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Thermomechanobiology as a new research field in soft tissues

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During intense galloping, the difference in temperature between the external and the central part of an equine superficial digital flexor tendon can be as high as 7°C. Thirty minutes of jogging modifies the temperature in human knee cartilage from 32°C to 37°C. Intrinsic dissipative phenomena related to the viscoelastic behavior of soft tissues have been identified to be primarily responsible for the observed temperature increase, a situation referred to as self-heating in mechanics. While a 5°C increase may be considered negligible from a mechanical point of view in the cartilage at first sight, it can have a significant biological impact. It has been recently proposed that self-heating and the resulting increase of temperature in cartilage following mechanical stimulation can be necessary for its maintenance. This new concept complements the general acceptance that mechanobiology is central to the homeostasis of musculoskeletal tissues. In most biomechanical and biological studies on cartilage or other soft tissues, the temperature is set at 37°C and considered constant, despite human knee cartilage at rest being around 32°C, for example. Therefore, there is a deficit of information on the role and effect of physiological temperature variation induced through mechanical loading in soft tissues, opening a new research avenue that we coin thermomechanobiology.

KEYWORDS

dissipative materials, self-heating, osteoarthritis, bioreactor, physical therapy

1 Introduction

Most of the existing literature in biomechanics considers the studied processes as isothermal (T = cst) because mammalians have a regulated system for maintaining temperature constant. However, there are two situations where the isothermal hypothesis is no longer valid: when an external or an internal heat source is present. For these two situations, the temperature has to be considered a variable, and a biothermomechanics (coined by Prof J.D. Humphrey) description must be used to quantify the temperature effect on the tissue biomechanical properties.

2 External heat source

The motivation to study the effect of temperature on tissue biomechanical properties comes mainly from the therapies using heat. In this situation, heat is generated externally from the body and transferred to the treated body part. The heat can be transferred to the body by direct contact between the source and the body (Mayer et al., 2005) or by radiation (B. I. Lee et al., 1989). The amount of heat transferred is usually important and consequently induces a temperature rise to supra-physiological levels such as 41°C–150°C. However, very little is known about the mechanical heat-induced effect (Humphrey, 2003), rendering the optimization of the heat therapy difficult. Heat therapy is then essentially based on

empirical approaches. Consequently, a significant drawback of heat therapy is the inherent uncertainty of dosage, which makes it difficult to prove the efficacy of this therapy scientifically.

3 Internal heat source

Viscous dissipation (which is an irreversible process in contrast to the elastic reversible situation) is a process that transforms a part of the mechanical energy into heat. In this situation, the isothermal hypothesis may be locally wrong in the tissue when considering viscoelastic tissues submitted to dynamic loads. Indeed, a viscous material will dissipate the deformation energy into heat, inducing a local temperature increase. This aspect of internal heat source in biomechanics has been studied even less than external heat source, although its effect may be spectacular. It has been shown that the difference in temperature between the external and the central part of an equine superficial digital flexor tendon can be as high as 7°C during intense running (Wilson and Goodship, 1994). The central core of the tendon, which is the site of the most marked temperature increase, is also the site of degeneration and subsequent injury in the equine superficial digital flexor tendon (Webbon, 1977). It is tempting to correlate the temperature increase to injury. This proposed correlation was based on the fact that a good blood supply will cool an overheated tissue, and it may be that the avascular regions of the tendon lack this protective mechanism and, as a result, suffer hyperthermic damage during exercise (Wilson and Goodship, 1994). But an exciting finding has been highlighted. Tendon fibroblasts are significantly more resistant to hyperthermia than dermal fibroblasts. The tendon fibroblasts may have developed a heat adaptation (Rem et al., 2001), possibly by producing heat shock proteins such as HSP70 (Moseley, 1997).

The key to obtaining an increase in temperature in tissue (a phenomenon called self-heating in mechanics) is an insufficient blood supply to transport the generated heat. A temperature rise would then be expected to occur mainly in avascular tissues. So, to induce locally an increase in temperature in a biological tissue, two conditions must be present: insufficient or inexistent blood supply and viscous dissipation due to the tissue's viscoelastic nature.

4 Viscoelasticity of soft tissues in large deformations

Description of internal heat source through viscous dissipation is complicated in biological tissues as large deformations are usually involved. Viscoelastic descriptions of biological tissues have then to be valid for large deformation, which again is not commonly developed in the existing literature. Besides presenting hysteresis stress-strain behaviors, biological soft tissues are rate-dependent and possess a nonlinear (elastic or viscous) behavior. The strain-rate dependency of soft biological tissues has been well documented in the literature, including the works on ligaments (Pioletti et al., 1998; Puso and Weiss, 1998), tendons (Johnson et al., 1996), blood vessels (Michael Lee and J Wilson, 1986), and on cartilage (Hayes and Mockros, 1971). The time-dependent behavior of biological tissues can be attributed to the interstitial fluid flow, the inherent dissipation of the solid phases, and the viscous interaction between the tissue phases (Mak, 1986). For self-heating in tissue to induce a significant local temperature increase, a high dissipation, and an almost adiabatic system should be present. Three soft tissues fulfill these requirements: tendon, nucleus pulposus, and (knee) cartilage. We already discussed the situation for the tendon; we will focus on the two others.

5 Nucleus pulposus

The largest tissue in the body without blood perfusion is the nucleus pulposus, the central part of the intervertebral disc. This tissue showed a viscoelastic behavior characterized by stress relaxation and shear strain rate dependency of the shear stress (Iatridis et al., 1997). A very intriguing observation comes from quantifying the viscous characteristic of human intervertebral disc versus age. The hysteresis was the lowest for people in the middle decade of their lives (Virgin, 1951). Another study confirmed and expanded these results (Koeller et al., 1986). When we look at the incidence of degeneration versus age in the population, we can observe that it mainly begins at around 30 years old (Paajanen et al., 1997). A correlation between disc degeneration and the viscosity of this tissue could be suggested. To the best of our knowledge, no such observation has been exploited.

A tentative explanation for the observed viscosity variation during aging was proposed by considering the water content of the nucleus pulposus. Disc degeneration is usually associated with water loss, which is clinically observed by quantifying disc height through MRI imaging (Roberts et al., 1997). Water loss was then proposed to explain decreased viscous behavior. However, it was shown that water content alone did not explain the different age-dependent viscoelastic behavior, which probably must also be attributed to alterations in the biochemical composition of the tissue and changing structures of collagen fibers (Koeller et al., 1986). It could be very tempting to state that the decrease of the viscous component of the intervertebral disc might be at the origin of the disc degeneration. As previously mentioned, the nucleus pulposus is avascular and viscoelastic, so a local increase in temperature is expected under dynamic loading. If we consider the decreased viscosity versus age, we can associate the observation on viscosity to heat generation and propose a completely new paradigm in intervertebral disc degeneration. Locally increased temperature could be necessary to keep this tissue healthy. In other words, as the viscosity of the intervertebral disc significantly decreases at around 30 years, and this age corresponds to the initiation of disc degeneration, we could propose that after 30 years, the heat generated due to dynamic loading is no longer sufficient to induce a temperature increase necessary to keep the disc healthy. So far, this is still a hypothesis that needs to be tested. Following similar reasoning, we will now focus on the knee cartilage.

6 Knee cartilage

Thirty minutes of jogging modifies the temperature in the human knee from 32°C to 38°C (Becher et al., 2008). Combining an experimental and numerical study, we confirmed this

temperature increase inside healthy knee cartilage submitted to cyclic loading (Abdel-Sayed et al., 2014), highlighting the self-heating property of the knee cartilage. In parallel, we discovered that the temperature increase following mechanical stimulation is limited in degenerated cartilage. We explained this observation because degenerated cartilage has a much lower dissipative capability due to its increased porosity and lower mechanical properties. This can be verified by quantifying the hysteresis stress-strain curves, which are much smaller in degenerated cartilage (Szarko et al., 2010). Hysteresis may encompass multiple anelastic phenomena, including intrinsic viscosity, poroelasticity, and plasticity (Adams and Farris, 1989). Besides intrinsic dissipation as an internal heat source responsible for local tissue temperature increase, different thermoregulation phenomena could be considered, such as heat exchange with the blood supply, metabolic heat generation, or heat transfer by muscle activities. Cartilage is avascular, so heat exchange with blood is absent for this tissue. Regarding metabolic heat activity, this heat source is also negligible for cartilage as this tissue has a low concentration of cells. The only possible heat source affecting cartilage temperature, except its intrinsic dissipation, would be the one coming from the heat generated by the muscles. However, this heat source would negligibly affect cartilage temperature as knee cartilage is surrounded by synovial fluid, which presents a high heat capacity, putting this tissue in a pseudo-adiabatic situation, and in addition the muscles are not close to this tissue.

Studies on the temperature dependence of mechanical parameters specifically for cartilage are rare, probably because of the underlying invalid assumption that the knee cartilage temperature is constant. As for other tissues, these studies were primarily performed at supraphysiological temperature to evaluate some therapeutical aspects of heat treatments or at low temperatures to quantify the impact of tissue preservation mode on its mechanical properties (Szarko et al., 2010). The initial studies used cartilage specimens from animal sources, bovine (June and Fyhrie, 2010) or porcine (Chae et al., 2003), and showed moderate effects at temperatures between 24°C and 40°C. However, clear effects were observed on viscoelastic parameters at supraphysiological temperatures. In recent studies using human knee cartilage samples, confirmation of the impact of temperature on the mechanical responses of this tissue at supraphysiological was given. Still, a marked effect was also noted within the *in vivo* physiological temperature variation (Marshall et al., 2020). The cartilage bulk mechanical properties decrease significantly between 24°C and 40°C, particularly the dissipative ones. From a biological point of view, a significant corpus of evidence suggests that temperature may generally influence the cell's behavior, protein biosynthesis (Bernstam, 1978), or thermal stability, which may differ between proteins, particularly for type-I and type-III collagen (Danielsen, 1982). However, again, due to the lack of awareness that the physiological knee cartilage temperature in humans can vary, there was almost no available experimental data on chondrocyte sensitivity to the temperature. We are pioneers in showing that the metabolic activity of chondrocytes was modified after varying the temperature for 1 hour in the physiological temperature variation range of 32°C–38°C (Abdel-Sayed et al., 2013). Later, in the quest to determine the optimal *in vitro* culture conditions for preventing chondrocytes from de-differentiation (loss of chondrogenic phenotype), it has been shown in two successive studies that 3D pellets cultured at 37°C induced chondrocyte re-differentiation (return to chondrogenic phenotype) compared to a culture temperature of 32°C (von Bomhard et al., 2017; Ito et al., 2015). We recently confirmed the positive effect of temperature increase on chondrocyte markers cultured in 3D and demonstrated for the first time that this process is a TRPV4-mediated and calcium-dependent signaling mechanism (Nasrollahzadeh et al., 2022). However, the impact of heat should be well controlled; temperature above 42°C may affect chondrocyte viability and inhibit collagen production (Ito et al., 2019).

As mentioned, we have reported the intriguing result of cartilage's self-heating ability being lost when this tissue degenerates (Abdel-Sayed et al., 2014). We have then extensively evaluated the effects of mechanical loading and thermal stimulus, individually or in conjunction, to test the idea that self-heating would be essential for cartilage homeostasis. A bioreactor has been developed where loading, temperature, and oxygen concentration can be individually controlled (Guo et al., 2023a; Nasrollahzadeh et al., 2022; Guo et al., 2023b). Testing human chondrocytes embedded in a cartilage-like matrix under hypoxia conditions (Stampoultzis et al., 2023a) and human knee cartilage explants under physiological conditions (Stampoultzis et al., 2023b), we systematically observed that the combination of mechanical and thermal stimulations, mimicking a self-heating situation in the knee cartilage, induce an increase chondroinduction and chondroprotection of the tested samples. As for the fibroblasts in the tendon, heat shock protein, specifically HSP70, might be a key player in chondrocytes' positive reaction to thermomechanical stimulation (Guo et al., 2024) All these results support the concept that the self-heating property of cartilage is essential for its maintenance. On the contrary, in the situation where this property is lost, as in degenerated cartilage (osteoarthritis condition), a vicious circle starts to establish itself, and the degeneration of the cartilage continues its progression.

7 Thermomechanobiology and its potential therapeutical applications

While heat therapy has been proposed to treat different clinical conditions such as arteriovenous malformation, joint laxity, Parkinson's disease, and skin lesions, the most common use of this therapy is in the musculoskeletal field. Heat and cold therapy are the standard of care to manage pain for different musculoskeletal conditions (Malanga et al., 2014). In particular, the American College of Rheumatology (Hochberg et al., 2012) and the European League Against Rheumatism (Jordan et al., 2003) support this therapeutical approach for pain and stiffness relief associated with hip and knee osteoarthritis. While both heat and cold therapy may reduce pain sensation, the sensory pathway is different for the two therapies, TRPV 1-4 receptors being sensitive to heat in primary afferent neurons and may regulate the pain sensation. Besides reducing pain, heat was mentioned to reduce tissue stiffness and consequently allow for an increased range of motion in affected joints. The impact of temperature on collagenous tissue's viscoelastic properties was proposed as a possible

explanation for this observation (Hardy and Woodall, 1998). Heat is supposed to increase tissue metabolism and consequently could favor tissue healing. However, only a handful of clinical data support this healing claim.

While the combination of heat therapy and physiotherapy has been proposed in treating low back pain for more than 15 years (Freiwald et al., 2018; Mayer et al., 2005), only very few studies evaluated this therapeutical strategy for knee osteoarthritis. It has been shown that a combination of exercise and heat therapy decreases knee pain and increases functional mobility in elderly Japanese women with chronic knee pain. Interestingly, the results were better than heat therapy or exercise alone (Kim et al., 2013). Heat and physical therapies effectively reduce pain associated with osteoarthritis knee (Beydağı et al., 2021).

The clinical use of thermal therapies associated or not with physical exercises is based on empirical approaches (Malanga et al., 2014). A possible rationalization of these therapies could be proposed by considering the new concept of thermomechanobiology associated with the self-heating capacity of different soft tissues. Thermomechanical treatment could eventually be developed to break the vicious cycle of cartilage degeneration. Thermomechanobiology then opens a new field of research in soft tissues.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

DP: Writing–original draft, Writing–review and editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization.

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Conflict of interest

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