IOWA STATE UNIVERSITY
College of Veterinary Medicine

EXTRACORPOREAL SHOCK WAVE THERAPY: What? Why? Safety?

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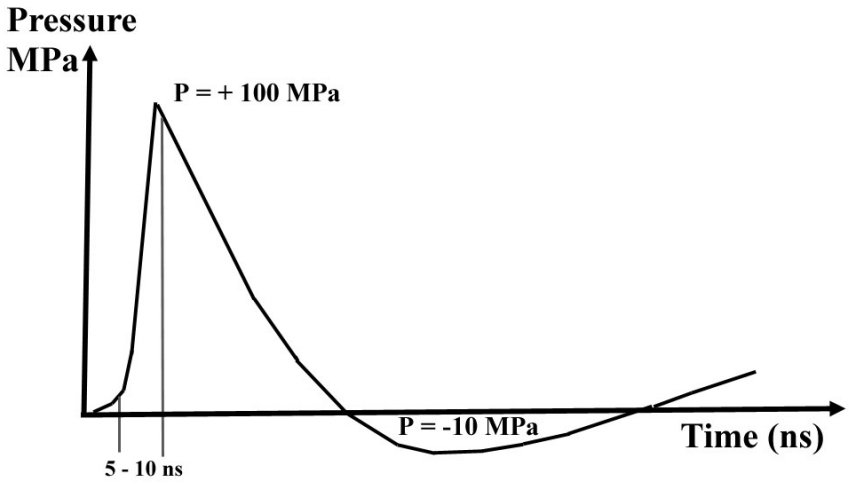
What are shock waves?

Extracorporeal shock waves are pressure waves generated outside the body that can be focused at a specific site within the body. Shock waves are characterized by high positive pressures, up to 100 MPa (over 100 times atmospheric pressure), and negative pressures of 5-10 MPa. They have a rapid rise time of 30-120 nanoseconds (10^{-9}) and a short, 5 microsecond (10^{-6}) pulse duration.[1]



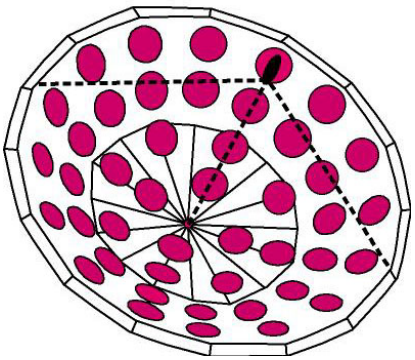
The pressure waves travel through fluid and soft tissue and their effects occur at sites where there is a change in impedance, such as the bone-soft tissue interface. The common use for shock waves is to break kidney stones into fragments that can then be passed.[2] Shock waves are deflected at the border zones of tissues with different acoustic impedances including reflection and refraction of the wave.[1] This results in release of kinetic energy at the junctions, which can cause tissue alterations. For example, a kidney stone can be cracked by a certain amount of shock wave energy, whereas in bone, the same amount of shock wave energy does not result in fragmentation. The release of kinetic energy at interfaces of different acoustic impedances is crucial in planning ESWT. Shock waves must never be focused on gas-filled cavities like lung or intestine. The acoustic impedance of air is markedly lower than the acoustic impedance of soft-tissue such as muscle. Thus, virtually all acoustic energy is reflected at the border zone. As a consequence, maximum pressure at the border zone may turn into rarefaction pressure up to twice the extent of the former pressure wave and may result in considerable tissue damage at the border zone.

Material/Tissue	Acoustic Impedance [x 10^3 Ns/m^3]
Air	429
Lung	260-460
Fat	1,380
Water	1,480
Kidney	1,630
Muscle	1,650-1,740
Bone	3,200-7,400
Kidney Stone	5,600-14,400

When the shock wave meets an interface of different impedance, pressure and shear loads develop. Additionally, cavitation, which is the development of gas bubbles as a result of the rapid interaction between pressure and shear, occurs. The collapse of the gas bubbles leads to the development of fast flows or jet streams that contribute to the effect on the tissue. In addition to these mechanical effects, there are also cellular effects. Shock waves can increase cellular permeability, stimulate cellular division and stimulate cytokine production by cells. [3,4] Recent studies have demonstrated that shock waves induce neovascularization at the tendon-bone junction, which in turn relieves pain and improves tissue regeneration and repairing. [5] Extracorporeal shock wave therapy was also found to have a positive effect on the concentration of transforming growth factor-beta 1, which has a chemotactic and mitogenic effect on osteoblastic cells. There is also some evidence that shock waves may have an effect on nitric oxide synthase systems implicated in bone healing/remodeling. [6] However, at this time, the mechanism or mechanisms that shock waves utilize to stimulate healing *in vivo* is unknown.

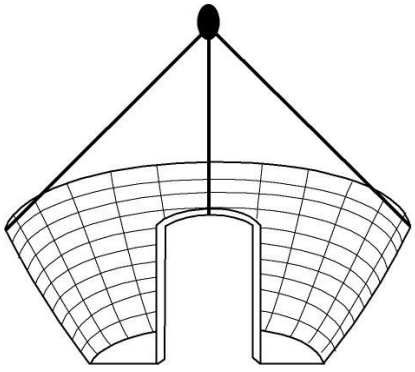
The energy level utilized is important in determining the outcome. Tendon necrosis and microfractures in laboratory rodents have been seen at high energies. In a rabbit Achilles tendon dose effect study, tendon necrosis occurred at energy densities over 0.28 mJ/mm^2.[7] Lower energy shock waves have been shown to be stimulatory effects on cell cultures and wound healing. Studies in pig skin defects found that low energy shock waves stimulate skin healing whereas high-energy shock waves slowed healing.[8] In studies involving the application of shock waves on bones, it was determined that relatively low energy levels do not stimulate bone formation whereas those that use high energy levels result in bone formation.

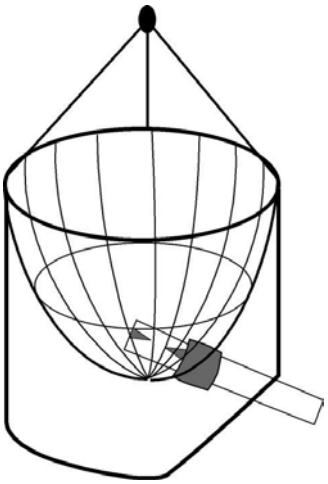
The three mechanisms to generate a focused shock wave are: 1) Piezoelectric, 2) Electromagnetic, and 3) Electrohydraulic. All of these mechanisms convert electrical energy into a pressure wave within a fluid media.



The piezoelectric system utilizes a crystalline material, that when stimulated with high voltage electricity can expand or contract to initiate a pressure wave in the surrounding fluid. The crystals are arranged so that the pressure wave is aimed towards a focal point.

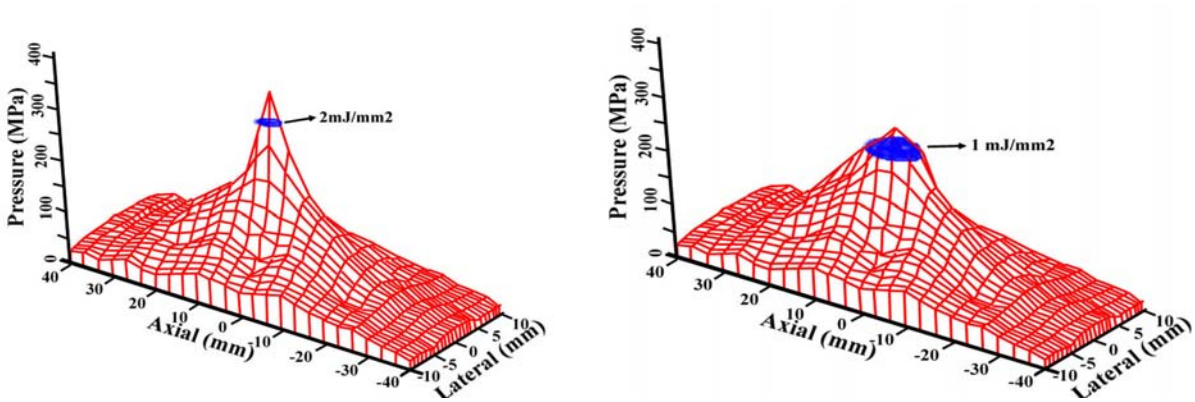
The electromagnetic mechanism has coils that create opposite magnetic fields when an electric current is applied to them causing a submerged membrane to move, starting a pressure wave within the fluid. The pressure wave is reflected by the parabolic design towards the focal point.





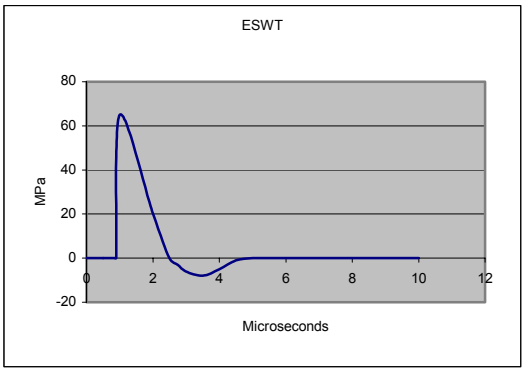
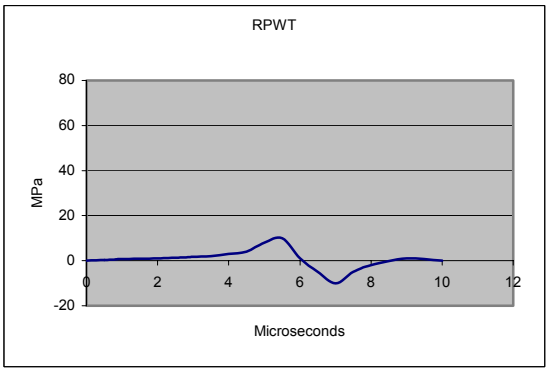
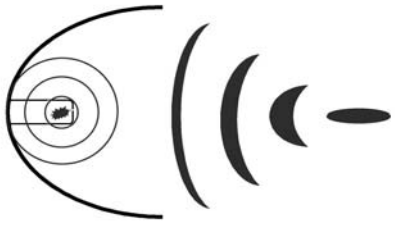
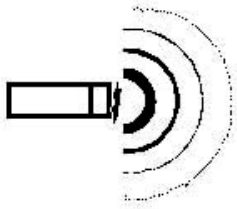
The electrohydraulic method uses a high voltage spark gap. The spark generates a plasma bubble that compresses the liquid, initiating the pressure wave. Each mechanism creates a characteristic waveform and energy density.

The energy levels for all of the focused shock wave systems are documented by International Musculoskeletal Shockwave Society and are available online at http://www.stosswellentherapie.net/fach/index.html. While it seems quite straight forward that comparisons can be made directly between systems, this may not be true. Each of the focused shock wave systems has some variation in waveform that appears to have different effects in tissue. The three different mechanisms to generate a focused shock wave also result in variations in the size of the focal point and therefore the energy density or the total energy being delivered to the desired treatment area. Also, the laboratory measurements of energy may not indicate what happens *in vivo*.



The figure on the left shows a high energy density associated with a fine focal point. On the right the same total energy is distributed to a large focal point resulting in a lower energy density.

More recently, radial pressure wave therapy (RPWT) has been developed as an alternative to ESWT. Radial pressure wave therapy utilizes a projectile mechanism to stimulate a pressure wave. The system utilizes a pneumatically operated ballistic pressure pulse generator. The kinetic energy of a projectile driven by compressed air is transmitted by an elastic concussion to the probe inside the hand-piece. During treatment the proximal end of the applicator is in contact with the patient's skin and applies a pressure pulse to the skin and the underlying tissue. Pressure waves generated by this mechanism are transmitted radially, decreasing in energy proportional to the square of the distance from the surface.

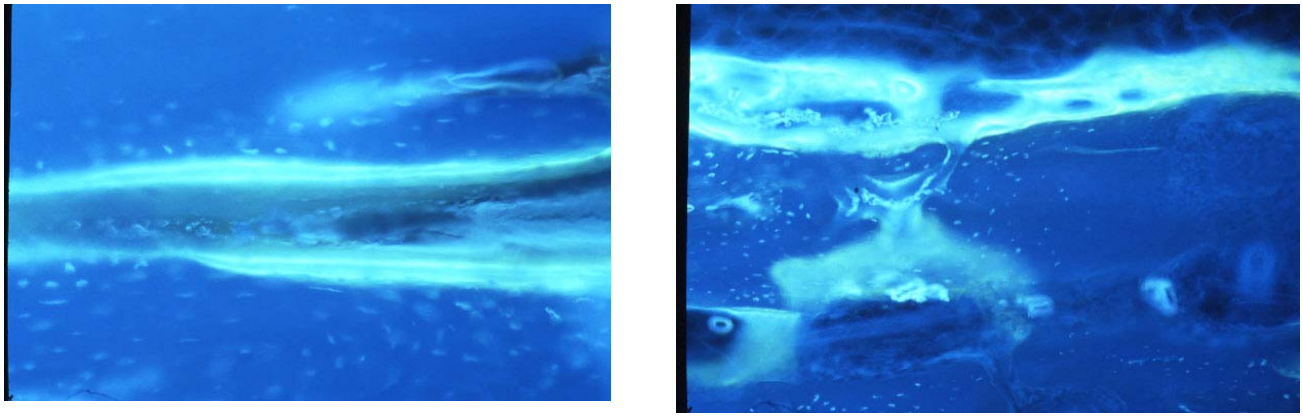
Therapy	ESWT	RPWT
Wave	Focused	Unfocussed
Maximal Energy	At focal point	On surface
Pressure	Up to 100 Bar	Up to 10 Bar
Rise time	<1 μsec	1000 μsec
Pressure of wave relative to time		
Diagram of pressure wave within tissue		

Why use shock wave therapy in the horse?

There appears to be two logical applications of shock wave therapy. First, the stimulation of bone formation or remodeling and second, treatment of insertional desmitis and tendonitis The applications in humans reflect this. Shock waves are now routinely used in Europe to treat common orthopedic conditions in humans including plantar calcaneal spurs (heel spurs) epicondylopathic humeri radialis (tennis elbow), and nonunions and are approved by the FDA for treatment of heel spurs in the United States.

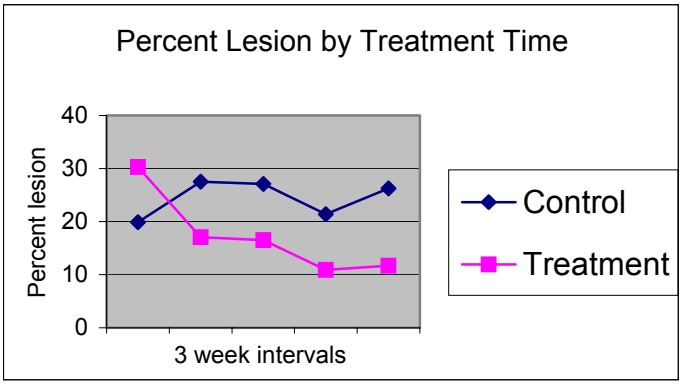
In veterinary medicine, similar applications are being tried.[9-12] Initial clinical investigations show promise in treating bone spavin, stress fractures, navicular syndrome, and high suspensory disease among other musculoskeletal diseases. At this time, solid data about efficacy is limited. Clinically, multiple investigators have noted the potential benefits of treating suspensory desmitis. Stress fractures appear to heal faster as reported by two separate users of focused shock wave systems. Beyond clinical cases, we have some initial data on the effects of focused shock waves on equine bone and soft tissue. As expected with a focused shock wave system, there was no damage to the soft tissue surrounding the focal zone when tested on the dorsal aspect of the equine metacarpus. In a study of two horses in which bone formation was measured by

fluorescent labeling of bone, there appeared to be an increase in bone formation at the treated site.[11]



The figure on the left shows a double-labeled osteon indicating that bone formation was occurring each time the tetracycline was administered. There were a greater number of the double-labeled osteons in the cannon bones treated with shock wave therapy. The bone formation was also present on the endosteal surface as seen on the right.

In a study of the effects of extracorporeal shock wave therapy for collagenase induced suspensory ligament desmitis in horses the treated ligaments healed faster than untreated ligaments. Four horses with ultrasonographically normal suspensory ligaments were utilized for the study. Lesions were induced in both forelimbs then one suspensory ligament served as a control and one was treated with the ESWT at 0.13 mJ/mm^2 3 times at 3-week intervals. The lesions were recorded ultrasonographically at 3-week intervals from induction of lesions to the completion of the project at 12 weeks. An image analysis system was used to measure the cross sectional area of the ligament and defect at 2 cm intervals. The percent cross-sectional area of ligament damage decreased faster in the treated limbs when compared to the control limbs. The groups are significantly different ($p=0.0285$). Subsequently, the treated limbs healed faster with a subjective assessment of better fiber alignment than control ligaments.



What are the safety issues with ESWT?

No matter which type of therapy, ESWT or RPWT, there have been anesthetic effects reported. In humans, the anesthetic effects have been noted, but no studies that identify the mechanism or duration have been completed. There have been hypotheses as to the mechanism issued, including destruction of nerves, nerve receptors, and central control of sensory input, but none

truly supported. Some data are available as to the direct effect of shock waves on nerves. Sciatic nerves from frogs were studied *in vitro*.[13] Shock waves were used to repetitively generate action potentials from the nerves. The conclusion was that shock waves do not directly affect nerves, but the nerves are affected through the interaction with small gas bubbles. This mechanism as shown *in vitro* may not be applicable *in vivo*, particularly in the distal equine limb. Furthermore, particularly with RPWT, the nerve would essentially be trapped between the generator and the bony structures which would appear to make it more susceptible to direct damage by the therapy. To date, there have been no investigations into this.

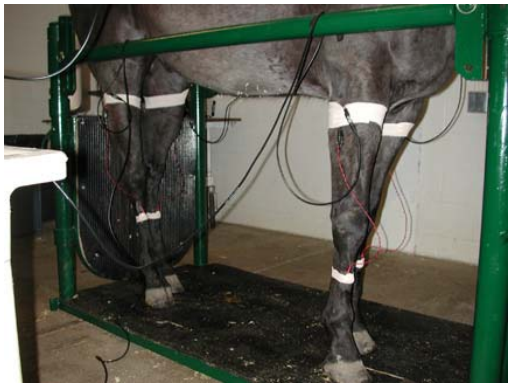
The other plausible mechanism of anesthesia is depletion of neuropeptides. Neuropeptides such as substance P (sP) and calcitonin gene-related peptide (CGRP) are contained in small diameter afferent fibers. These fibers conduct impulses that lead to the sensation of pain and can contribute to the inflammatory response.[14] Substance P and CGRP can be released from peripheral nerve endings of nociceptive primary afferents and exert pro inflammatory effects in peripheral tissues. Elimination of primary afferent fibers reduces the pain and inflammatory response.

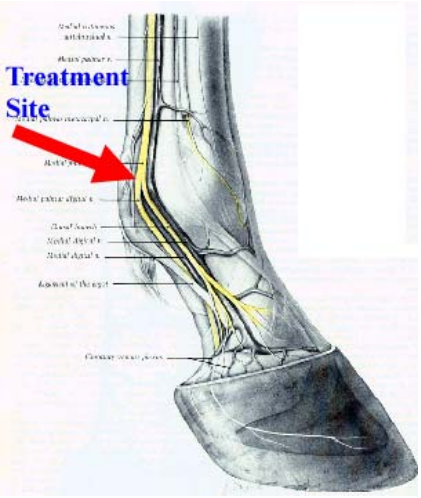
Substance P and CGRP have been identified in the periosteum and joint capsule of multiple species. The periosteum is highly vascular and well supplied with both free nerve endings and encapsulated nerve endings. Substance P and CGRP have been identified in the marrow, periosteum and cortex of long bones.[15] In horses, sP innervation was identified in areas of disease suggestive that sP is important in signaling and maintenance of pain associated with osteoarthritis.

The importance of the anesthetic effects of ESWT and RPWT are quite evident. The risk to both horse and rider when working without full comprehension of pain is significant. There are multiple questions about the anesthetic effects of shock wave therapy that need to be answered. We are currently investigating some aspects of the anesthetic effects of shock wave therapy in a project funded by the Grayson Foundation.

Effect of Shock Waves on Cutaneous Sensation

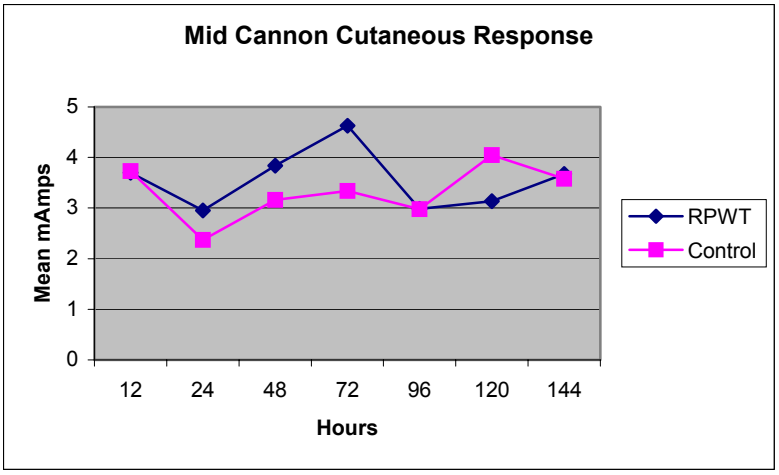
We studied the effect of shock waves on skin sensation of the horse in two ways. First, we looked at the sensation of the skin directly in the treatment area of the mid cannon bone.

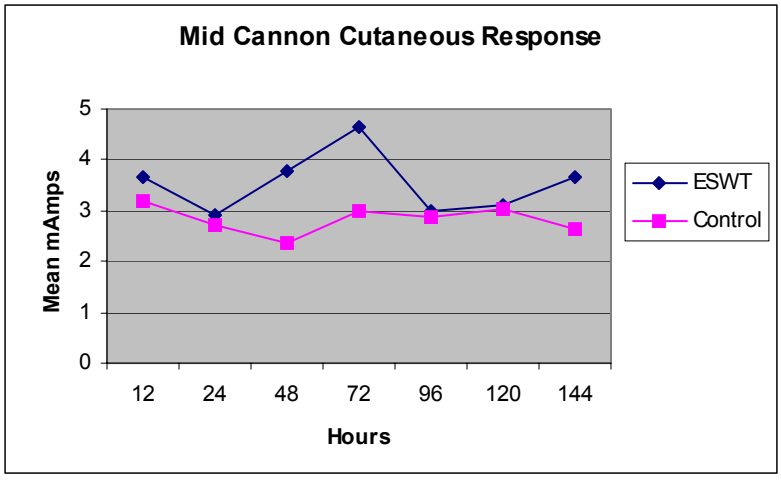




Second, we measured the skin sensation distal to the treatment site that included the palmar digital nerve. This allowed us to study the effect on skin sensation, directly and indirectly by treating the nerve that innerved the skin distal to the treatment site.

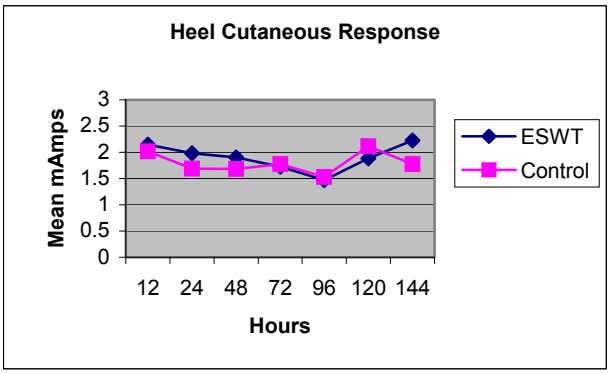
The horses had small electrodes taped to the skin surface and a constant current stimulator was used to pass a small wave of electrical current through the electrodes. The milliamperes were gradually increased until the horse first noticed and responded to the stimulation. Therefore, if there is an analgesic effect associated with the treatment, the stimulation prior to response will be greater.

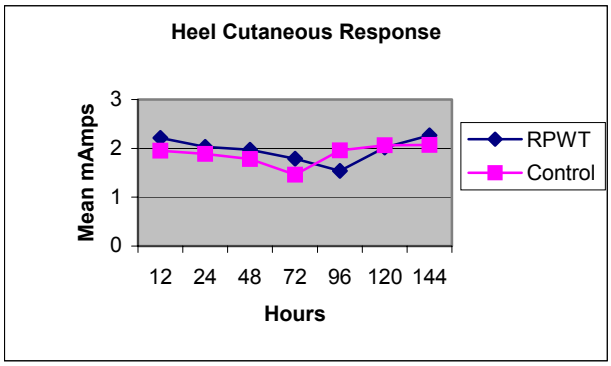




All of the horses were measured for three days prior to treatment to establish a baseline. The horses were then treated and measured daily for another seven days. In the horses that were treated on the cannon bone there was a difference from baseline for both ESWT and RPWT for the first four days following treatment, indicating there was some cutaneous anesthesia for the first four days after treatment. These graphs illustrate the milliamperes required for the horse to respond. For both treatments, it took higher amperage to illicit a response when compared to the control sites.

When the nerve that innervates the heel was treated, there was not a notable analgesic effect. The response for the control limbs mirrored the response for the treated limbs, as shown in these two charts.

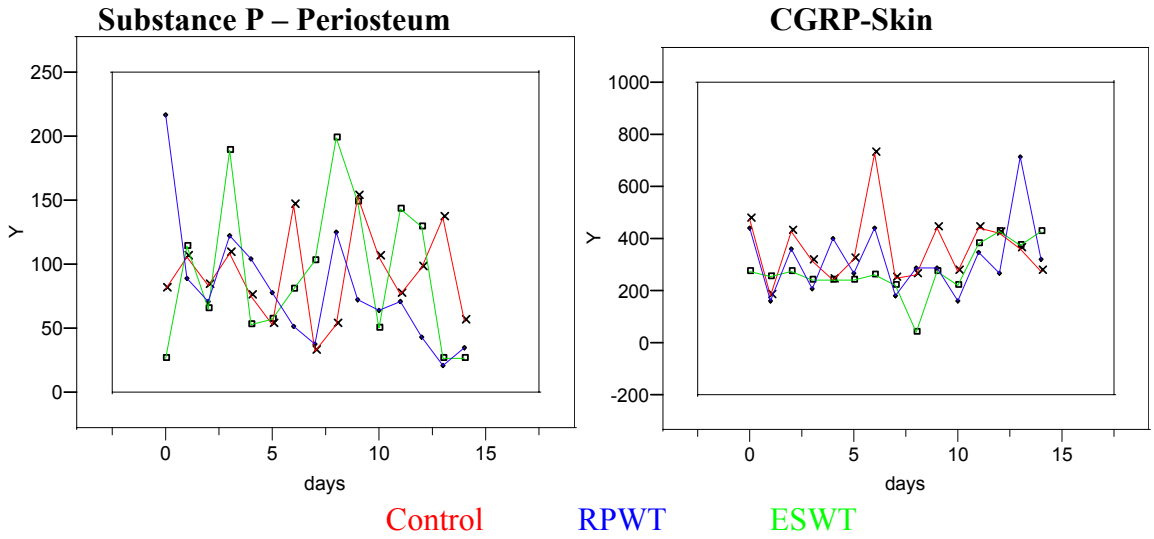




Effect of Shock Waves on Nerves and Neurotransmitters

To study nerves and neurotransmitter substances following shock wave therapy we needed to collect tissue after treatment so we utilized a sheep model. For this study we treated the legs of 30 sheep over the mid cannon bone area. This allowed us to have a treatment site from which we could collect nerve, skin, and periosteum. We collected specimens from 2 sheep immediately post treatment and at daily intervals for 14 days. The skin and periosteum were evaluated for concentrations of substance P and CGRP. The nerves were fixed and evaluated histologically for any changes associated with the treatment.

A 2-way analysis of variance which looked for both the treatment and time effects for substance P and CGRP for the skin and periosteum was completed. There were no significant differences found. One of the limitations is that we saw substantial within group variation. These two charts are representative of the data.

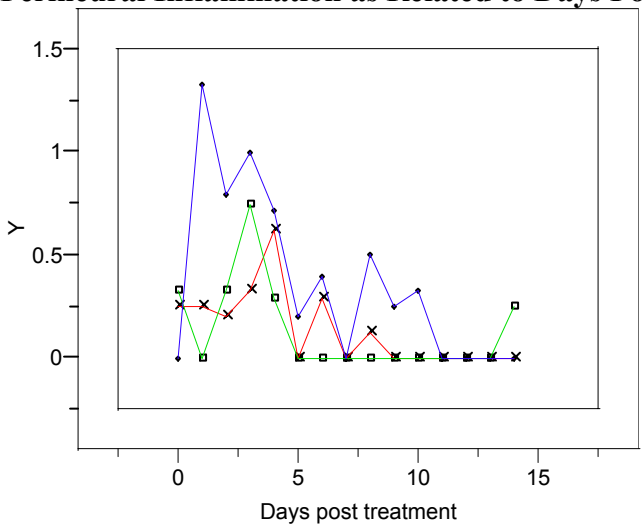


Out of the entire project, this part of the study could have been improved. A biopsy of skin that included a small nerve fiber would have higher concentrations of Sub P and CGRP than one without. We may have induced too much variability by utilizing this technique that resulted in the substantial within group variation. An alternative technique of using immunofluorescence histologic evaluation may have decreased this variation.

The histologic evaluation of the nerves provided more information. For each nerve multiple histologic factors were evaluated. The categories that had significant findings were perineural inflammation which was scored from (0-3) and the presence or absence of axonal swelling and fat saponification.

The effect of time post treatment was significant for perineural inflammation ($p<0.001$) and axonal swelling ($p = 0.04$). Nerve inflammation could contribute to the analgesic effect noted in the previous study. This chart shows that the inflammation was present for the similar time frame, approximately 4 days, as the response noted with the electrical stimulation response.

Perineural Inflammation as Related to Days Post Treatment

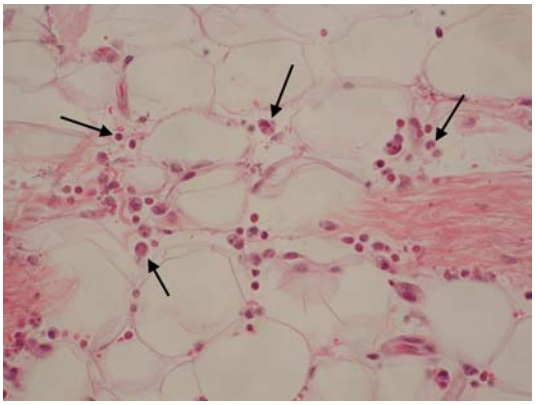


Treatment = Control RPWT ESWT

Perineural Inflammation and Fat Saponification as Related to Treatment

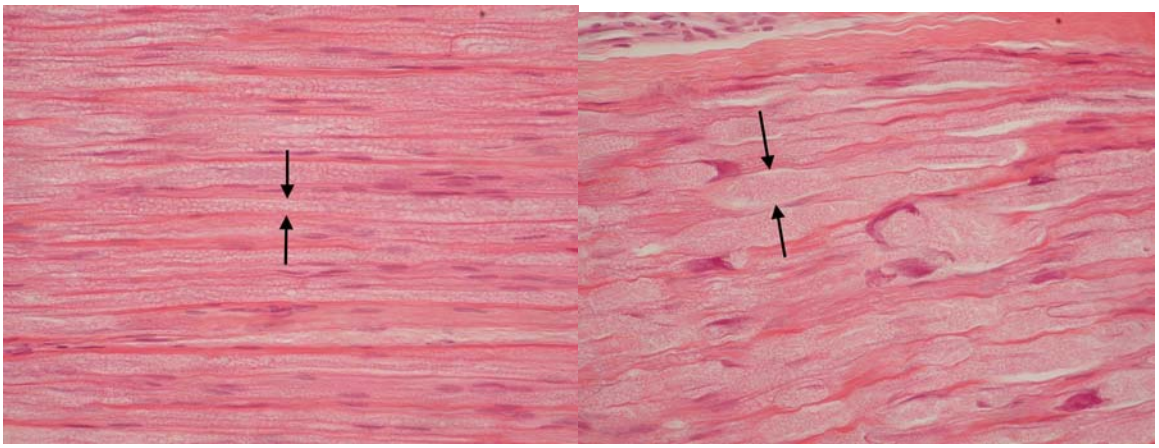
	ESWT-RPWT	Control-RPWT	Control-ESWT
Perineural Inflammation	0.0035	0.0034	0.0278
	ESWT-RPWT	Control-RPWT	Control-ESWT
Fat Saponification	0.0091	<.0001	0.076

For each comparison between treatments the p value is shown in the box, with those <0.05 highlighted. For each comparison, the larger of the two is in red. The RPWT created more changes in the nerve than did the ESWT. Interestingly, the control nerve had more perineural inflammation than the ESWT treated nerve.



This is a high power view of a nerve in cross section (left) showing an influx of inflammatory cells. Normal nerve tissue has very few inflammatory cells. Some of the abnormal cells are marked with arrows.

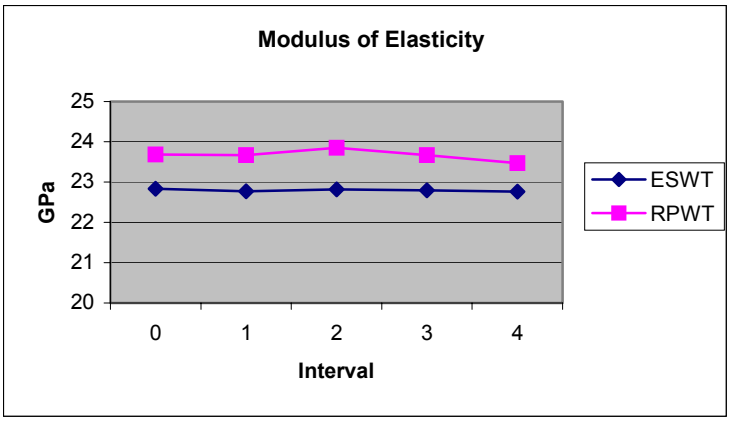
Below on the right a longitudinal section of nerve with swollen axons is compared to a normal nerve on the left. The swollen axons are wider as shown by the arrows.



Another issue that has not been addressed, but is important in the risks associated with these therapies is the effect on the bone. There are anecdotal reports of horses that have fractured bones following shock wave therapy, but the cause of the fracture is unknown. There have been no studies that address effect of ESWT or RPWT on the mechanical properties of the bone. Any effect on the material properties of the bone leaves the bone at risk of failure when the horse is working at high speeds. Early studies on the effects of ESWT on bones induced microfractures and gross cortical fractures dependent upon the energy levels and number of pulses used. Subsequently, microfracturing of the bone and the resultant repair was thought to be the mechanism that resulted in increased bone remodeling. In our preliminary investigation with ESWT on a limited number of horses, no microfactures were seen with 1000 pulses. However, this study did not include RPWT and was stopped after 1000 pulses. There are no published studies of the effect of RPWT on bone. Further evaluation of the effect of ESWT and RPWT on the material properties of bone is indicated.

Effect of Shock Waves on Material Properties of Bone

To evaluate the effect of shock waves on cortical bone, 1 cm square by 3 cm long cubes of bone were cut from the dorsal cortex of the cannon bone. The density of the bone was measured and then they were placed in a saline bath and 2.5 MHz ultrasound waves were passed through them to measure the speed of ultrasound through the bone. The ultrasound speed is greatly affected by small changes in the material properties such as microfractures. The modulus of elasticity (E) of the bone was calculated as: [E= $velocity^2 \times$ density]. The bones were then treated with either RPWT or ESWT for 500 pulses, measured again, and repeated until 2000 pulses had been administered. After this the bones were evaluated histologically. We found no difference in E associated with the shock wave treatment. Furthermore, histology showed that there were no new microfractures in the bone associated with the treatment. This information, coupled with similar findings from another study looking for microfractures in the equine metacarpus, would indicate that ESWT and RPWT do not affect the material properties of bone.



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