of impulses with an energy flux density of 0.08 or 0.28 mJ/mm^2 caused only minor changes. In contrast, the application of impulses at 0.60 mJ/mm^2 (high energy) caused formation of paratendinous fluid and swelling of the tendon. Histologic assessment showed fibrinoid necrosis and infiltration of inflammatory cells. Rompe et al recommended caution in the application of high energy extracorporeal shock waves to patients with tendinopathies (Achilles, patellar).

Although the tissue effects in bone (cell death followed by osteoblast elaboration and recruitment) to reinitiate the fracture healing response, the mechanism in soft tissues has yet to be determined.[37,38] Presumably a similar microdisruption of dense, fibrotic, poorly vascularized tissue allows initial microvascular ingrowth, followed by tissue-appropriate stem cells. In bone and contiguous tissues, the focal microinjury also undoubtedly causes tissue changes and responses that concentrate autologous growth factors (platelet-derived) conducive to establishing more appropriate target tissue healing. There is a distinct paucity of (and obvious need for) animal studies, cellular studies or both of the specific tissue effects of the clinically applied shock waves (high- and low-energy intensity).

Although there is obvious enthusiasm to apply extracorporeal shock waves to various musculoskeletal conditions, there still are many unanswered questions. It is unclear as to which parameters of extracorporeal shock wave delivery may cause detrimental changes in tissues such as muscle, nerve, or even fat in the shock wave pathway. Tissue damage may correlate with one or more factors alone, or with multiple parameters in a combined effect. It is not clear which body tissues or organs are damaged acutely or chronically by shock waves, and which are most susceptible to cellular or organ injury (lung tissue is damaged unequivocally). Many acute changes have not been followed chronically to determine when and if the changes resolve, or whether they lead to subsequent chronic changes. There has been limited assessment of extracorporeal shock wave application to cell cultures to determine direct cell response acutely (often cell death) and subsequently (osteocyte proliferation). Extracorporeal shock waves may affect lysosomes and mitochondria, interfering with metabolic activity within the cell. Metabolic activity of the osteoblast (phosphate turnover, elaboration of extracellular matrix components) may be altered by extracorporeal shock waves.

Future applications in orthopaedics may rely on modification of the extracorporeal shock wave devices. Bailey and coworkers[5] found that dramatically different cavitation was produced by acoustic pulses that had different shapes but similar duration, frequency content and peak positive and negative pressure. The main effect involved cavitation, which was 50 times longer and 3 to 13 times stronger in one device versus the other. A better understanding of the differences between

orthopaedic extracorporeal shock wave devices, particularly as based on the Gilmore equation,[207,208] may help to better understand tissue effects and device response differences.

In other studies, Zhong et al[207] used the Gilmore formulation coupled with zeroth-order gas diffusion to investigate cavitation. They found that cavitation dynamics could be enhanced when a slightly different antecedent shock wave and interpulse delay were used before the primary shock wave. Kodama and coworkers[93] developed a shock wave device that can be used in an arbitrary position in the human body percutaneously. This device might have application such as introduction, by a drilled channel, into a region of ischemic necrosis within the femoral head.

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