HIGHLIGHTED TOPIC | Fatigue Mechanisms Determining Exercise Performance

Hyperthermia and fatigue

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Nybo L. Hyperthermia and fatigue. J Appl Physiol 104: 871–878, 2008. First published October 25, 2007; doi:10.1152/japplphysiol.00910.2007.—The present review addresses mechanisms of importance for hyperthermia-induced fatigue during short intense activities and prolonged exercise in the heat. Inferior performance during physical activities with intensities that elicit maximal oxygen uptake is to a large extent related to perturbation of the cardiovascular function, which eventually reduces arterial oxygen delivery to the exercising muscles. Accordingly, aerobic energy turnover is impaired and anaerobic metabolism provokes peripheral fatigue. In contrast, metabolic disturbances of muscle homeostasis are less important during prolonged exercise in the heat, because increased oxygen extraction compensates for the reduction in systemic blood flow. The decrease in endurance seems to involve changes in the function of the central nervous system (CNS) that lead to fatigue. The CNS fatigue appears to be influenced by neurotransmitter activity of the dopaminergic system, but may primarily relate to inhibitory signals from the hypothalamus arising secondary to an increase in brain temperature. Fatigue is an integrated phenomenon, and psychological factors, including the anticipation of fatigue, should not be neglected and the interaction between central and peripheral physiological factors also needs to be considered.

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exercise intensities discussed, fatigue is likely a hybrid of both peripheral and central mechanisms, with the relative contribution depending on the specific exercise situation. Furthermore, it is yet to be elucidated how the fatigue arising with hyperthermia interacts with the fatigue that develops during normothermic exercise, e.g., depletion of muscle substrates and CNS changes.

HEAT STRESS AND CARDIOVASCULAR FUNCTION

Heat transfer from the body core to the skin depends on the perfusion of the skin and the core to skin temperature difference. During exercise in the heat, the temperature gradient between the body core and the skin narrows, and for thermoregulatory purposes skin blood flow must therefore increase (34, 85). Redistribution of cardiac output, derived through reduced perfusion of the internal organs, may deliver some of the additional blood flow to the skin (68), but an increased heart rate becomes necessary to secure adequate cardiac output. At the onset of low- to moderate-intensity exercise in the heat, and as long as severe hyperthermia is prevented, cardiac output may increase to meet the increased need for perfusion of the skin (27, 45, 59). However, when the exercise intensity and the heat load are of such magnitude that endogenous heat production surpasses the capacity for heat dissipation to the environment, hyperthermia develops and the ability to maintain cardiac output is jeopardized because stroke volume declines as the core temperature increases (26, 27, 69).

Originally, Rowell et al. (67, 69) ascribed the lower stroke volume exclusively to impaired venous return arising secondary to vasodilatation in skin areas, but as demonstrated by Fritzsche et al. (17) the decline in stroke volume may be influenced by the reduced diastolic filling time that arises as a consequence of the increased heart rate and therefore shortened cardiac cycle. On the other hand, when trained subjects exercise without heat stress a shorter cardiac diastole does not reduce stroke volume on condition that the cardiac filling pressure is maintained or enhanced (20, 82; see Ref. 30a for discussion). Therefore, the lowering of stroke volume with hyperthermia seems to be a combined effect of reductions in cardiac filling pressure due to reduced central blood volume and a shorter diastolic filling time that will reduce both right and left ventricular end-diastolic volumes and subsequently cause a lowering of the stroke volume (17, 27, 69). To what extent the reduced stroke volume affects cardiac output appears to depend on the exercise intensity, the body position, and the severity of the heat stress (29, 30, 50, 52). If the exercise intensity is low and/or the heat stress is not to severe, the compensatory increase in heart rate will be sufficient to maintain cardiac output or limit the reduction to $<1$ l/min (27, 52, 57). Although heat stress requires an increased perfusion of the skin, this may be derived from reduced splanchnic and renal flow (68), and the arterial blood and oxygen delivery are sufficient to maintain unaltered perfusion of the exercising muscles and whole body and muscle oxygen consumption ($\dot{V}\text{O}_2$) remains unchanged (52). However, during upright exercise with intensities from $\sim 60\%$ of $\dot{V}\text{O}_{2\text{max}}$ and above, cardiac output may be reduced by $2–4$ l/min when high levels of hyperthermia are approached (25, 30), and especially so if the fluid intake is insufficient to match the sweat losses and dehydration develops (2, 23, 24). Under such conditions, the reduction in cardiac output becomes of such magnitude that muscle blood flow declines (Fig. 2). Yet, during submaximal exercise with severe hyperthermia and concomitant dehydration muscle $\dot{V}\text{O}_2$ is preserved, because the arteriovenous oxygen difference widens as combined effects of hemocoena-
tration that increases the arterial oxygen content and a slightly higher oxygen extraction, which lowers the venous oxygen content (24). Although muscle $\dot{V}\text{O}_2$ is maintained, the lower muscle blood flow during exercise with combined dehydration and hyperthermia is accompanied by a minor increase in leg lactate release, and glycogen utilization increases at the expense of fat metabolism (28). However, muscle glycogen stores are far from depleted at the point of exhaustion. Although, the interpretation of bulk space changes should be made with caution because depletion of muscle glycogen may occur at localized sites around myofilaments or the sarcoplasmatic reticulum, the glycogen levels that are observed following exhaustive exercise with hyperthermia does not support that glycogen depletion is an important issue (28, 31). Furthermore, blood and muscle lactate levels are much lower than the levels observed following exhaustive maximal exercise or submaximal exercise with hypoxia (28, 66). Thus hyperthermia-induced changes in muscle metabolism during submaximal exercise are not of such magnitude that they explain the fatigue that arises with the increase in core temperature (24).

In contrast, during maximal exercise with severe core and skin hyperthermia both pulmonary and muscle $\dot{V}\text{O}_2$ become reduced and anaerobic metabolism markedly enhanced (25, 56). The reduction in $\dot{V}\text{O}_{2\text{max}}$ in the heat is not provoked by a high core temperature in itself, but arises only when both core and skin temperatures are increased simultaneously (48, 56). In trained individuals, intense exercise is associated with very high rates of endogenous heat production, and it may in less than 10 min cause an increase of the core temperature to $\sim 40°C$ even if the environmental temperature is $>25°C$. But as long as the skin temperature remains low, it will not impede $\dot{V}\text{O}_{2\text{max}}$ (48, 56). However, $\dot{V}\text{O}_{2\text{max}}$ becomes markedly reduced if the same exercise is performed under conditions that cause a concomitant elevation of the skin temperatures, e.g., very high environmental temperatures or a moderately hot and humid environment (3, 36, 56, 62, 71). Under such circumstances, the impairments of aerobic capacity and exercise performance are related mainly to failure of the heart to maintain cardiac output and subsequently the delivery of oxygen to locomotive muscle.

Fig. 1. Time to complete a cycle ergometer sprint (−9.66 kJ) vs. vastus lateralis muscle temperature without warm-up (○), following hot showers (□), with muscle heating through diathermia (▲), and with warm-up via exercise (●). [From Asmussen and Bøje (4).]

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Compared with submaximal exercise where hyperthermia in itself did not impair muscle blood flow and where a widening of the arteriovenous difference for oxygen could compensate for the \( \approx 2 \) l/min reduction in leg blood flow observed with combined hyperthermia and dehydration, the hyperthermia-induced reduction in leg blood flow during maximal cycling is much larger and may approach 4–5 l/min (25). Although dehydration may develop during the heat stress period that precedes maximal exercise, the associated increase in arterial hemoglobin concentration and arterial oxygen content is not sufficient to compensate for the marked reduction in blood flow, and consequently muscle VO\(_2\) declines. In turn anaerobic metabolism is accelerated causing a faster decline in muscle ATP and creatine phosphate (CrP) levels and increased rates of muscle lactate and \( \text{H}^+ \) accumulation (25). The estimated oxygen deficit as well as muscle ATP, CrP, and lactate levels are similar at the point of exhaustion and it appears that the muscular mechanisms causing fatigue during maximal exercise in the heat are not different compared with control exercise and relates to inadequate oxygen delivery and homeostatic disturbances induced by anaerobic metabolism (25, 56). It is beyond the scope of the present review to discuss the fatigue mechanisms that are provoked by anaerobic metabolism (for review see Refs. 16, 37, 40), but it is likely that the faster decline in pH both directly and indirectly via disturbances in \( \text{K}^+ \), \( \text{Ca}^{2+} \), and phosphate homeostasis may impair the contractile properties of the skeletal muscles (16, 37).

**PERIPHERAL FATIGUE AND MUSCLE FUNCTION**

In contrast to maximal exercise, oxygen delivery remains adequate during submaximal exercise, and anaerobic metabolism is therefore not enhanced to levels that is associated with muscle fatigue. Furthermore, there is no evidence that exercise-induced hyperthermia, within the temperature limits observed in healthy subjects \([-40°C to 38°C] \) in trained subjects exercising to exhaustion, but with individual body core temperatures up to \([-41°C to 38°C] \) and muscle temperatures that are 0.5–1°C higher (30, 58) in itself will hamper the contractile function of the skeletal muscles. Thus, following prolonged exercise in the heat to exhaustion, both Nielsen et al. (50) and Nybo and Nielsen (58) observed unchanged force production during brief MVCs for...
both exercised and “nonexercised” muscle groups. Passive heating studies have confirmed these results (47, 77) and when electrical nerve stimulation is applied it becomes clear that the skeletal muscles are able to produce force that is similar following prolonged exercise with hyperthermia compared with exercise with a normal temperature response (58). However, as shown in Fig. 3, although the skeletal muscles are capable of producing similar force levels when they are electrically stimulated, the ability to sustain force production during prolonged voluntary contractions is markedly impaired by hyperthermia. In regard to the capacity of the muscles to produce power, a higher muscle temperature will increase the speed of the cross-bridge cycle and, consequently, power output during a single sprint increase (4). However, the ability to sustain power output for prolonged periods deteriorates and performance during repeated sprinting is also impaired by hyperthermia (Fig. 4). Thus force and power production appears to be unchanged or improved when the activation period is shorter than some seconds and the contractile function of the skeletal muscle does not seem to be impeded by hyperthermia per se. However, during prolonged or repeated efforts, motor performance becomes hampered due to the effects of hyperthermia on the function of other bodily systems (i.e., the cardiovascular and CNS).

In acclimatization studies where subjects exercise to voluntary exhaustion and are exposed to a heat stress that elevates the core and muscle temperatures to above 40°C for 10 consecutive days, they gradually improve performance (50, 53). This improvement in performance would seem unlikely if the high temperatures caused serious muscle damage. The possibility that high temperatures have a detrimental effect on mitochondrial function is often mentioned referring to the work by Brooks et al. (7) and Willis et al. (86) because they reported a 20% reduction in the ADP/oxygen ratio at 43°C compared with that at 37°C. Therefore, they suggested that high muscle temperatures might compromise the properties of the inner mitochondrial membrane and cause a nonspecific proton leak-age (7, 86). However, the transferability of the results from these in vitro measurements to in vivo situations is not clear. In humans exercising at submaximal work intensities, no differences in \( \dot{V}O_2 \) are observed over a wide range of core and muscle temperatures (−37°C to −41°C) (30, 58), and it appears that hyperthermia-induced exhaustion in exercising humans occurs before mitochondrial respiration is perturbed and probably before other functions of the muscle cell are jeopardized.

CENTRAL FATIGUE

The importance of central fatigue during exercise in the heat was experimentally supported by the data presented in Fig. 3 demonstrating that exercise-induced hyperthermia reduces voluntary activation during a sustained maximal knee extension. The maximal contractions were preceded by bicycle exercise at 60% of \( V_{O2\text{max}} \), which in the hyperthermic trial increased the core temperature to −40°C and exhausted the subjects after 50 min, whereas during the control trial the core temperature stabilized at −38°C and exercise was maintained for 1 h without exhausting the subjects. Although the hyperthermic exercise trial exhausted the subjects, it did not impair the ability of the knee extensors to generate force when electrical

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**Fig. 3.** force production (A), voluntary activation level (B), and rectified integrated surface electromyography (IEMG; C) from the vastus lateralis muscle during 2 min of sustained maximal knee extension during hyperthermia (hyper; core temperature of −40°C) and control (core temperature of 38°C). The subjects were instructed and verbally encouraged to make a maximal effort throughout the contraction, and electrical stimulation (EL) was superimposed every 30 s to assess the level of voluntary activation, which was calculated as voluntary force divided by the force elicited when EL was superimposed. Values are means ± SE for 8 subjects (error bars not included in A). % of max, Percentage of maximum. *All values in this period are significantly lower than control, \( P < 0.05 \). [From Nybo et al. (58).]
stimulation was superimposed, and voluntary force production was similar during the initial phase of the MVC. However, in the hyperthermic trial the subjects were unable to sustain the same activation, as during the control trial, and the voluntary force production as well as the rectified integrated surface electromyogram (EMG) from the vastus lateralis muscle became low. In addition, following a resembling bicycle protocol, force development during a sustained handgrip contraction followed a similar pattern of response as for the knee extensors, indicating that the attenuated ability to activate the skeletal muscles did not depend on whether the muscle group had been active or inactive during the preceding exercise bout (58). Conversely, hyperthermia did not affect maximal force development or central activation during brief maximal knee extensions (2-s duration) even if the MVCs were repeated 40 times and interspaced by only 3-s recovery (58). This indicates that although hyperthermia provokes central fatigue, the CNS regains the ability to activate the skeletal muscles within a short period of recovery (58). Also, if we compare the effect of hyperthermia with that of hypoglycemia on the development of fatigue during prolonged exercise and the activation pattern during a sustained MVC (cf. Refs. 55 and 58), it seems that both hyperthermia and hypoglycemia cause central fatigue. However, in both conditions, voluntary force production may be maintained for a brief period of time, whereas central activation becomes low if the contraction needs to be sustained for more than some seconds. Depletion of substrates and metabolic disturbances within the CNS and/or alterations in the release or synaptic levels of certain neurotransmitters are potential mechanisms underlying the decline in central activation during the sustained muscle contraction (54, 73). However, sensory feedback from the contracting muscles could also be a major factor influencing the pattern of CNS activation. Inhibitory feedback from muscle chemore- and metaboreceptors may be of minor importance for the activation level during the initial phase of isometric contractions, whereas it may inhibit motor activation when the contraction is sustained and muscle metabolites accumulate (1, 35). Also, heating will cause a decrease in time to peak twitch force as well as the half-relaxation time of the skeletal muscles. Consequently, hyperthermia may increase the firing frequency necessary to sustain maximal activation of the motor units and it becomes difficult or impossible for the central nervous system to maintain maximal force (47). In accordance with the notion that fatigue is composed of many factors, it appears that central activation becomes markedly impaired when hyperthermia is combined with inhibitory signals from the skeletal muscles, whereas inhibition from a high brain temperature (9) may be overridden providing inhibitory feedback from chemoreceptors is low.

Several studies indicate that there is an internal temperature above which animals as well as humans will not continue to exercise voluntarily (19, 30, 38, 50, 81). It seems clear that voluntary muscle activation is impaired by elevations of the core temperature and not the local muscle temperature (76), and the experiments by Caputa et al. (9) where brain and body core temperatures in exercising goats were separately manipulated (by changing the temperatures of implanted thermoelements) indicate that a high hypothalamic temperature is the main factor inhibiting motor activity. It has been proposed that the end-point core and brain temperature is “critical” and represents a definitive safety break against catastrophic heat injury (38, 50), as supported by the observation that trained subjects during repeated trials with different starting temperatures or rates of heat storage stop exercising at similar body core temperatures of ~40°C but after dissimilar exercise durations. However, the consistency of the core temperatures at voluntary exhaustion in laboratory experiments both in trained (30) and untrained subjects (10) may relate to the study designs, where low- to moderate-intensity exercise is combined with a large external (uncompensable) heat stress. Accordingly, other factors that may influence fatigue become of minor importance under such conditions, whereas the progressive inhibition of motor activation that arises simultaneously with the rise in brain and hypothalamic temperature becomes the dominant factor dictating the point of exhaustion. However, fatigue is complex and the body core temperature at exhaustion may be influenced by factors such as training status, exercise mode, intensity, and motivation; for example, differences in motivation between laboratory experiments and sports competitions combined with the influence of the subjects personality.
and training status could explain why untrained subjects during hot exercise conditions become exhausted at core temperatures between 38 and 39°C (10, 72). Whereas trained subjects may attain core temperatures as high as 41°C during sports competitions (64), although they as described above become exhausted, or unwilling to continue exercising, when their core temperature exceeds ~40°C in a laboratory setting (30, 58). Also, if the development of central fatigue is counteracted by enhancing the synaptic dopamine levels (83) or by caffeine administration (Nybo, unpublished observations) the end-point temperature may become ~0.5°C higher. Hyperthermia-induced central fatigue should accordingly not be considered as an all-or-none phenomenon that occurs only if the core temperature becomes critically high, but as a progressive inhibitory signal of the brain areas responsible for motor activation that together with other central influences, including feedback from the periphery provokes CNS fatigue (47). During exercise with constant power output, the central fatigue seems to emerge as a gradual increase in perceived exertion, which is accompanied by a gradual slowing of the electroencephalogram as the core temperature increases above ~38°C (60), whereas hyperthermia-induced fatigue will result in a reduction in power output during time trials (79, 83) and during exercise where subjects are instructed to adjust their power output to maintain a predefined perception of effort (78). Also, peak and average power output during repeated sprinting becomes reduced by hyperthermia (15), and it is noteworthy that the “performance pattern” during repeated sprinting resembles that observed for sustained isometric contractions (cf. Figs. 3 and 4), and that the impaired performance is accompanied by reduced and not enhanced accumulation of substances involved with peripheral fatigue such as plasma K⁺, H⁺, and muscle lactate (15). This indicates that fatigue is not caused by inadequate oxygen delivery or disturbances of muscle homeostasis, but rather by the direct temperature influence on the CNS. Although the evidence for central fatigue during repeated sprinting and prolonged work is circumstantial (15, 18, 33, 60, 63), it seems unlikely that hyperthermia influences voluntary motor activation markedly during isometric contractions but not at all dynamic exercise. In accordance, Martin et al. (39) report that exercise-induced hyperthermia also lowers voluntary drive to the skeletal muscles in an exercise protocol with repeated maximal isokinetic contractions.

Although, the central fatigue that arises with hyperthermia seems to relate primarily to inhibitory signals from thermoreceptors in the hypothalamus, it may be influenced by alteration in the cerebral metabolism and oxygen delivery as discussed by Secher et al. (73) and Nybo et al. (54, 61). In brief, hyperthermia results in hyperventilation, which lowers the arterial carbon dioxide tension and consequently also reduces the cerebral blood flow by as much as 20–25%. Also the increase in brain temperature implies that the global cerebral metabolic rate for oxygen increases due to the Van’t Hoff Q₁₀ effect on cerebral tissue energy turnover (8). A scenario where the cerebral oxygen uptake increases by ~7% and the global cerebral blood flow decreases by ~20% (57) will cause a lowering of the cerebral oxygenation level and a reduction in mitochondrial oxygen tension by 5–6 Torr (61). This may approach the limit of reduction in cerebral oxygen tension that is tolerated before the cerebral metabolism and motor function become affected (65). However, in vitro studies have shown that mitochondrial respiration is not deteriorated even at very low oxygen tensions (21, 22), and the observation that lactate spillover from the brain remains unchanged (57) also argues against the notion that oxygen delivery becomes inadequate during exercise with hyperthermia. This is so at least in a laboratory setting, where subjects seem to stop exercise within a safe limit before the cerebral perfusion becomes critically low, whereas during sport competitions they may push themselves beyond that limit (51).

Several hypotheses have connected central fatigue with alterations in the activity of different neurotransmitter systems with special attention to the influence that exercise may have on the synthesis and metabolism of serotonin [5-hydroxytryptamine; 5-HT (5, 12, 14, 49)]. However, it seems to simple to ascribe central fatigue to changes in the global cerebral level of one neurotransmitter as fatigue remains more complex (13, 43, 44). It is clear that several neurotransmitter systems are activated during exercise (42, 44) and that several of these systems affect the preoptic area and anterior hypothalamus, which is of major importance for thermoregulation. Inhibition of the preoptic area and anterior hypothalamus deteriorates thermoregulatory function in exercising rats (32), and inhibition of the serotonergic system via administration of the serotonin (5-HT₂C receptor) antagonist pizotifen increase the rectal temperature at rest and tend to induce a greater rate of core temperature increase during exercise in humans (74). However, 5-HT₂C receptor blockade does not influence exercise performance, plasma prolactin or cortisol. These parameters were also unchanged following administration of paroxetine, a selective 5-HT reuptake inhibitor, which in addition does not influence the core temperature response to exercise (41). Furthermore, the exercise capacity in hot environments is not affected by branched-chain amino acid supplementation (11, 84), although such supplementation has been proposed to benefit performance during exercise by reducing serotoninergic activity. In contrast, Mittleman et al. (46) observed that branched-chain amino acid supplementation extended time to exhaustion in both men and women exercising in a warm environment (34°C and ~40% relative humidity). However, it remains a concern that the exercise intensity was quite low in this study and that the subjects were not hyperthermic by the end of the exercise trials because their core temperatures remained below 38°C. Thus it is likely that exhaustion was related to other factors than hyperthermia-induced central fatigue. Although the rationale for the “serotonin-fatigue hypothesis” is clear and is supported by results from animal studies, the experimental evidence is not convincing in humans and it does not seem to be of importance for hyperthermia-induced fatigue (12, 54, 80).

There is an equal interest in the relation between dopaminergic activity and central fatigue (42, 51). Bridge et al. (6) indicate that subjects with a high activity may demonstrate a higher tolerance to exercise in the heat. Further support for an influence of dopaminergic activity was provided by Watson et al. (83), who investigated the effect of the dual dopamine and norepinephrine reuptake inhibitor, bupropion, on time trial performance in both temperate and warm conditions, and although they observed no influence of bupropion on performance in temperate conditions (time trial performance ~31 min in both placebo and bupropion trials), a significant improvement from ~40 min to ~36 min was apparent following administration of bupropion in the heat. Thus dopamine and...
norepinephrine reuptake inhibition may enable subjects to dampen or override inhibitory signal arising from the central nervous system to cease exercise due to hyperthermia (83). However, administration of bupropion may not only postpone fatigue and enhance exercise performance in the heat, it may also interfere with thermoregulatory functions as adrenergic and dopaminergic neurons are richly represented in the preoptic area and anterior hypothalamus. Therefore, dopamine and norepinephrine reuptake inhibition could increase the risk of overheating because it may allow the subjects to push themselves beyond or closer to the safety limit of internal body temperatures.

CONCLUSION

Although an increased temperature of the skeletal muscles benefits the ability to produce power during a single sprint, performance becomes markedly impaired when exercise in the heat results in whole body hyperthermia. During high-intensity exercise, the reduced performance is highly associated with failure of the cardiovascular system to maintain arterial oxygen delivery to the exercising muscles, whereas hyperthermia-induced fatigue during prolonged exercise originates mainly from perturbations of the brain’s ability to sustain sufficient activation of the skeletal muscles. The cerebral perfusion is reduced, but oxygen delivery to the brain does not appear to be critically low during laboratory experiments. Rather, the elevated brain temperature in itself seems to be the main factor affecting motor activation, but feedback from the skeletal muscles and activity of the dopaminergic system also appear to be of importance.

REFERENCES

Hyperthermia and Fatigue


