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# The influence of temperature on function of mammalian skeletal muscles

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**Abstract**
**The influence of the thermal environment on physiological processes and body temperature have been widely studied. Skeletal muscles are one of the tissues that are very sensitive to different thermal conditions. The temperature of muscle, especially in limbs, is frequently different than core temperature and fluctuates daily. For example, the resting muscle temperature of humans (core temperature 37°C) may vary from 29.4 to 34°C but may be increased to 40°C in the same muscle during activity [3]. The change in temperature between resting and working muscle has the potential to considerably alter the rate of contractile muscle properties and power outcomes. This review presents the current state of knowledge regarding the effect of temperature on properties of mammalian skeletal muscle contractions, specifically the biomechanical, metabolic, and neuromuscular aspects.**

**KEYWORDS: skeletal muscle, physiology, contraction, hypothermia, hyperthermia, metabolism.**

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## Introduction

In the mid-1950s, Huxley detailed the sliding filament theory, which described muscle structure and proposed theories of contraction. Active muscle contraction involves the relative sliding between two sets of filaments in a sarcomere (the thin, actin filaments and the thick, myosin filaments). The repetitive mechanical interaction of cross-bridges (myosin heads) on actin filaments are the biomechanical basics underlying muscle force generation. The cross-bridge attaches to the actin, changing the conformation and starting the muscle contraction, before they detach. This mechanical cycle is combined with an enzymatic reaction: hydrolysis of ATP by actomyosin and ATPase, release of phosphate ($P_i$) and adenosine diphosphate (ADP), and liberation of energy, which is converted into work and heat [14]. This mechanism is responsible for changes in muscle temperature during activity. The potential muscle elements featured in temperature changes are the biomechanical properties of soft tissue, biochemical properties of metabolism, and neuromuscular components. It is hard to divide all these components in independent research; however, some studies shed a light on these processes. Bits of knowledge about biomechanical properties of muscle tissue come from *in vitro* muscle experiments.

## Non-contractile muscle fiber structures

For the most part, muscle experiments have been done in three functional and mechanical states: relaxed (or resting), rigor, and active state. The tension of a relaxed muscle is largely insensitive to temperature. In the relaxed state, the cross-bridges remain detached and force develops when stretching beyond the rest length. This tensile-resistance results from the stretch of non-cross-bridge structures in the sarcomere. However, stretched, relaxed muscle can develop a type of "elastic" force due to heat-contracture at higher temperatures

(30-40°C) [25]. In the rigor state, there is no ATP, all cross-bridges are attached to actin (there is no cross-bridge cycle), and the muscle is stiff (after death, the muscle stays in the rigor state). As the temperature rises, force decreases slightly and linearly (exothermic process). In active muscle, cross-bridges attach to actin, develop force, and detach. The development of force, in this case, is very sensitive to temperature and increases with the absorption of heat (endothermic process) [24].

Muscle fibers are composed of two primary components, which are biomechanically distinct but structurally interconnected, called exo- and endosarcomeric lattices. Exosarcomeric lattices are a network of intermediate filaments that surround and interconnect myocyte organelles and sarcomeres with costamere and sarcolemma. The sarcomere, a basic unit of the contractile apparatus of striated muscle, are linked longitudinally to adjacent sarcomeres of the same myofibril by Z and M lines and radially to parallel myofibrils. On the other hand, an endosarcomeric lattice refers to extensible titin filaments, which attach between the M line region and the Z line, and inextensible nebulin, which runs along the thin actin filament [32, 33].

Previous findings have shown that elasticity characteristics of muscle fibers are more dependent on myofibrils than connective tissue [16]. Titin (connectin)-containing cap filaments were identified as a component of muscle fibers and are largely borne to resting tension [11, 13]. Titin is a protein connecting the myosin thick filament to the Z-disc in a sarcomere [19]. Maruyama et al. [18] showed that the isometric tension of isolated titin has a positive temperature coefficient. Furthermore, the resting tension of skinned fibers from a rat's extensor digitorum longus muscle increased with warming, from 20°C to the highest physiological temperature (30--40°C), and decreased with cooling, lowering back to the initial temperature. The reversibility of warming-cooling procedures was repeated until the temperature reached an upper limit of 43-45°C [25]. Summarizing the available evidence shows that the non-contractile endosarcomaric components, which build muscle cells, are temperature sensitive.

**Relationship between length and resting tension**

In general, mammalian muscles consist of two main types of muscle fibers: slow- and fast-twitch fibers. A rat's soleus muscle is often used as an example of a slow-twitch muscle and the extensor digitorum longus is used as an example of a fast-twitch muscle for studies of muscle properties [7]. In one of the first studies of mammalian muscle, Hill observed, in temperatures below 15°C, that rat muscle showed different characteristics than frog muscle [12]. The resting tension of the rat's slow soleus muscle, at the optimal length, started to rise when temperatures decreased from 15°C to 10-8°C. At the lowest temperature, the resting tension was increased roughly four fold. The "cold tension" effect was very unpredictable and not reproducible below 2°C. The opposite effect was observed in the fast-twitch extensor digitorum longus muscle. Below 15°C, resting tension decreased and near 0°C resting tension was slightly increased. As a function of time (in 5-8 hour experiments), developed resting tension was always higher than at the beginning of experiments (20 g vs 100 g) [12]. These experiments revealed that fast and slow-twitch muscles have different passive effects during temperature changes.

**Relationship between length and tetanic tension**

One of the classical physiological properties of muscle is the length/tetanic tension relationship, which is another feature sensitive to changes in muscle temperature. This relationship describes the force produced by progressively increasing muscle or sarcomere length and has a characteristic reversed U-shape. In a rat's short head of biceps brachii muscle (fast-twitch muscle), the largest force was developed when sarcomere length reached 2.2-2.5 μm and by 4.0 μm the tetanic tension was predicted to be 0. Interestingly, the U-shape of the length/tetanic tension curve was similar at both examined temperatures (27 and 15°C) [10]. Moreover, Elmubarak and Ranatunga [10] showed that cooling sensitivity (measured as a rate of change in muscle tension rise under change in temperature) for a short head of biceps brachii muscle increased below 23°C. A similar observation was noted in extensor digitorum longus and soleus muscles, where the temperature sensitivity rose below 25°C [26]. In conclusion, the experimental data demonstrated that the relationship between sarcomere length and tetanic tension does not change based on temperature.

**Isometric twitch and tetanic contraction**

The twitch is a single contraction of muscle in response to a single command (stimulus) from the nervous system. In physiological experiments, twitch contractions could be evoked by electrical stimulation delivered directly to muscle fibers, via a cut axon in the supplying nerve, or by the filament of the ventral roots containing axons of motoneurons. Furthermore, the isometric tetanic contraction (also called tetanus) is a sustained muscle

contraction evoked by a train of stimuli delivered at a high rate. Using these two kinds of muscle contractions researchers can describe basic characteristics of twitch (twitch force, contraction time, half relaxation time) and tetanus (plateau tension, maximum tetanic force, rate of tension development), as well as, a possible range of changes in the force, including the minimum and the maximum force, which can be modulated by changes in motoneuronal firing rate.

In female rats, the peak twitch tension and the isometric tetanic tension of intact soleus muscle decreased when the temperature dropped from 35 to 20°C, whereas in the extensor digitorum longus muscle the isometric tetanic tension decreased, but the maximum twitch tension increased 1.7 fold [8, 23]. Surprisingly, in the other fast-twitch muscle, short head of biceps brachii, the peak twitch tension rose 1.65 fold with cooling at the same temperatures [10]. The peak twitch tension for soleus muscle at 12, 8, and 4°C (compared to that at 22°C) was 74, 61, and 47%, respectively. This tension didn't drop when exposure to cooling was prolonged, except when the temperature was decreased to 3°C. For example, cooling the soleus muscle from 21 to 3.8°C reduced tension to 29.5% after 1 minute, and 27.1, 24.8, and 23.2% after 2, 6, and 20 minutes, respectively. At 0.3°C, the peak twitch tension was reduced to 31.0, 17.1, and 6.2% after 1, 3, and 10 minutes, respectively [12]. The twitch time-to-peak, also called the twitch contraction time, was prolonged during cooling in both types of muscles, but consistent results could only be obtained above 3°C. It is worth it to mention that in the soleus muscles, twitches after cooling to 0.5°C could last up to 60 seconds. At physiological temperatures, the contraction time is 0.15 seconds in the soleus muscle and about 0.095 seconds in the short head of biceps brachii muscle [10, 12]. The prolonging of twitch contraction time was not associated with a delay in restoration of the normal membrane potential. In such a case, a second pulse applied during the twitch would produce a multiple mechanical response, which was observed [12].

The course of twitch relaxation is very important from a physiological point of view as it considerably influences summations of individual twitches into tetanic contractions. This process is crucial to produce force in unfused tetanic contractions, which are generated by muscle fibers during voluntary activity. Experimental data indicate that with cooling, retardation of the time-to-half relaxation was even longer than that of the time-to-peak. The $Q_{10}$ (temperature coefficient for the rate of relaxation) was estimated to be 10, at a length of $l_0$ + 1 mm ($l_0$ is the length of the muscle during a maximal isometric twitch – 1 mm), for twitches in soleus and extensor digitorum longus muscles at 4-14°C; whereas, at length $l_0$ + 3 mm, this coefficient was lower, 5.4 and 6.5 for soleus and extensor digitorum longus muscles, respectively [12]. Segal and Faulkner [29] investigated changes in peak twitch tension, time-to-peak twitch tension, twitch half relaxation time, the maximum rate of twitch tension development, and maximum tetanic tension at 20-40°C. In both muscles (soleus and extensor digitorum longus), there was a shorter time-to-peak twitch tension at higher temperatures. In comparison to the soleus muscle, the extensor digitorum longus muscle had a faster time-to-peak twitch tension at each temperature. The peak twitch tension for the soleus muscle did not vary with a range in temperature, but tension in the extensor digitorum longus muscle rose when the temperature increased [29].

Experimental data from skinned muscle fibers and intact muscle models showed with plateau tension (tetanic force), maximum rate of tension development, time to half-rise of tension, and time to half-relaxation of tension in isometric tetanus, that mammalian skeletal muscle's temperature dependence was biphasic in nature between 10 and 36°C. There was an increase in cooling sensitivity for the rate of muscle tension rise at temperatures below the border temperature level (23-25°C) [26, 31]. When the extensor digitorum longus muscle was cooled from 35 to 10°C, a nearly 40% depression of tetanic tension occurred and after rewarming the tetanic tension was 10% less than tension was prior to cooling. Relative to the initial values, tetanic tension after rewarming was higher in the soleus muscle (104.0 ± 2.3%) than in the extensor digitorum longus muscle (91.2 ± 3.9%). This disparity in tension may have resulted from differences in fatigue resistance of muscle fibers. Most of the tetanic tension was recovered between 10 and 25°C in both muscles [22, 26]. The rate of tetanic tension development and time to half-relaxation of tetanic tension was also biphasic with cooling. The temperature sensitivity of the rate of tetanic tension development and half-relaxation of tetanic tension was more pronounced below 22°C in both muscles. However, at higher temperatures (24--36°C), the rate of tetanic tension development was more temperature-sensitive in the soleus than extensor digitorum longus muscle [26].

**Force-frequency curve**

Two studies examined the dependence of force on the frequency of stimulation at a physiological (35°C) and reduced (25°C) temperature. Ranatunga [23] found that cooling shifted the steep part of the force-frequency

curve to the left side in both the soleus and extensor digitorum longus muscles. This means that a higher relative force (relative to tetanic tension) was achieved at a considerably lower frequency of excitations [23]. Similar dependencies were observed by Segal et al. [30] for the soleus muscle at 20 and 40°C and for the extensor digitorum longus at 20, 30, and 40°C.

**Fatigue resistance**

Elevated muscle temperatures are associated with changes in time parameters associated with a muscle twitch. The contraction and relaxation time were shortened [23, 29], the intramuscular pH declined [27, 34], and the rates of anaerobic [9] and aerobic metabolism increased [5, 29, 35] with an increase in temperature.

An increase in temperature (43°C compared to 37°C) of a mouse's soleus muscle does not change fatigability [21]. However, Segal et al. [30] determined that the soleus muscle requires more stimuli to develop fatigue at 25 and 30°C than at 20 and 40°C. They also showed that the extensor digitorum longus muscle had a higher fatigue resistance at 30°C, than at 20, 25, 35, and 40°C. The similar nature of these changes were observed in *in vivo* studies in humans. The highest resistance to fatigue was found when the quadriceps muscle temperature was 31.6°C (30.3-32.6°C). A significantly lower fatigue resistance was observed at a higher muscle temperature (38.2-39.6°C), but at a lower muscle temperature (19.4-25.8°C), the difference was not significant. On the other hand, the fatigue resistance of the extensor digitorum brevis muscle (fast-twitch) decreased at a lower temperature, which was measured at 10, 20, and 30°C. Similar trends were observed in the mechanical power output calculated based on the shortening contractions. Moreover, an increased fatigue effect was more pronounced in the isotonic contraction (shortening mode) than in the isometric contraction (non-shortening mode) [28]. It is important to note that acidosis impaired the skinned mammalian muscle fibers kinetics at a low temperature (10°C), but only slightly impaired it's kinetics at high temperatures (30°C). This data showed that a decreased pH had less of an effect in the fatigue development process at higher temperatures [20, 34]. Metabolic changes were observed in analyses of human muscle biopsies taken during rest at 22.5, 31.6, and 38.6°C, after a water bath at 12, 26, and 44°C, respectively. The resting level of glucose, glucose 1-P, glucose 6-P, fructose 6-P, glycerol 1-P, pyruvate, and lactate were significantly higher at 38.6°C than at 31.6°C in the quadriceps muscle. When compared to 31.6°C, similar trends were observed at 22.5°C, but it was not as consistent as at 38.6°C [9]. Enhanced levels of a few glycolytic intermediates could be associated with an increased rate of glycolysis at higher temperatures during rest. After a series of sustained isometric contractions, ATP levels decreased to nearly 80%, but after the first contraction at 38.6°C, levels were significantly lower compared to the concentration of ATP at 22.5 and 31.6°C. There were no differences in the concentration of ADP and AMP at each of the studied temperatures. In addition, at high temperatures, phosphocreatine levels dropped to about 23% (compared to resting levels), and this almost depleted those resources. There was no effect of temperature on the levels of glucose, hexose monophosphates, dihydroxyacetone-P, glycerol 1-P, fructose 1,6-diP, and dihydroxyacetone-P [9].

**Enzymatic activity**

Contraction time is strongly dependent on ATPase activity and it likely plays a significant role in temperature-dependent impairment of skeletal muscle contractions [1]. In the fast-twitch muscles of rabbits (gastrocnemius and extensor digitorum longus), ATPase activity was 2-3 times higher than in the slow-twitch muscles (soleus and crureus). The isolated myosin experiment by Bárány et al. [2] showed that actin-activated ATPase was biphasic in behaviour, with a break at 15°C and greater activity at 35°C than at lower temperatures. Additionally, Zoladz et al. [35] studied the effect of temperature on fatty acid metabolism in a series of experiments on isolated skeletal muscle mitochondria. They observed that the capacity for fatty acid oxidation was more efficient at higher temperatures (25 vs 35 vs 42°C) under phosphorylating conditions (state 3). The upgrade to non-phosphorylating respiration (state 4) was observed with a rise in temperature. Previously, Brooks et al. [5] reported that the elevation of temperature from 25 to 45°C was associated with an increased rate of mitochondrial state 3 (60%) and 4 (200%), with pyruvate and malate as respiratory substrates.

**Neuromuscular junction**

Electromyographic studies suggest that the mechanism of transmission at the neuromuscular junction may be temporarily impaired in humans by temperatures near 20°C [6]. Only one study has investigated the influence of decreased temperatures on the motor endplate and these effects were compared at 20-23°C and 15-17°C. These data were obtained for the motor endplates of the sciatic nerve in the sartorius muscles of frogs. Kordaš et al. [15] found that the amplitude of the endplate current was depressed and that the time course of the post-synaptic potential was lengthened.

**Motoneuronal firing properties**

Under reduced muscle temperature by 5°C (from initial at 30°C), the motor neuron discharge rate did not decrease; although there was a reduction in contractile speed of the first dorsal interosseous muscle. Additionally, as fatigue developed, differences in the motor neuron discharge rate were not significant. However, differences did include a lengthened duration and declined amplitude in the M wave. The authors suggested that changes in the M wave under reduced temperature conditions were associated with the increase in the propagation time of the muscle fibers action potentials [4]. Temperature changes considerably influence the electromyogram recorded during muscle activity. Temperate decreases may evoke a loss in synchrony of motor unit recruitment. Using surface EMG and decomposition techniques in the forearm, Mallette et al. [17] observed a prolonged duration in motor unit action potentials (10.5%) and a lower amplitude (10.9%) at 22°C, when compared to 32°C. Moreover, more motor units were recruited (20 ± 7 vs 16 ± 5) at a lower temperature, which suggested that the cold muscle needed to compensate for the attenuated muscle force.

**Future challenges**

Despite a long history of research, there is still much to explore about the effect of temperature on the properties of mammalian skeletal muscle contraction. Three specific topics are of particular interest: 1) the effect of temperature on individual motor units of the three physiological types; 2) the temperature dependence at motor endplates of fast- and slow-twitch muscle fibers; and 3) the effect of core hypothermia and hyperthermia on the excitability of motoneurons and the temperature sensibility of origin neurons in the pyramidal tract of the motor cortex. Moreover, the development of experimental technology allows simultaneous recording of activity in individual motor units of muscles and their synchronization over time while performing motor tasks. The possibility of such an assessment would allow a more comprehensive understanding of the effect of temperature on neuromuscular performance.

**Conclusions**

As with almost all biological systems and structures, skeletal muscle is notably temperature sensitive. The change in temperature of mammalian skeletal muscle occurs under the influence of internal processes (endothermic) and the environment (exothermic processes). The final effect observed in the efficiency of muscle contraction and/or performance of motor skills is the result of combining the changes on the properties of non-contractile (connective tissue) and contractile elements (sarcomeres) and metabolic and neuronal processes at lower and higher than physiological temperatures. These changes in single structures are inseparably connected with each other. A deeper understanding of the nature of these changes requires further research.

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