Hyperthermia and Shock Waves: New Methods in the Treatment of Sports Injuries

19

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Definition of Hyperthermia

Hyperthermia is the therapeutic technique which raises a pre-established part of the body to a temperature range between 41.5°C and 45°C, and maintains it at this range, for a given period of time.

Introduction and Historical Background of Diathermy

The primary rationale for the employment of therapeutic heat in physical medicine is the inducement of blood flow (BF) increase, which is anticipated to occur with the increase of temperature in the treated region.

This rationale is so because the mechanism for healing is thought to be highly dependent upon the transport of blood-nurturing substances and removal of toxic waste products [1]. The secondary rationale is the increase of the metabolic rate of a specific tissue volume, assuming that this behavior is comparable to the increase of the overall body metabolic rate on the basis of a 13% increase per degree above the normal temperature [2].

Shortwave (27.33 MHz) and microwave (2450 MHz) diathermy, together with ultrasound therapy, have been used over the decades as major heat methods for stimulating various beneficial physiological responses, and for the relief of a variety of pathological conditions.

Despite the widespread use of these methods in routine clinical practice, it appears that the major problem has been the lack of a correct scientific approach in the design and use of diathermy apparatus for optimal results.

Interest in the interaction of electromagnetic (EM) energy with biological tissues dates back to the first man-made EM sources. A. D'Arsonval, a French physiologist, found in 1892 that currents of frequency 10 KHz or greater would produce an increase of temperature without painful muscular contractions [3].

The word 'diathermy' was introduced by Nagelschmidt in 1907 to describe the relatively uniform heating produced in the tissue by the conversion of high frequency currents into heat [3]. Between 1900 and 1935 in fact, physicians were using high frequency currents of between 0.5–3 MHz and 10 MHz (long-wave diathermy: 118 cm in muscle tissue at 10 MHz) for the above purposes.

In 1928, EM radiation as high as 100 MHz (short wave diathermy: 27 cm in muscle tissue at 100 MHz) was being produced by Esau, and used clinically by Schliephake [3]. Holmann in 1939 discussed the possible application of radio-waves of 25 cm wavelength for therapeutics, and predicted that these waves could be focused to produce heating of the deep tissues without excessive heating of the skin [3, 4].

The first therapeutic application of microwaves was at the Mayo Clinic (USA) in 1946 by Krusen and Leden, and involved the exposure of test animals to 65 W of 3000 MHz radiation (microwave diathermy: 1.45 cm at 3000 MHz). Despite the fact that the average temperature rise was greater in the skin and subcutaneous fat than in the deep muscle tissue, this work launched the use of microwave diathermy for application to physical medicine [5, 6]. It must be remembered, however, that these conclusions were based on the use of microwaves in dogs, which have thinner layers of subcutaneous fat and muscle than humans.

As a result of this study and the research done at MIT (Massachusetts Institute of Technology) in 1947, the FCC (Federal Communications Commission) assigned the frequency of 2450 MHz to physical medicine based on its alleged superiority in therapeutic value.

In 1950, Schwan demonstrated that 2450 MHz was not a good choice of frequency for the following reasons [7]:

1. Excessive heating in the subcutaneous fat
2. Poor penetration of energy into the muscle tissue due to small skin depth
3. Poor control of energy absorption due to large variation in the electrical thickness of subcutaneous tissues

Schwan recommended a frequency of 900 MHz or less. Lehmann and Guy, between 1960 and 1980, verified experimentally that 900 MHz or lower frequencies could produce better heating patterns than obtained with 2450 MHz or with other natural and technological heating modalities [8, 9].

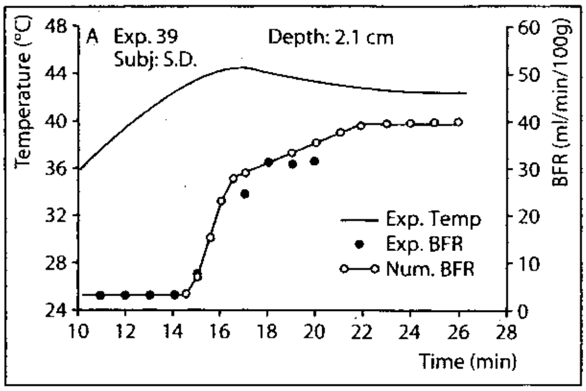

Fig. 2. Transient temperature and experimental and numerical blood flow rate (*BFR*) response at site of xenon injection depot. (From [28])

It is curious to note that there is no significant improvement in BFR in the range of temperature from 37°C (average normal temperature) to 41°C and only hyperthermic temperatures above 41°C are effective in producing significant hyperemia in the tissue targets.

Physics and Heating Technology Comparison

In 1972, Johnson and Guy published data regarding the main factors determining the energy absorption in human tissues [10]. Dielectric properties of the tissues, size, geometry, and depth, together with amplitude, frequency, duration, polarization, size, and shape of applicators, as well as space and coupling between the applicators and the tissue, are mandatory elements for transferring electromagnetic energy at depth to produce a proper heating effect.

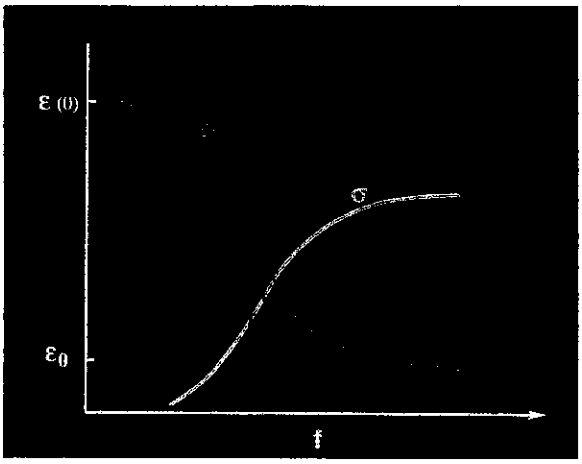

Fig. 3. Dielectric properties vary as a function of frequency. ε_1, dielectric constant; σ, conductivity; ε_2, dissipation factor. (From [31])

It must be stressed that the heating effect is mainly due to the attenuation of transferred energy in tissue. Energy attenuation is a complex phenomenon due to the interaction of dielectric tissue properties (dielectric constant, conductivity, dissipation factor, permittivity), which vary as a function of the frequency [31], (Fig. 3).

As the frequency of the energy transferred in the tissue increases, the dielectric constant of the tissue decreases and the conductivity increases. So the higher the frequency is, the higher is the attenuation of the energy transferred in the tissue and consequently the lower is the penetration depth. The penetration depth is the depth at which the electromagnetic field is reduced to 37% and the power to 14%. Tables 1 and 2 clarify the ratio between Frequency (FQZ) and tissues with high and low water content.

The heating pattern in tissue is synonymous with the specific absorption rate (SAR) pattern. The SAR, mandatory for the evaluation of the heating efficiency of all hyperthermia applications, is physically defined as "the time derivative of the incremental energy absorbed by an incremental mass contained in a volume element of a given density" (NCRP 1981: National Council on Radiation Protection and Measurements).

The applicator efficiency can be quantified by measuring the SAR in the sagittal and coronal planes or on a given surface parallel to the applicator plate (effective fields size: EFS) and at depth perpendicularly to the applicator plate. The result of each of the three measurements gives a graphic design representing an isotherm showing the energy transferred from applicator into the tissue.

These studies are generally performed on phantoms having the same dielectric properties as human tissues [32].

It is strongly recommended to avoid FQZ and applicators since, due to difficult coupling and poor homo-

Table 1. Muscle, skin and tissues with high water content

Frequency	Dielectric constant	Conductivity [s/m]	Penetration depth [cm]
27.16 MHz	113	0.612	14.3
433 MHz	53	1.43	3.57
915 MHz	51	1.60	3.04
2450 MHz	47	2.21	1.70
10000 MHz	39.9	10.3	0.343

Table 2. Fat, bone and tissues with low water content

Frequency	Dielectric constant	Conductivity [ms/m]	Penetration depth [cm]
27.16 MHz	20	10.9–43.2	159
433 MHz	5.6	37.9–118	26.2
915 MHz	5.6	55.6–147	17.7
2450 MHz	5.5	96.4–213	11.1
10000 MHz	4.5	324–549	3.39

geneity of absorbed energy, hot spots are produced. Hot spots are in fact points at which the energy deposition is much higher than that absorbed in the irradiated volume, which raises temperature over 48/50°C.

One has to remember that temperature distribution is also a function of thermal diffusion, blood circulation and time. Since the heating/SAR pattern may vary considerably over a three-dimensional volume, due to the geometrical shape, and tissue composition of the body section to be irradiated, strong attention may be paid to the average size, depth, and tissue type of the targets usually treated in rehabilitation.

With the exception of the hip joints, average depth in physical medicine goes from 1 to 5 cm, average size goes from a few cubic centimeters to 200–300 cm^3 and tissues to be heated are mainly muscles and tendons with respectively high and low blood perfusion.

Since 1966, a group of researchers, led by Lehmann and Guy, investigated the heating patterns of each technology or method used to increase the temperature in physical medicine during clinical practice [33].

In January 1974, a masterpiece of the contemporary *Therapeutic Application of Electromagnetic Power, published in the Proceedings of the IEEE Transaction,* made a comparison between different heating modali*ties like hot packs, infrared lamp, short-wave diather*my (27.13 MHz), microwave diathermy (2450 MHz), and microwave diathermy (915 MHz with surface cooling: hyperthermia prototype). Each heating pattern of the above modalities has been investigated, measuring the muscle temperatures every 1 cm (approximately) from the skin to 4–5 cm at depth in a thigh [26]. The results confirmed that:

1. Hot packs (conductive heating) increases the temperature only at the skin level and not at the therapeutic value.
2. Infrared increases the temperature to a therapeutic value only at the skin level.
3. Short wave diathermy (27.13 MHz) with an inductive applicator, increases the temperature to the therapeutic value only in the first 1.6 cm, without overheating the skin tissue.
4. Microwave diathermy (2450 MHz) reached the therapeutic value at 1.85 cm with the skin temperature above 45°C.
5. Microwave diathermy (915 MHz with surface cooling: hyperthermia prototype) reached the therapeutic temperature level (42–45°C) from 1 to 4 cm deep, keeping the skin temperature under 36°C.

On the other hand, ultrasound (US) technology for physical therapy does not permit ideal HT treatments, and consequently an ideal increase of blood flow rate, due to the physical behavior of sound waves on human tissue, the presence of hot spots, discomfort [34–36], and low power energy usable in commercial equipment.

The Ideal System for Proper Heating Patterns on Human Tissues

The choice of the ideal heating system depends on the medical requirements as regard to the therapeutic effects produced by hyperthermia. Physical medicine requirements dictated from physiology and physics applied to human tissues to produce effective hyperthermia treatments are subjected to the average three-dimensional target volumes, the average depth and the average tissue damage of the lesions.

For this reason, a modern hyperthermia system for thermotherapy in orthopedics, sports medicine, and rheumatology needs the following characteristics:

1. The correct frequency to reach at least 3–4 cm in depth
2. 50% SAR depth around 2–2,5 cm
3. 50% SAR at the surface around 50 cm^2
4. An efficient cooling system to keep the superficial tissue (skin, fatty tissue) under 42°C
5. A multipoint thermometry system to control the temperature
6. A computerized system to control and memorize the treatment

Actually, the medical equipment market offers devices with such requirements. Currently used in oncology for the treatment of superficial cancer [37–40], these hyperthermia systems have been developed to increase and maintain the temperature of a target volume of up to 300–400 cm^3 from 41.5 to 45°C at a depth of 1–5 cm.

Figure 4 shows hyperthermia equipment built according to the 43/92 EEC (European Economic Community) rules, supplied with a microwave power generator at 434 MHz, an applicator at 434 MHz with a water bolus, a temperature-controlled system for invasive and non-invasive temperature measurement and specific software to control and memorized the temperature reached in the treated target.

The heating of three target volumes placed at three different depths, calls for a progressive increase of power (Watts) followed, within certain limits, by a lowering of the water temperature (WT), necessary to lower the temperatures of the surface tissues.

If the target is very superficial (< 10 mm), the water bolus will be maintained at a temperature close to the target temperature, to facilitate the heating patterns produced at depth by the electromagnetic energy.

Temperature sensors placed at the surface or, if

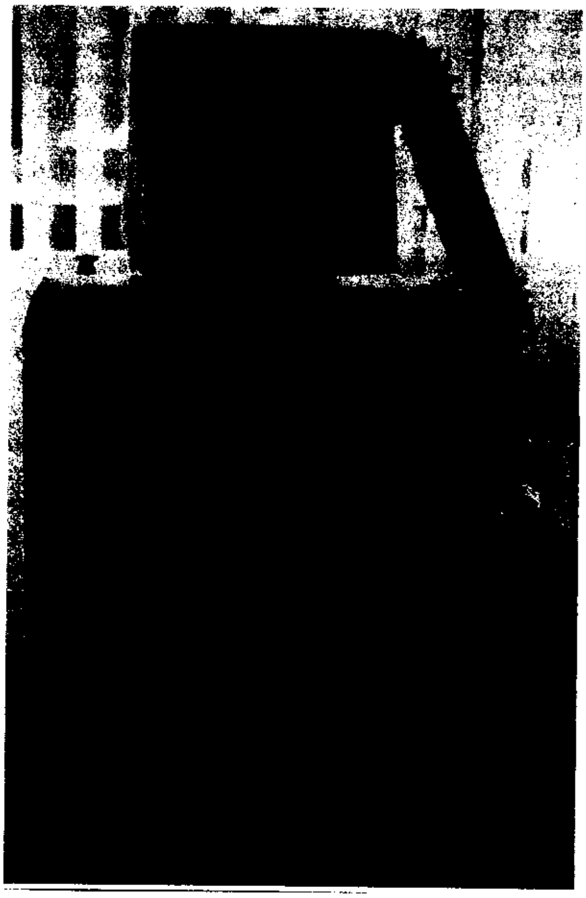

Fig. 4. Hyperthermia equipment supplied with a microwave power generator at 434 MHz (Alba System)

needed, at depth, measure the temperature reached in the target and give feedback to the computerized system to optimize each hyperthermia treatment.

Regarding the safety and quality requirements dictated by government, it is important to note that some ISM (industrial scientific medical) frequencies are different in the EU (European Union) compared with the USA. The frequency of 434 MHz is allowed in the EU and is forbidden in the USA, while 915 MHz is allowed in the USA and is forbidden in the EU.

Therapeutic Applications of Hyperthermia

Hyperthermia equipment is used to treat both acute and chronic conditions, to facilitate healing and for the relief of pain. The rationale of hyperthermia as a therapeutic method in physical medicine has been supported by Lehmann (1970–1983) and Weinberger (1989–1992) with studies made on animals and humans. The use of hyperthermia in musculo-skeletal pathologies produces one or more of the following effects:

1. Increase of tendon extensibility
2. Reduction of pain and relief of muscle spasm
3. Increase of blood flow
4. Hematoma relief
5. Decrease of muscular and articular stiffness

A few experimental studies have shed some light on the clinical efficacy of microwave diathermy.

In an experimental study, Lehmann investigated the methods of elongating collagenous tissue to produce maximum length increase under therapeutic conditions [22]. He demonstrated that the exclusive use of heat or stretch does not produce elongation of the rat tail tendon, whereas combining the application of a sustained load and temperature of 45°C, produces significant residual length in the tendon.

In clinical practice, therefore, it seems reasonable to treat contractures using heat at therapeutic temperatures, (from 41°C to 45°C) while applying sustained stretch, and to maintain this stretch well after the heating period, in order to retain the achieved elongation. It is common practice to use heat to treat joints which have been damaged by trauma or disease.

In the last decade, a growing body of clinical evidence suggested that a local deep microwave hyperthermia (LDMWH) may be of therapeutic value in treating patients with different rheumatic conditions, because it has the advantage of heating the target organ (e.g., synovium), inhibiting several enzymatic systems (e.g., collagenase, cyclo-oxygenase, etc.), while sparing the surrounding tissues [41, 42].

In particular, the beneficial effects of LDMWH were demonstrated by Weinberger et al. [43] on seven rheumatoid arthritis patients with knee effusion who were treated with a 915 MHz device for 1 h twice a week for 2 weeks, reaching an intra-articular temperature of 41.3°C. Walking time for 50 feet, knee circumference, pain score index, together with synovial fluid samples were determined before and after each treatment.

The results demonstrated an improvement in the walking time ($P=0.04$) and a significant decrease in pain ($P=0.01$) at the end of treatment.

The exact mechanism of the hyperthermia effect in inflammatory joint diseases is not completely understood. It was suggested that an increase in tissue temperature up to 42°C might cause an intracellular metabolic arrest with an inhibition of DNA and protein synthesis, accompanied by an enhanced permeability of the cell membrane. A decrease in hyaluronate synthesis at 42°C has also been demonstrated in synovial fluid [43].

The efficacy and safety of LDMWH was further confirmed in a study on normal and Zymosan-induced arthritis in rabbits [44]. It was demonstrated that a repeated therapeutic dose of hyperthermia at 42.5°C for 1 h is well tolerated by the periarticular mesenchymal tissues and that after 1 month, no damage could be observed in normal rabbit knees, whereas in the arthritic joints it brought about a reduction in the degree of granulomatous reaction, decreasing the inflammatory process.

Muscle injuries quite often involve the development of intramuscular hematomas and these are a common occurrence in the athletic population [45]. So, during the resolution phase, the purpose of the physical therapy is to accelerate the healing process and the absorption rate of the hematoma. Even if heat application has been advocated by several authors to accelerate this resolution, no experimental data were available until 1983, when a study showed that selective heating of the muscle could increase the rate of intramuscular hematoma absorption [46].

Lehmann [46], first quantified the resolution rate of hematomas produced in the musculature of experimental animals comparable in size to humans; hematomas in the biceps femoris muscle were created in pigs by bilateral injections of blood, labeled with CR^{51}. One side was treated with microwave diathermy at 915 MHz and the other side was used as a control.

The results demonstrated that tissue temperature achieved at the treated hematoma site was in the therapeutic range between 42°C and 45°C, the optimal temperature to elicit a maximal local vascular response [1, 46]. A decay curve for the radioisotope, showed that the time to the half-life value was significantly shorter for the treated side. This study supports the use of heat as an adjunct to other therapies aimed at resolution of muscular hematomas.

In a recent clinical study, the efficacy of hyperthermia at 434 MHz in the early treatment of muscle injuries in a group of 62 patients was evaluated and compared with conventional diathermy like ultrasound [47], (Fig. 5). All the patients underwent pain measurement with a VAS scale and ultrasonography before, at the end, and after 1 month.

The results demonstrated how the percentage of improvement was greater in the group treated with hyperthermia together with a faster resolution of the hematoma after 2 weeks of treatment, as compared with the ultrasound group. There were neither complications nor reoccurrences at the follow-up in the hyperthermia group while two reoccurrences and one calcification occurred in a case of pectoralis major injury in the ultrasound group.

This investigation confirms that hyperthermia at 434 MHz is a highly innovative, safe, and reliable method in the treatment of acute sport muscle injuries. The use of local hyperthermia (LH) has also been recently advocated in the treatment of neuropathies. Compression of the median nerve in a fibro-osseus canal on the palmar surface of the wrist is one of the most frequently described tunnel syndromes.

A recent study evaluated the efficacy of hyperthermia as a treatment in 32 patients affected by primary carpal tunnel syndrome (CTS), comparing the clinical results with instrumental examinations such as electroneurography (ENG), ultrasonography (US), and teletermography (TTG) [48].

The results demonstrated an improvement in the clinical score in 90% of the patients treated, and in ENG ($P < 0.05$), especially in the conduction velocity of the sensory median nerve in the third and the fourth fingers. The treatment was equally highly effective in the group that received only five applications instead of ten.

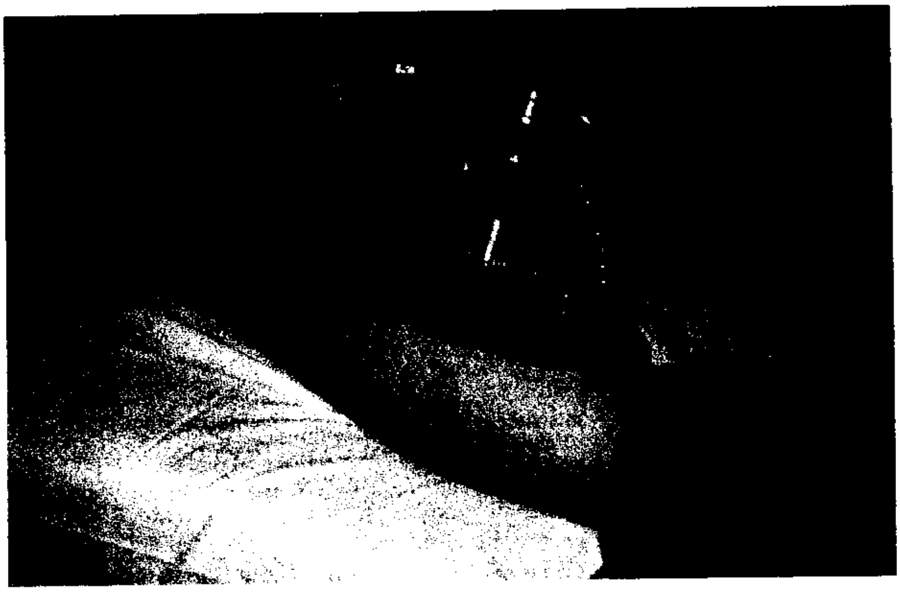

Fig. 5. Hyperthermia application in a case of medial gastrocnemius muscle injury

The indication for LH in the management of carpal tunnel syndrome could be questioned, since there is no controlled study comparing LH with the other widely accepted methods of treatment (e.g., local infiltration with corticosteroids or hand surgery). However, LH is not an invasive procedure and these primary results support its use in the early stages of CTS, in particular whenever standard treatments are contraindicated.

The use of heat methods in the treatment of tendon injuries has long been an accepted part of treatment protocols [49]. A wide variety of methods, including ultrasound and lasers are still employed to treat tendinopathies. Such methods are claimed to decrease inflammation and promote healing, but there is only limited evidence as yet to support many of these claims [50].

Treatment of any organic medical condition is ideally based on an understanding of the pathophysiology. Unfortunately, chronic overuse tendon conditions in athletes have been treated as inflammatory conditions when the histopathology clearly reveals, in most of the cases, degenerative tendinosis. Of course, many etiological factors may lead to degeneration, thereby reducing the tensile strength of the tendon.

There is evidence suggesting that decreased arterial blood flow, with resulting local hypoxia and impaired metabolic activity and nutrition, may be the key factors [51, 52], together with a failed cell matrix adaptation to excessive changes in load [53].

A study recently reported on the effectiveness of hyperthermia at 434 MHz in the treatment of 67 athletes affected by chronic painful tendinopathies, compared with an ultrasound-treated group [54]. Both groups were clinically (VAS scale) and instrumentally (ultrasonography) evaluated before, at the end and after 1 month.

The hyperthermia group showed a significant reduction of pain ($P < 0.001$) with a percentage of improvement of 68% as compared with the ultrasound group. The overall outcome, based on the resolution of pain and return to sports activity, demonstrated excellent and good results in 87% of the hyperthermia group compared with 43% of the ultrasound group. The early results of this study are encouraging, supporting the use of hyperthermia in the treatment of chronic tendinopathies.

Unfortunately, in this study the ultrasonography imaging was unable to demonstrate significant changes in tendon structure, due to its technical and diagnostic limitation and because of the short follow-up, despite the fact that many authors have suggested that in chronic tendinopathies the healing process is best indicated by relief of pain and abnormal imaging was absolutely compatible with excellent clinical results [55]. If microwaves at 434 MHz are to continue to be used as a therapeutic method, it is clearly essential that their efficacy must be evaluated with further well-designed controlled studies, in a variety of clinical conditions, as well as with long-term follow-ups.

Conclusions and Future Directions

It is particularly curious, that experimental and clinical work on the use of electromagnetic power to produce therapeutic temperatures (range 41–45°C), demonstrated by some authors more than 25 years ago, have not had, until today, a large following from the physical medicine world community.

In most countries, including the USA, heat therapy is still performed utilizing devices such as ultrasound, short wave or microwaves and lasers of different powers, although the physical characteristics of such systems have been proved to be inefficient to reach the necessary therapeutic heating levels in the range of depth of the damaged tissues.

Recently, in a few EU countries such as Italy, Spain, and the UK, hyperthermia equipment, operating at a frequency of 434 MHz and developed according to the requirements described by Lehmann and Guy in the 1980s, and by the EECin the 1990s, have been employed for clinical use in sport traumatology, rheumatology, and sport medicine.

After 2 years of clinical work and analysis of almost 30 years of worldwide scientific literature on the use of heat in physical medicine, it is our opinion that this hyperthermia equipment will permit a better comprehension of the biological mechanisms which regulate the relationship between the thermal dose and the healing process of soft tissues with low or high water content or with low or high blood flow perfusion.

The knowledge of the in situ real time blood perfusion rate increase during a hyperthermia treatment, together with the in situ tissue sample biopsies performed at the end of a hyperthermia treatment session or cycle will be of paramount importance to better define the biological cell response to a heat 'dose'.

Up-to-date advanced scientific work on hyperthermia in cancer therapy is now suggesting a fascinating association between hyperthermia and anti-inflammatory drugs to potentiate each other's therapeutic effects, thanks to the increased (several fold) cell uptake of drugs which happens at high temperatures compared with normal temperature [56].

Extracorporeal Shock Waves in Orthopaedics

In 1980, the first patient with renal calculi was successfully treated with minimally invasive extracorporeal shock wave lithotripsy (ESWL). Since then the medical field of application of this form of energy has been extended. The most recent result of the medical and technical development of application is extracorporeal shock wave therapy (ESWT) for the treatment of orthopaedic pathologies.

At the beginning of the 1990s the first reports were published on the use of ESWT beyond nephrolithiasis and colelithiasis. The sonic sources and systems employed in ESWL and ESWT are very similar, which is no wonder, as the first ESWT trials were undertaken with conventional kidney and gallbladder lithotriptors.

Valchanov and Michailov [57] and Sukul et al. [58] inaugurated ESWT for the treatment of delayed and non-union of fractures, describing local decortication and fragmentation with stimulation of osteogenesis. These positive aspects were corroborated by Haist et al. [59], who noticed bony consolidation in 32 out of 40 cases with a pseudoarthrosis. In case reports, Dahmen et al. [60] and Loew and Jurgowski [61] achieved good results in calcifying tendinitis of the shoulder.

The indications for ESWT are progressively moving to cover a large part of the rest of the tendinous pathologies, especially at the insertional areas, and their limits of application, on the bone side of the orthopaedic diseases, have already reached the field of osteochondritis and osteonecrosis of the hip and the knee as a new promising technique of treatment.

Definition

A shock wave is scientifically defined as an acoustic or sonic wave, at the wave front of which the pressure above atmospheric rises from ambient pressure to maximum pressure (amplitude) within a few nanoseconds (10^{-9}). Current therapeutically used pressure amplitudes, range between 10 MPa and more than 100 MPa [62] (1 MPa = 10 bar, approximately tenfold atmospheric pressure). As a shock wave propagates at a specific speed – as do all sonic waves – determined by the medium in which it propagates and the intensity of the shock wave itself, one can calculate the shock front thickness. This is the spatial dimension between the locations where the pressure amplitude has been reached. In tissue, for example, the shock front thickness is in the range of 1.5 – 6 µm [63]. During transition of, for example, a cell wall, which has a thickness of a few molecular layers, significant forces can already come to bear on the wall, as there are immediate differences in pressure in front of and behind it. The pressure gradient, i.e., the change in pressure between two locations, reaches its maximum at a given wave amplitude in the shock front as compared with other forms of sonic signals, e.g., sinusoidal ultrasound.

Sources

In practice, all extracorporeal shock wave (ESW) generators consist of an electrical energy source, an electroacoustic conversion mechanism and a device for focusing the sound waves.

There are three methods of generating shock waves, namely by piezoelectic, electrohydraulic, or electromagnetic means.

Without entering into a detailed discussion on the technical data about the ESW generators, it is important to know that the electrohydraulic system produces high energy ESW, but with marked oscillations in the values of the energy flux density through the tissues, which do not remain constant during the therapeutic application. They need a spark electrode to work, but a fast deterioration in use reduces its life to about 1000 sparks [64, 65] before the electrode needs to be changed, while a single application, lasts some thousands of impulses, on average.

The piezoelectric device is very precise and has a long life, but, in spite of a very sophisticated technology, produces only low-energy ESW, often requiring, repeated treatments to reach the desired result [64].

The more actual electromagnetic generators are mainly differentiated into two types because of their shapes: flat and cylinder coils. The average value of pressure, expressed in terms of energy flux density, is almost constant and the coil is a very long-lasting device.

To achieve a specific effect, the sound waves must be focused. When employing point sources (e.g., sparks) or cylinder sources, a focusing mirror is used. When employing areal sources, lenses or a self focusing appliance of partially spherical shape are used.

ESW in Medical Practice

Shock waves employed in medical practice are characterized by high positive pressures up to 80 – 100 MPa and negative pressures of 5 – 10 MPa Furthermore, they have a short rise time of 30 – 120 ns and a shorter pulse duration (5 µs),. In contrast to ultrasound, shock waves have low frequencies. Just in this respect, there is less absorption by the tissue. Moreover, the shock waves are applied with a lower repetition frequency of 1 – 2, maximum 4 Hz, which means that they have a low time-averaged intensity. The only thing that can be said for sure is that the shock wave does not cause tissue warming [66]. None of the known shock wave effects are due to thermal effects.

During the ESWT, it is important to know the energy dose administered for each treatment. All the authors, under a general agreement, distinguish the ESW into high-energy waves and low-energy waves; the level of energy turns out to be a complex parameter which is defined by the ratio between the applied power and the tissue density [64, 67].

Treatments with intermediate and high energy levels produce energy flux densities which range from those used for treatment of nephrolithiasis to many times this energy level, i.e., densities from 0.37 to 1.2 mJ/mm². This form of treatment nearly always requires analgesia or anesthesia. The indications are represented by pseudoarthrosis and some species of tendinosis calcharea.

Low-energy treatment employs 10%–20% of the dose used for renal calculi, i.e., densities between 0.08 and 0.23 mJ/mm². In most cases anesthesia or analgesia is not required. The low energy range is mainly reserved for the treatment of localized soft tissue disorders.

Modes of Action

Regarding the action of shock waves on tissue, four phases have been postulated:

1. *Physical phase*: extracellular cavitations, ionized molecules and an increase of membrane permeability are direct effects of the shock waves.
2. *Physicochemical phase*: diffusible radicals and interactions with biomolecules (in both phases mitochondrial lesions were observed).
3. *Chemical phase*: may be accompanied by intracellular reactions and molecular changes.
4. *Biological phase*: noted if these changes persist.

Many of the shock wave tissue interactions are not yet completely understood.

Several theories have been formulated to explain the mechanism of action of ESW on bone-related soft tissue pain:

1. The shock wave locally alters the chemical environment in such a way that pain-inhibiting substances are produced.
2. The shock wave damages the cell membrane; no more generator potential is produced in the pain receptor for the formation of the pain signals.
3. The shock wave stimulates the pain receptor to emit a high frequency of nerve impulses. The retransmission of pain impulses is inhibited as it is subject to external stimuli (gate-control theory).
4. The shock wave induces a release of endorphin resulting in the reduction of (local) sensitivity to pain.

Therefore, there seem to be two possible modes of action in tissue; direct effects, or those caused by cavitation.

Direct Effects. Direct effects are mechanical effects caused by temporary positive pressure amplitudes during the propagation of a pressure pulse. The stability under load of the material (tissue) may be exceeded at the interface between the materials with different acoustic impedances. At such interfaces, the shock waves lead to changes in the excursion, which result in tensile and shearing loads. In soft tissue, where there are no great differences in acoustic impedance, the direct effects of shock waves do not appear to play a significant role.

Cavitation. The definition of cavitation is: expansion and oscillation of gas-filled cavities (pre-existing as cavitation nuclei) due to the tensile portion of a pressure wave with subsequent collapse. The cavitation results in mechanical and chemical effects:

1. Mechanical: shearing loads develop due to the oscillation of the developed cavitation bubbles. Due to the collapse of the bubbles, there are fine jets of water (jet streams). These high-flowing water masses can reach velocities of between 100 and 800 m/s [66], which corresponds to the velocity of bullets. One can clearly imagine the effect of this jet stream on a mechanical basis.
2. Chemical: during the collapse of the cavitation bubbles, high temperatures develop locally inside the bubbles, which lead to the development of radicals. The induced radicals can subsequently lead to damage in the tissue.

The discussion as to which of the above types of effect is responsible for the biological effects is currently still under way.

In experiments on cells in suspension, Brümmer [68] and Smits [69] found a cell damage pattern which is dependent on the number of shock waves and the shock wave energy applied:

1. Transient membrane rupture (permeability) with secondary damage (cell edema)
2. Transient damage to endoplasmatic reticulum and cell nucleus
3. Dose-dependent vacuolization of the cytoplasma
4. Lesion in cytoskeleton (actin and vimentin fibers)
5. Complete cell rupture (e.g., hemolysis)

To understand the mode of action of the ESW on the bone tissue we need to consider their mechanical effects on the bone trabeculae. When the shock wave hits the anterior surface of a trabecula, because the impedance inside it (II medium) is lower compared with the one outside it (I medium), at the level of the I interface (I medium/II medium), part of the energy is reflected back (stretching force), while the remaining energy (compressing force) advances through the trabecula (II medium) to reach the posterior surface of it up to the II interface (II medium/I medium), where the acoustic impedance gradient is inverted and the reflected wave is negative.

At the level of both interfaces, the cavitation bubbles are formed and are then submitted to a deforming compression by the gradient of pressure, with a consequent reduction of the volume and increase in energy; they collapse progressively, the anterior wall hit by the shock wave introflects, while the posterior wall is extroflected by the stretching components, until the bubble releases part of the stored energy generating the jet streams directed toward the gradual shattering of the trabeculae.

According to Sukul and Johannes [58] these effects on the bone structures are comparable to the effects of lithotripsy on kidney and gallbladder stones. In the literature, several hypotheses have been considered:

1. [illegible] of the [illegible]
2. Development of [illegible]
3. Development of [illegible]
4. Transformation of [illegible] cells

Steinbach [66] observed that in the focus center, the endotelial cells were no longer monolinearly next to each other, but were scattered around, partly ripped down to the basilemma and unica muscularis. A further effect was an increase in the fibrillic actin content in the endotelial cell; the closer the cells had been to the focus, the greater the fibrillic actin content in the cytoplasm (so-called stress fibers develop due to a variety of stimuli). Owing to the increased content of fibrillic actin in the endothelial cells, the latter retract and the intercellular distances increase, which might explain a higher vessel permeability.

Also, the phenomenon of neoangiogenesis might be related to the presence of chemiotactic factors, very close to the ESAF (endothelial stimulating angiogenetic factor), released by the stress fibers.

ESW has important effects on nerves and nerve cells. It could be hypothetically assumed that the mode of action is based on a direct mechanical effect of the shock wave on the axon membrane in the sense of an increase in permeability with consecutive depolarization and triggering of an action potential. However, it appears more probable that a cavitation-based effect plays a role in the triggering of the cumulative action potentials. A hyperpolarization of the neurons is achieved by means of shock wave treatment, whereby an energy dependency was discovered, i.e., the higher the energy of the emitted shock wave, the greater the polarization. These effects lasted for approximately 1 h after the shock wave. During hyperpolarization, a stimulus is necessary which is larger than that required before shock wave treatment, to excite an action potential. Whether this effect could play a role in palliative therapy will require further study.

Indications and Protocols of Therapy

From the first reports of Valchanou and Michailov [57] who inaugurated high energy ESWT for the treatment of delayed and non-union fractures, the clinical indications have been largely expanded toward other orthopaedic disorders, both in hard tissue pathology, i.e., osteonecrosis and osteochondritis or the problems of osteointegration at the metal-bone interface of the loose cementless prosthesis, and the soft tissue pathologies, i.e., almost all the insertional tendinitis and enthesopathies or muscles strains.

There is a general agreement among the authors that high energy treatments should be reserved for bone affections whereas low energy ESWT is the most indicated treatment for soft tissues lesions.

During soft tissue therapies, usually without any form of analgesia or anesthesia, the application of shock waves is also based on a sort of 'pain feedback', by asking the patient when he recognizes his symptomatology, and the quality and the site of pain; but it must always be remembered that there are algogenic structures, i.e., the periosteum of the superficial bones or the sensitive nerve bundles, easily stimulated by the ESW: their activation always induces strong pain and it might confuse the operator. For this reason it is important that an in-line ecographic aiming device is available to precisely individuate the site of pathology.

The high energy ESWT almost always requires pain control by means of analgesic/anesthetic treatment. An image intensifier is absolutely necessary to position the focus of the ESW right on the site of pathology, otherwise it is impossible to individuate it exactly.

Pseudarthrosis

Delayed union is defined when a fracture is not healed completely within 4 months. Healing that does not happen within 6 months is called pseudarthrosis. Congenital forms of pseudarthrosis are known. According to radiological criteria, pseudoarthrosis can be hypertrophic or atrophic. The present studies show that ESWT is not indicated in cases of congenital non-unions, and that results are better in hypertrophic forms than in atrophic ones.

The protocol schemes according to Russo et al. [70] distinguish between small bones and other bones.

In the first case, two applications, the latter 24 – 48 h after, 4000 impulses, 0.7 – 1.0 mJ/mm², are recommended.