Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries

A. Giombini†, V. Giovannini‡, A. Di Cesare‡, P. Pacetti§, Noriko Ichinoseki-Sekine‖, M. Shiraishi#, Hisashi Naito‖, and Nicola Maffulli***

†Institute of Sport Medicine and Science, Rome, Italy, ‡Department of Biological Science 'A. Rossi Fanelli', University of Rome, La Sapienza, Italy, †Post-Graduate School in Physical Medicine and Rehabilitation, University of Rome 'La Sapienza', Rome, Italy, ‡Department of Physics, Tor Vergata University, Rome, Italy, †Juntendo University, Imba, Japan, §Division of Sports Medicine, Jikei University School of Medicine, Nishi-Shinbashi, Minatoku, Tokyo, Japan, and ***Department of Trauma and Orthopaedic Surgery, Keele University School of Medicine, Stoke on Trent, Staffs, UK.

Introduction: Hyperthermia induced by microwave diathermy raises the temperature of deep tissues from 41°C to 45°C using electromagnetic power. Microwave diathermy is used in the management of superficial tumours with conventional radiotherapy and chemotherapy and, recently, its use has been successfully extended to physical medicine and sports traumatology in Central and Southern Europe.

Methods: We searched the literature for relevant studies. Most of the published studies in these fields have used 434 and 915 microwave diathermy, as these wavelengths are most effective.

Results: Hyperthermia induced by microwave diathermy into tissue can stimulate repair processes, increase drug activity, allow more efficient relief from pain, help in the removal of toxic wastes, increase tendon extensibility and reduce muscle and joint stiffness. Moreover, hyperthermia induces hyperaemia, improves local tissue drainage, increases metabolic rate and induces alterations in the cell membrane.

Conclusions: The biological mechanism that regulates 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 perfusion is still under study. Microwave diathermy treatment at 434 and 915 MHz can be effective in the short-term management of musculo-skeletal injuries.

Keywords: hyperthermia/microwave/hyperaemia/muscle/tendon
Introduction

Hyperthermia is a physical therapy technique which raises the temperature a given tissue between 41.5°C and 45°C and maintains in this range for a given period.\(^1\) Hyperthermia has been used in oncology for more than 35 years, in addition to radiotherapy, in the management of different tumours.\(^2\) In 1994, hyperthermia has been introduced in several countries of the European Union as a modality for use in physical medicine and sports traumatology.\(^6,7\) This review will focus on the use of hyperthermia induced by 434 and 925 MHz microwave diathermy as a support in the rehabilitation of both acute and chronic muscle-skeletal injuries.

Frequencies historically used in the rehabilitation were 2450,\(^8\) 915,\(^9-15\) 434 (with surface cooling)\(^12,13,15,16\) and 27.12 MHz.\(^17,18\) These frequencies differ because of the peculiar range of depth in which they can generate heat inside tissues. The efficacy of an electromagnetic wave device is strictly related to the ability of the heating device to achieve a certain temperature at the target site.

Some studies compared different heating modalities.\(^19-21\) Guy et al.\(^1\) investigated several heating patterns by measuring the temperature every centimetre from the skin to 4–5 cm below the surface in a human thigh. Their results confirmed the following.

- Hot packs increase the temperature of the skin only.
- Infrared energy produces superficial heating only.
- Shortwave diathermy (27.13 MHz) does not overheat the skin and increases the temperature at a maximum depth of 1.6 cm below the skin surface.
- Microwave diathermy (2450 MHz) reached therapeutic values at 1.85 cm with skin temperature above 45°C.
- Microwave diathermy (915 MHz with surface cooling, a prototype of modern hyperthermia machines) reached therapeutic values from 1 to 4 cm below the skin surface, keeping the skin temperature under 36°C.
- Ultrasound was unsuitable for hyperthermia, especially in those sites where bone is present, because it generates hot spots and pain and does not increase the blood flow.

These studies suggest the use of microwave diathermy in rehabilitation medicine, as the average depth of interest in physical medicine ranges between 1 and 4 cm. In addition to the frequency of the wave which is of primary importance for the effectiveness of a device, the variables to be considered when administering microwaves are time and power.\(^1,22\) These variables affect the penetration depth of irradiation in a given tissue, and the water content of which will also
exert an influence on the depth of penetration\(^1\) (Table 1). A tissue with high water content absorbs more energy, as water has a high dielectric constant, and the higher the dielectric constant, the deeper the penetration.\(^9,23,24\)

The size and geometry of both the applicator and the tissue to irradiate are also important variables.

The rate of heating is also related to the heat dissipation from thermal conduction and to the ‘washing out’ effect induced by blood flow: blood perfusion increases by about 15 times when the tissue temperature raises from 36\(^\circ\)C to 45\(^\circ\)C.\(^9,25\)

An important variable that includes most of the above factors, and can therefore give a measure of the efficiency of an apparatus, is the specific absorption rate (SAR), i.e. the rate of absorption per unit mass of tissue. SAR is defined as ‘The time derivative of the incremental energy absorbed by an incremental mass contained in a volume element of a given density’.\(^23\) SAR depends on the frequency, intensity, polarization, radiation source of the applicator and on the size, shape and electrical properties of the tissue.

The efficiency of an apparatus is as important as its safety. A modern microwave diathermy heating device must be able to reduce the dispersion of the electromagnetic radiation as well as hot spots to minimal values. With regard to patient’s safety, the control of the temperature is mandatory. Hyperthermia is safe if the temperature is kept under 45\(^\circ\)C.\(^1,24,26–28\) The absolute temperature is, however, not sufficient to predict the damage that it may produce. Probably, one should refer to a hyperthermal dose effect, thus defining both temperature and time of its application. The concept of thermal isoeffect dose (TID) represents also an attempt at both treatment planning and clinical data comparison. It also makes it possible to predict tissue thermal damage by using an Arrhenius analysis or the Separeto–Dewey isoeffect thermal dose relationship.\(^29\) In certain circumstances, 0.1 min at 46\(^\circ\)C is enough for the patient to report pain. In contrast, 200 min at 44\(^\circ\)C, 100 min at 45\(^\circ\)C and 50 min at 46\(^\circ\)C are necessary to induce an injury more severe than erythema.\(^22\) In terms of thermal dose, the most common therapeutic protocol in physical medicine suggests a session of 30 min at 41.5/42\(^\circ\)C.\(^30\)

### Table 1  Average penetration depth of tissues with high and low water content.\(^1\)

<table>
<thead>
<tr>
<th>Frequency (MHz)</th>
<th>Penetration depth (cm)</th>
<th>High water content tissues</th>
<th>Low water content tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>434</td>
<td>3.57</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>915</td>
<td>3.04</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>2450</td>
<td>1.70</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>
Concluding, as the average size of the tissue of interest in physical medicine ranges from 1 to 200–300 cm$^3$ in a depth varying from 1 to 4 cm, an efficient hyperthermia system for sport injuries, orthopaedic and physical medicine application should have the following$^{15,23}$:

- a penetration capability of 3–4 cm;
- a 50% SAR depth of $\sim$2–2.5 cm;
- a 50% SAR at the surface of $\sim$50 cm$^2$;

and, given the necessity of avoiding burns, scars and pain in the patients treated:

- a multipoint temperature monitoring system;
- a computerized system to control and memorize the treatment variables;
- an efficient cooling system to keep the superficial tissues below 42°C (Fig. 1).

**Thermal effects: physiological and biochemical aspects**

The most important physiological response induced by hyperthermia is the regional increase in the blood flow.$^{30,31}$ This event produces most
of the beneficial effects of hyperthermia. The increase in blood perfusion\textsuperscript{25,31} results from physiological vascular changes such as opening of vessels and contemporary increase in capillary permeability. These two events must be related to the physiological response of the central nervous system (hypothalamic control), to local afferent reflex and to the relief of vasoactive compounds such as bradikinin and histamine. The degree of change depends on both time and temperature of exposure. Some experimental studies using the anterior musculature of the thigh in healthy subjects showed that the pre-treatment flow of $2.6 \text{ ml} \times 100 \text{ g} \times \text{min}^{-1}$ rose to $\sim 32 \text{ ml} \times 100 \text{ g} \times \text{min}^{-1}$ after irradiation at 915 MHz with coincidental skin cooling for 20 min to 40 W absorbed power.\textsuperscript{31} Further studies concluded that flow in the heated muscle approaches $48 \text{ ml/100 g/min}$ once the threshold temperature of 45°C is achieved\textsuperscript{32}. Hence, to produce observable variations in blood perfusion, temperature must rise above 41.5°C as fast as possible.\textsuperscript{31}

Hyperthermia produces an increase in nutrients and oxygen in the heated region. Both nutrient and oxygen are critical for any of the anaerobic processes that take place in an organism, and they are necessary to effect tissue repair. pH normalization\textsuperscript{33} is another remarkable effect. Moreover, extravasion is increased, so that macrophages and granulocytes reach the injured area. This effect of hyperthermia can be useful for the development of novel drug delivery systems.\textsuperscript{34,35}

Both necrotic debris and excess of fluids, if present, are more easily removed because of a more efficient drainage. This means, for example, improved haematoma absorption.\textsuperscript{14,36}

Hyperthermia enhances apoptosis,\textsuperscript{26} with production and secretion of cytokines that induce a strong stimulus for repair.\textsuperscript{37}

Heat improves the contractile performance of muscle, as it increases ATPase activity and changes the mechanical properties of collagen in tendons.\textsuperscript{17} Hyperthermia may affect pain sensation, producing an alteration in sensory nerve response. Two major hypotheses try to explain the analgesic effect of hyperthermia, namely, the metabolic and the neurological hypotheses. According to the metabolic hypothesis, analgesia is produced by washing out inflammatory mediators from the area of injury.\textsuperscript{25,31} This would interrupt stimuli to the free nerve endings responsible for pain (Aδ endings). The metabolic hypothesis would explain the analgesic effect of hyperthermia in acute pain, whereas in chronic pain, non-myelinized c-type neuronal fibres are mainly involved. In this instance, pain is due to hyperexcitability of the local painful stimuli conduction system (neuroaxial pain) or to altered periferal spinal gating. Experimental studies on the analgesic effect of hyperthermia in chronic pain showed that the pain conduction velocity on the sciatic nerve is markedly reduced for $\sim 60$ min after a hyperthermia session.
This reduction in conduction velocity can indirectly produce a decrease in the pool of afferent signals carrying pain stimuli, allowing reset of the gate control at the spinal level.  

Hyperthermia can alter the permeability of cell membranes. Agents acting specifically at the membrane, such as local anaesthetics, all act synergistically with heat.  

Hyperthermia induces a general increase in the metabolic rate, as most enzymes enhance their activity when temperature raises. As a consequence, tissue locally increases its oxygen consumption, and hyperthermia-induced hyperaemia enhances oxygen contribution to the heated site.

Heat shock proteins (HSPs), also called stress proteins, are a group of proteins present in all cells. Ogura et al. recently reported that HSPs were generated by a rise in the muscle temperature above 41°C induced by microwave hyperthermia. HSPs are also present in cells under normal conditions, acting as ‘chaperones’, making sure that the cell’s proteins are in the right shape and in the right place at the right time. For example, HSPs help new or distorted proteins fold into their correct functional shape, which is essential for their function. They also shuttle proteins from one compartment to another inside the cell, transporting old proteins to ‘garbage disposals’ inside the cell. Hence, elevated HSP levels increase protein synthesis and decrease protein degradation. In addition, HSPs induced by heat stress preceding eccentric contraction may prevent skeletal muscle breakdown during exercise. This suggests that hyperthermia is effective not only in a muscle trauma, but also for exercise preconditioning.

HSPs production induced by hyperthermia plays an important role in the presentation of peptides on the cell surface to help the immune system to recognize diseased cells. HSPs are responsible for the thermo-tolerance phenomenon, whose consequence is the need for a more intense treatment application after application.

Non-thermal effects

The non-thermal effects of hyperthermia have not been yet fully documented. They may result from an interaction between the imposed electromagnetic field and specific types, or assemblages, of receptors molecules. Weak inter- and intra-molecular bonds, reversibly disrupted by the field, will allow these structures to change shape and exhibit altered biological activity. Other events such as the homogeneous orientation of large molecules in the field (including pearl-chain formation) and induction of transmembrane potential sufficient to alter ion flow are highly unlikely, except at very high field strengths.
Evidence for a direct effect of the electromagnetic field upon the shape of biologically active molecules, often referred to as ‘the electroconformational coupling model’, is drawn in part from work with Na\(^+\)/K\(^+\) ATPases. These molecules occur within the cell membrane and appear to receive energy directly from an applied electric field. The energy appears subsequently as an enhanced rate of Na\(^+\) and K\(^+\) pumping across the cell membrane. This mechanism is fundamental to many cellular activities, is dependent on both frequency and field intensity and requires that the energy of the weak electric field is amplified at the cell membrane to exert an effect.\(^{48}\) However, there is no evidence that ‘non-thermal’ effects play any significant role in relation to the use of hyperthermia as a diathermy modality. At the moment, none of these potential non-thermal effects have been related to a clearly identified therapeutic response.

**Muscle–tendon damage features**

Muscle damage is characterized by a number of intracellular events, including loss of energy supply, increase in oxidative damages to the structural elements of the cells\(^{37}\) and Ca\(^{2+}\) accumulation.\(^{49}\) All these events have been observed in the processes in which muscle damage occurs after different types of stresses, including injuries.\(^{49}\)

Loss of energy supply occurring consequently to the damage (a fall in the ATP concentration) is responsible for a considerable efflux of enzymes from the cell membrane. Energy depletion, in fact, causes an increase in the cell membrane permeability.\(^{50}\) Efflux of enzymes from the cell is a damaging event itself for the whole tissue and, at the same time, loss of energy inhibits all the anabolic pathways necessary for tissue repair.

Local hyperthermia can increase oxygen and nutrient supply that allows the cell to recover from the fall in ATP cellular concentration by increasing local blood flow.\(^{33}\) Most of ATP, in fact, is synthesized in eukaryotic cells through oxidative phosphorylation, which, by definition, takes place only in the presence of oxygen. This would help the repairing processes to take place and the damaging events in progress to stop.

Protection from oxidative damage is also an energy-dependent event, in which many important molecules and processes are involved. A damaged tissue loses its ability to efficiently recover from oxidative damage. Moreover, free radicals, responsible for the largest part of cellular oxidative damage, are involved, in particular, in muscle degeneration in several disorders, including Duchenne dystrophy\(^{49}\) and malignant hyperthermia.\(^{51}\) There has also been considerable speculation that
free radicals are involved in exercise-induced damage.\textsuperscript{52} The role of free radicals in skeletal muscle damage is not completely understood. Free radicals can cause damage to the muscle–tendon structure by lipid peroxidation.\textsuperscript{52} They can also alter DNA and proteins, including protecting antioxidant enzymes.\textsuperscript{53} HSPs provide biochemical and ultrastructural protection against ischaemic injury in rat skeletal muscles.\textsuperscript{54} HSPs can be efficiently induced by hyperthermia,\textsuperscript{41} and hyperthermia can limit free radical damage to muscles.

Intracellular Ca\textsuperscript{2+} accumulation is implicated in cell death, and there is considerable literature on the role of Ca\textsuperscript{2+} in muscle damage.\textsuperscript{49} Several different processes have been proposed to explain how muscle could be damaged by elevated intracellular Ca\textsuperscript{2+} content. This includes stimulation of Ca\textsuperscript{2+}-activated proteases\textsuperscript{55} (for example, Calpain I and II), activation of lysosomal processes,\textsuperscript{56} mitochondrial overload\textsuperscript{57} and activation of lipolytic enzymes.\textsuperscript{49} All these events produce cellular degradation.

This kind of damage is elicited by extracellular Ca\textsuperscript{2+}-induced intracellular Ca\textsuperscript{2+} release.\textsuperscript{58} In fact, efflux of cytosolic enzymes and ultrastructural damage caused by excess of Ca\textsuperscript{2+}-dependent contractile activity are reduced when extracellular Ca\textsuperscript{2+} is removed, and it has been proposed that the damaging process is initiated by extracellular accumulated Ca\textsuperscript{2+}.\textsuperscript{59}

Therefore, hyperthermia can play an important role by inducing Ca\textsuperscript{2+} removal from the damaged site by inducing an increase in local blood perfusion and more efficient drainage of the site itself.

Tendon damage, furthermore, results in alterations of cellular homeostasis of this tissue. Hypoxia alone may also result in degeneration, as tendons rely on oxidative energy metabolism to maintain physiological ATP levels.\textsuperscript{60,61} Recovery can occur through cell proliferation and protein synthesis under aerobic conditions.\textsuperscript{62} Local hyperthermia increases local blood flow and oxygen supply between 2.7 and 40 ml x 100 g x min\textsuperscript{-1},\textsuperscript{33} favouring drainage of cellular debris and stimulating protein synthesis.

**Therapeutic applications**

Diathermy, whether achieved using short-wave radio frequency (range 1–100 MHz) or microwave energy (range 434–915 MHz), exerts physical effects and elicits a spectrum of physiological responses,\textsuperscript{63} the two methods differing mainly for their penetration capability.\textsuperscript{1} The thermal effects of diathermy on biological tissues, in fact, reflect closely the more general effect of heating. However, the use of short waves and microwaves in clinical practice appears to have declined since the early
1980s, even though it is still extremely popular in physiotherapy departments and private practices of several EU countries, Australia and North America. In the last few years, minimal research has studied the efficacy of these modalities, and most published studies date back 15 years and are of mixed quality. Physiological effects attributable to short-wave diathermy in the management of skeletal muscle injuries have been shown only in two laboratory studies. All these studies showed a trend towards faster resolution of the healing site of the muscle injury in diathermy-treated animals when compared with controls. The molecular mechanisms, which, however, might account for the effects of short-wave diathermy in cell proliferation, remain unclear. All the clinical trials published have investigated the efficacy of short-wave diathermy, especially, in its pulsed mode (PSWD), on acute soft tissue injuries. All but one are randomized control trials investigating the use of PSWD in acute injuries in the lateral ligament of the ankle. However, the conclusions of these studies are conflicting. Several studies found beneficial effects from PSWD, but only one of them gives subjective and objective evidence in favour of PSWD-treated patients. Other studies concluded that PSWD was no more effective than placebo.

Heat is commonly used in the management of limitation of range of movements of a joint. This often follows contracture of the periarthritic connective tissues and shortening of other soft tissues crossing the joint, which can frequently include a tight joint capsule, a scarred and thickened synovium or fibrotic muscles. In most instances, the tightness results from abnormal deposition of collagen. Until recently, little research had been conducted on diathermy to ascertain the variables necessary to increase flexibility, or even whether short wave or microwave used prior to or during stretching could improve flexibility. An investigation on the methods of elongating collagenous tissue to produce maximum length increase under therapeutic range with a microwave unit at 915 MHz concluded that the exclusive use of heat or stretch does not produce elongation of the rat tail tendon, and only the application of a sustained tensile load and temperature of 45°C produce significant tendon lengthening. A subsequent study of Warren et al. with the same microwave apparatus confirmed that low-load, long duration stretching performed once the tissue reached significantly elevated temperature resulted in greatest increase in residual tissue length and produced the least amount of damage when compared with tissue stretched at lower temperatures with higher loads. De Lateur et al. reported a resolution of bilateral fibrous contractures of the rectus femoris, after a stretch and heating regime with an air-cooled direct contact applicator operating at 915 MHz. More recently, Draper et al. using a diathermy unit with a frequency of
27.12 MHz demonstrated that five daily sessions of a pulsed short wave and a low-load, long duration stretch in subjects with tight hamstrings increased hamstring flexibility more than an identical stretching regimen with sham diathermy application. However, they did not measure muscle and skin temperatures in the thigh muscles during the treatment. In clinical practice, it should be of great benefit to treat the tight structures, because of immobilization or inactivity, using heat at therapeutic temperature (41.5°C to 45°C) while applying sustained stretch and maintain this stretch well after the heating period, so as to retain the achieved elongation, and reduce the passive stiffness of the muscle–tendon unit.

Heat application has been advocated by several authors to accelerate the resolution of haematoma, but no experimental data were available until 1983, when a study showed that selective heating of the affected muscle could increase the rate of intramuscular haematoma absorption. Lehmann first quantified the resolution rate of haematomas produced in the musculature of experimental animals comparable in size with humans. Haematomas in the biceps femoris muscle were created in pigs by bilateral injection of blood, labelled with chromium (CR). One side was treated with microwave diathermy at 915 MHz and the other side was used as a control. The tissue temperature achieved at the haematoma site was in the therapeutic range between 42°C and 45°C, the optimal temperature to elicit a maximal local vascular response. 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 to a resolution of muscular haematomas. A recent study showed the benefits of hyperthermia at 434 MHz in 62 different muscle injuries in the general population. Benefits were expressed in terms of the visual analogue scale (VAS) scale and through an ultrasonographic investigation. In this work, results obtained were compared with the ones obtained in an ultrasound-treated group. Improvement was greater in the group receiving hyperthermia than the group receiving ultrasound. There were neither complications nor re-injuries at follow-up in the hyperthermia group, whereas two re-injuries and one calcification occurred in a patient with pectoralis major injury in the ultrasound group. A later randomized-controlled study investigated the effects of hyperthermia in 40 athletes, 29 males and 11 females, 18–35-year old, with acute muscle injuries of different sites and severity. Twenty-one of them received hyperthermia (group A) and the other 19 received ultrasound (group B). Each subject in each group received nine applications, three times per week, with a duration of 30 min for group A and 15 min for group B. Both groups had a significant decrease in pain. Hyperthermia showed a significantly higher effect on the VAS score and on haematoma resolution after
2 weeks of treatment. Hyperthermia at 434 MHz was safe and reliable for early management of acute muscle injury, contrary to the belief that the application of diathermy to acute injuries is contraindicated.

Protocols including heat therapy in the management of tendinopathies have been described. Chronic overuse tendon conditions have been traditionally managed as inflammatory conditions, although histopathology clearly shows a non-inflammatory failed healing response. Changes in the arterial blood flow, with resulting local hypoxia and impaired metabolic activity and nutrition, may be a key factor, together with a failed cell matrix adaptation to excessive changes in load. A randomized-controlled trial studied the effects of hyperthermia on 44 elite athletes, 33 males and 11 females (age 26 ± 4.56 years), with tendinopathies of the lower limb (31 patellar or 13 Achilles tendons). Twenty-two patients were randomly assigned to hyperthermia and 22 to ultrasound. The patients underwent standardized pain measurement and ultrasound scanning and received treatment for a total of 12 sessions, three times a week for 4 weeks. The same standardized examination was performed at the end of treatment and 1 month after the end of treatment. The assessing physician was unaware of the treatment allocation. The patients were asked to rate the ultimate outcome on the basis of pain resolution and return to sports activity. Both groups had a significant decrease in symptoms \((P < 0.001)\). Hyperthermia, however, demonstrated better effects on the reduction of VAS score and on subjective overall satisfaction (77%) of excellent and good results in comparison with 33% of ultrasound. In chronic overuse tendinopathies of the lower limb, hyperthermia at 434 MHz showed promising results, with short-term clinical improvement, good safety and no side effects. In this study, ultrasonography did not demonstrate changes in the tendon structure.

With the clinical impression that this management modality would be effective in tendinopathies of the rotator cuff as well, a pilot study was performed using a prospective randomized-controlled design to evaluate the effectiveness of the hyperthermia in the management of supraspinatus tendinopathy in athletes. A group of 37 athletes (29 males and eight females) with 3–6 months of symptoms were randomly assigned to three groups: group A (14 patients who received hyperthermia at 434 MHz); group B (12 patients who received continuous ultrasound at 1 MHz at an intensity of 2.0 \(W \times cm^{-2}\) three times a week for 4 weeks) and group C (11 patients who undertook passive exercise, consisting of pendular swinging and stretching exercises 5 min twice daily for 4 weeks). Subjects were evaluated at baseline, immediately on completion of treatment and at 6 weeks after the end of intervention. Patients who received hyperthermia showed significantly better results at follow-up as assessed by the visual pain scores, resistant...

Safety

The efficiency of an apparatus is as important as its safety.\textsuperscript{18,63} An up-to-date heating device must be able to reduce near to zero the dispersion of the electromagnetic radiation as well as hot spots. With regard to patient’s safety, an extensive literature provides accurate information on the effects of hyperthermia on mesenchymal tissues at different temperatures and durations.\textsuperscript{1,26–28} Temperature by itself is not sufficient to predict the probable heat damage. The thermal effects on tissues must be more correctly related to a thermal dose, which includes both temperature and time variables. As mentioned, the TID allows to predict tissue thermal damage by using an Arrhenius analysis or the Separeto–Dewey isoeffect thermal dose relationship.\textsuperscript{22,29}

The effects of radio frequency-induced hyperthermia in the range of temperature from 42°C to 48°C for 30 min were studied on swine mesenchymal tissues (subcutaneous adipose tissue and skeletal muscle).\textsuperscript{29} Acute lesions (18–24 h after the treatment) and chronic ones (28–31 days after the treatment) were investigated. In acute lesions, moderate damage was observed in sites heated from 44°C to 46°C both in muscle and adipose tissue. For chronic effects, temperature up to 45°C produced mild changes consisting mainly of scattered fibrotic foci and a few giant cells. The muscle, however, showed no residual damage in this temperature range. Skin damages were limited by the presence of a water bolus, which provided superficial cooling effect, so that they resulted irrelevant. This study emphasizes that ‘significant fibrosis was seen only at temperatures of 46°C and above’,\textsuperscript{29} which is comforting, given the nearly perfect agreement between the human and porcine data.\textsuperscript{29} Sekine et al. investigated the changes in muscle and skin temperatures in the human thigh during hyperthermia at 434 MHz and assessed the muscle damage after a severe hyperthermia session (high power of 70 W to rise the temperature close to 45°C). Their histological sections did not show any damage or inflammation of the muscle fibers induced by severe hyperthermia.\textsuperscript{85} Moreover, they showed a huge difference between thermal threshold to report pain and the one to induce injury.\textsuperscript{28,30} For example, 0.1 min at 46°C is enough for patients to report pain, in certain circumstances. In contrast, 200 min at 44°C, 100 min at 45°C and 50 min at 46°C are necessary to induce an injury more stable than a simple erythema.\textsuperscript{30} Moreover, all kinds of tissues share the same pathway of inflammatory
response. For these reasons, it is suggested to avoid the use of hyperthermia in the previous 72 h of an inflammatory event.

Given our experience, we suggest:

- trying to reach in a short time the desired temperature;
- performing the application of hyperthermia at least 3 days per week.

Obviously, both time and temperature of application must be controlled to avoid the collapse of the system: in practice, in musculoskeletal medicine, one should not exceed 45°C for 30 min. Specific contraindications to hyperthermia, however, include conditions known to be sensitive to increased cell proliferation rates, ischaemia, local thrombosis, impaired cutaneous thermal sensitivity, metallic implants including pacemakers, infections and pregnancy.63

Concerning safety for the operators, to reduce the effects of their exposure to microwaves, a limit of 10 mW × cm⁻² at a distance of 1 m in front of an active applicator and 0.5 m at the back has been established as a whole body safety limit by INRPA Committee and CEE safety rules for electromagnetic equipments.86,87

New diathermy systems for hyperthermia treatments at 434 MHz, thanks to the design of the water bolus microwave applicators and their efficiency in the focused transmission of energy to biological tissues, generate radiations at an intensity of 0.1 mW × cm⁻² at a distance of even 0.5 m in front of the applicator and 0.5 m at the back.88,89 These data are considerably below the maximum tolerated limits and allow physical therapists and clinical personnel to use this equipment in a very safe fashion. Moreover, to avoid accidental power reflection due to unexpected movements of the patients under treatment and consequently electromagnetic irradiation in the environment, new hyperthermia systems have a real in-time control of the electromagnetic coupling between the applicator and the patient. Dedicated software, furthermore, measures the return on signal as the percentage of emitted and reflected power from the applicator, in the case of reflected power above 35%, automatically stops the microwave emission. These technological improvements have definitively solved the problems delineated by some authors,90 concerning the observance of electromagnetic safety guidelines in the most used diathermy units, which, in a lot of cases, exceeded the electromagnetic limits for operators at distance currently recommended as safe.

**Conclusions**

Hyperthermia can be usefully applied in the management of muscle and tendon pathologies, stimulating the self-repair capacity of these
tissues,\textsuperscript{30} with tissue regeneration, oedema reduction, muscle and tendon pain reduction. Effective clinical responses occur when the temperature at the injured site reaches $41^\circ$C to $45^\circ$C, increasing blood perfusion up to 15 times. Only wavelengths of 915 and 434 MHz are able to guarantee an effective heating in a range of depth from 1 to 4 cm under the surface, with the 434 MHz wavelength being slightly more effective in terms of penetration and reaching the therapeutic temperature, while maintaining the skin temperature.\textsuperscript{87} Non-thermal effects of hyperthermia have not been clearly elucidated, but might contribute to the overall therapeutic effects.

Modern hyperthermia units work at these wavelengths, producing a 50\% SAR depth $\sim$2–2.5 cm on a surface of $\sim$50 cm$^2$, and have a computerized system for both temperature control and treatment planning. These apparatuses are safe, in terms of null electromagnetic field dispersion in the environment, sensitive temperature control system and no risks of skin burning during the application, and have an efficient cooling system.\textsuperscript{89} Studies on the effects of hyperthermia induced by microwave diathermy both in humans and in animals suggest that these devices can be usefully employed in rehabilitation medicine, especially in the treatment of musculo-skeletal injuries. Minimal research on this topic has been completed in the last 10 years. The lack of interest in hyperthermia as a physical modality might be caused by a lack of research-based evidence of its efficacy. The physical characteristics of most of the devices used clinically to heat tissues have been proved to be inefficient to reach the necessary therapeutic heating patterns in the range of depth of the damage tissue. The preliminary studies performed with new microwave devices working at 434 MHz have demonstrated encouraging results. Nevertheless, adequately designed prospective-controlled clinical studies need to be completed to confirm the therapeutic effectiveness of hyperthermia with large number of patients, longer-term follow-up and mixed populations.

\textbf{References}


