

Characteristics of hyperthermia-induced hyperventilation in humans

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ABSTRACT

In humans, hyperthermia leads to activation of a set of thermoregulatory responses that includes cutaneous vasodilation and sweating. Hyperthermia also increases ventilation in humans, as is observed in panting dogs, but the physiological significance and characteristics of the hyperventilatory response in humans remain unclear. The relative contribution of respiratory heat loss to total heat loss in a hot environment in humans is small, and this hyperventilation causes a concomitant reduction in arterial CO₂ pressure (hypocapnia), which can cause cerebral hypoperfusion. Consequently, hyperventilation in humans may not contribute to the maintenance of physiological homeostasis (i.e., thermoregulation). To gain some insight into the physiological significance of hyperthermia-induced hyperventilation in humans, in this review, we discuss 1) the mechanisms underlying hyperthermia-induced hyperventilation, 2) the factors modulating this response, and 3) the physiological consequences of the response.

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Introduction

In the evolution of thermoregulation, poikilothermic animals, whose body temperatures vary with the ambient temperature, came into existence first. Later, homeotherms, which can control their heat balance (i.e., heat production and dissipation) and thus body temperatures, appeared. The ways in which homeothermic animals dissipate heat differs greatly among species. For example, birds and mammals such as dogs dissipate heat by increasing their ventilation (panting). Other mammals such as goats, sheep, oxen, kangaroos and monkeys also pant, but in addition they possess sweat glands, enabling them to dissipate heat through evaporative heat loss. Camels living in the desert neither pant nor sweat until their body temperature becomes critical. Instead, they accumulate heat in their bodies during the daytime, when the ambient temperature is high, and dissipate the heat during the night, when the ambient temperature is low. Humans exhibit sweat function that is superior to that of other mammals, but they also increase their ventilation during heat stress (we will call this hyperthermia-induced hyperventilation throughout this

review). This response was first described by Haldane in 1905¹ (Fig. 1). He observed that in mines in which the air temperature (34.4°C) and humidity were high, hyperpnea became noticeable when the rectal temperature exceeded 38.9°C, and was distinctly noticeable at 39.4°C. Subsequent studies confirmed this hyperthermia-induced hyperventilation.^{2–8} The proposed mechanisms and the possible physiological significance of hyperthermia-induced hyperventilation in humans have been reviewed by White.⁹ However, the characteristics of the hyperventilatory response in humans, such as what factors modulate the hyperventilation, remain uncertain.

When exposed to heat stress, panting animals increase their respiratory frequency to more than 200 breaths/min while minimizing tidal volume.¹⁰ This greatly increases dead space ventilation with little change in alveolar ventilation, enabling panting animals to increase respiratory heat loss without changing blood gas partial pressure (O₂ and CO₂). However, greater increases in body temperature alter this pattern such that tidal volume increases with a reduction in respiratory frequency, resulting in an increase in

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EXPERIMENT NO. I.	
11.30 a.m.,	at surface. Rectum temperature, 100.2°; mouth temperature, 99.2°.
12.2 p.m.	Entered level and remained standing at place where air temperature was 94° dry and 93.6° wet. All clothing removed except boots and stockings, flannel drawers and canvas trousers.
12.15	Sweating profusely. Rectum, 101°; mouth, 99.8°. Took temperatures of two miners who had been in the end mending an air-pipe for nearly an hour, and were coming out to "cool off." In each the mouth temperature was 101.6°.
12.40	Rectum, 101.4°; mouth, 100.8°. No discomfort.
12.45	Urine, 101.5°.
1.0	Some throbbing of head.
1.7	Rectum, 101.6°; mouth, 101.5°.
1.12	Pulse (standing), 138. Walked slowly up and down the level till 1.20.
1.25	Rectum, 102.6°; mouth, 102°. Pulse (standing), 144. Marked throbbing. Breathing seems deeper, and there is a tendency to breathe through the mouth.
1.45	Rectum, 103.5°; mouth, 102.6°. Pulse (standing), 164; (sitting), 140. Respirations, 20; the breathing being both deeper and more frequent than usual. Much throbbing, and feeling of general discomfort.

Figure 1. Description of Haldane's experiment.¹ Temperatures are presented in degrees Fahrenheit [$^{\circ}\text{C} = 5/9 (^{\circ}\text{F} - 32)$]. Note the statement describing the increase in ventilation in a hot environment. Reproduced with permission from Cambridge University Press.

gas exchange in the lung and resultant effects on blood gas pressure (increases in O_2 and decreases in CO_2). Similar to the latter response, hyperthermia-induced hyperventilation in humans is accompanied by increases in alveolar ventilation and thus altered blood gas levels.^{5,7} No reduction in tidal volume is observed during heat stress in humans; instead, tidal volume reportedly changes little¹¹⁻¹⁴ or even increases.^{2,5,7,15} The resultant reduction in arterial CO_2 pressure (hypocapnia) ultimately causes a reduction in cerebral perfusion (see "**Consequences of hyperthermia-induced hyperventilation**"), the physiological significance of which remains unclear. To gain additional insight into this ventilatory response, we will review the characteristics of hyperthermia-induced hyperventilation in humans, focusing on 3 aspects of the response. First, we will discuss possible mechanisms underlying hyperthermia-induced hyperventilation in humans. We will then review the factors modulating hyperthermia-induced hyperventilation. Finally, we will review how hyperthermia-induced hyperventilation affects other physiological responses.

Mechanisms mediating hyperthermia-induced hyperventilation in humans

Because hyperthermia causes hyperventilation, temperature input should be an important factor causing

hyperthermia-induced hyperventilation in humans. The question then is, in what part of the body does temperature (skin, core or a combination of both) trigger hyperthermia-induced hyperventilation in humans? In ox, an increase in skin temperature evoke thermal tachypnea.¹⁶ In resting humans, however, immersion in hot (41°C) water up to the shoulder rapidly increases skin temperature, but this does not cause a sustained increase in minute ventilation until esophageal temperature (an index of body core temperature) reaches $\sim 38.5^{\circ}\text{C}$.¹⁵ Subsequent studies also confirmed that there is an esophageal temperature threshold for hyperventilation at ~ 37.8 ¹⁷ to 38.3°C ,¹⁸ and that this threshold varies substantially among subjects, as reflected by the standard deviation of $\sim 0.5^{\circ}\text{C}$. In addition, we found that in exercising humans minute ventilation increased linearly with increases in esophageal temperature and that this relationship was unaffected by skin temperatures ranging from 33 to 39°C .^{19,20} On the other hand, a study by Lucas *et al.*²¹ found that reducing skin temperature from 35.3 to 33.8°C through acute skin cooling decreased the ventilatory response during passive heating at rest without changing esophageal temperature. Thus, the effect of skin temperature on the ventilatory response to rising body core temperature may differ depending upon whether one is resting or exercising. More specifically, although body core temperature is a main factor

inducing hyperthermia-induced hyperventilation in both resting and exercising humans, skin temperature can have an effect on the ventilatory response only during hyperthermia at rest.

On the other hand, because invasive methods (e.g., direct temperature recording from brain) are difficult to apply to humans *in vivo*, we do not precisely know in which part of the body core temperature is important for hyperventilation in humans. Based on animal studies, it appears that brain temperature (i.e., spinal cord, hypothalamus and medulla oblongata) is important for hyperthermia-induced hyperventilation, as increases in its temperature robustly increase ventilation.²²⁻²⁵ In addition, carotid chemoreceptors are sensitive to temperature²⁶ and contribute to ventilatory regulation. To tease out the role of carotid chemoreceptors in hyperthermia-induced hyperventilation in humans, we performed hyperoxia tests (so called Dejours tests) during passive heating at rest, which demonstrated that hyperoxia reduced hyperthermia-induced hyperventilation by 30%.²⁷ This suggests that although changes in carotid body temperature may contribute to ventilatory responses during heat stress in resting humans, it may not be a major factor. It has also been shown that muscle (goats)²⁸ and intra-abdominal (rabbits)²⁹ temperatures contribute little to the increase in ventilation. It remains uncertain, however, how these temperatures affect ventilation in humans.

Modifying factors

The control of hyperthermia-induced hyperventilation in humans can be quantitatively characterized by evaluating the relationship between minute ventilation as the output response and body core (esophageal) temperature as thermal input.^{19,30} Similar analyses have been used to evaluate control of thermoregulatory heat loss through sweating and cutaneous vasodilation.³¹ This approach enables estimation of 1) the body core temperature threshold for the onset of hyperthermia-induced hyperventilation and 2) the sensitivity of the hyperventilation to rising body core temperature (the slope of body core temperature-minute ventilation relation). For instance, an elevated threshold would mean a reduction in the ventilatory response to the same body core temperature, whereas a lower threshold would mean an increase in the response. It has been established that the threshold

and sensitivity of 2 heat loss responses, sweating and cutaneous vasodilation, are influenced by exercise,^{32,33} exercise intensity,^{32,34,35} hypohydration,³⁶⁻³⁸ aerobic ability/training,³⁹ sex⁴⁰⁻⁴² and heat acclimation.^{43,44} We will focus on the ways these factors, which are well-known modulators of heat loss responses, influence hyperthermia-induced hyperventilation in humans. Their effects are summarized in Figure 2.

Exercise and its intensity

Although studies have shown that hyperthermia-induced hyperventilation can occur during both rest and exercise, the response patterns differ substantially. For example, Cabanac & White¹⁵ reported that during passive heating at rest, hyperthermia-induced hyperventilation occurs when body core (esophageal) temperature reaches a critical temperature, around 38.5°C (Fig. 3). Above this body core temperature threshold, minute ventilation reportedly increases at ~20–30 L/min per 1°C rise in body core temperature.^{15,17,18} During incremental exercise from rest to exhaustion, there is an esophageal temperature threshold for hyperthermia-induced hyperventilation at ~38°C.^{30,45} Importantly, incremental exercise alters not only body temperature but also metabolic rate, both of which can independently influence ventilation.

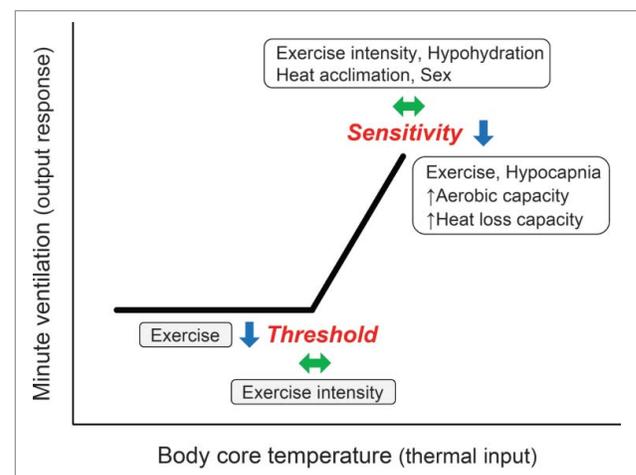


Figure 2. Modulators of human hyperthermia-induced hyperventilation characterized based on its threshold and sensitivity to increasing body core temperature. Note that exercise and heat acclimation reduce the threshold, and that exercise, hypocapnia, increased aerobic capacity and increased heat loss capacity reduce the sensitivity. By contrast, exercise intensity does not affect the threshold, and exercise intensity, hypohydration, heat acclimation and sex do not affect the sensitivity.

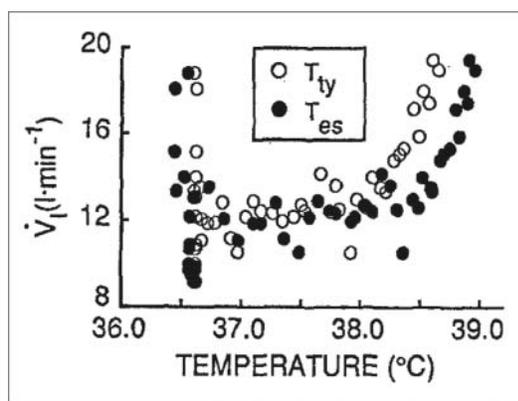


Figure 3. Body core (esophageal: T_{es} and tympanic: T_{ty}) temperature-dependent change in minute ventilation (\dot{V}_I) during passive heating at rest (41°C bath immersion). Note that \dot{V}_I increased at T_{es} of 38.5°C and T_{ty} of 38.1°C . Reprinted from Cabanac & White,¹⁵ with kind permission from Springer Science+Business Media.

Therefore, to distinguish the body core temperature effect on ventilation from metabolic effects, we employed moderate-intensity constant-workload exercise (50% of peak oxygen uptake) and found that minute ventilation increases linearly with increases in body core temperature, while oxygen uptake and blood lactate concentrations remain virtually constant.¹⁹ Earlier studies reported that ventilation increases at $\sim 5\text{--}12\text{ L/min}$ per 1°C rise in esophageal temperature

during moderate-intensity constant-workload exercise.^{17,19,46-48} In a subsequent study, we also found that during prolonged moderate exercise there is an esophageal temperature threshold for hyperthermia-induced hyperventilation at $\sim 37^\circ\text{C}$.²⁰ Because the threshold during exercise was at normothermia, it was only detected after the subjects' core temperature was lowered by cooling prior to the exercise. Fujii *et al.*¹⁷ and Tsuji *et al.*¹⁸ directly compared hyperthermia-induced hyperventilation between the same subjects at rest and during exercise. They demonstrated that the esophageal temperature threshold for hyperventilation is $\sim 1.5^\circ\text{C}$ lower and the sensitivity of hyperventilation to rising esophageal temperature is approximately 3 times lower during exercise than during rest (Fig. 4). These findings suggest that the characteristics of hyperthermia-induced hyperventilation, as reflected by differences in threshold and sensitivity, differ between passively heated and exercising subjects.

Thermoregulatory heat loss responses are reportedly affected by exercise intensity such that changes in exercise intensity from light to moderate increase the

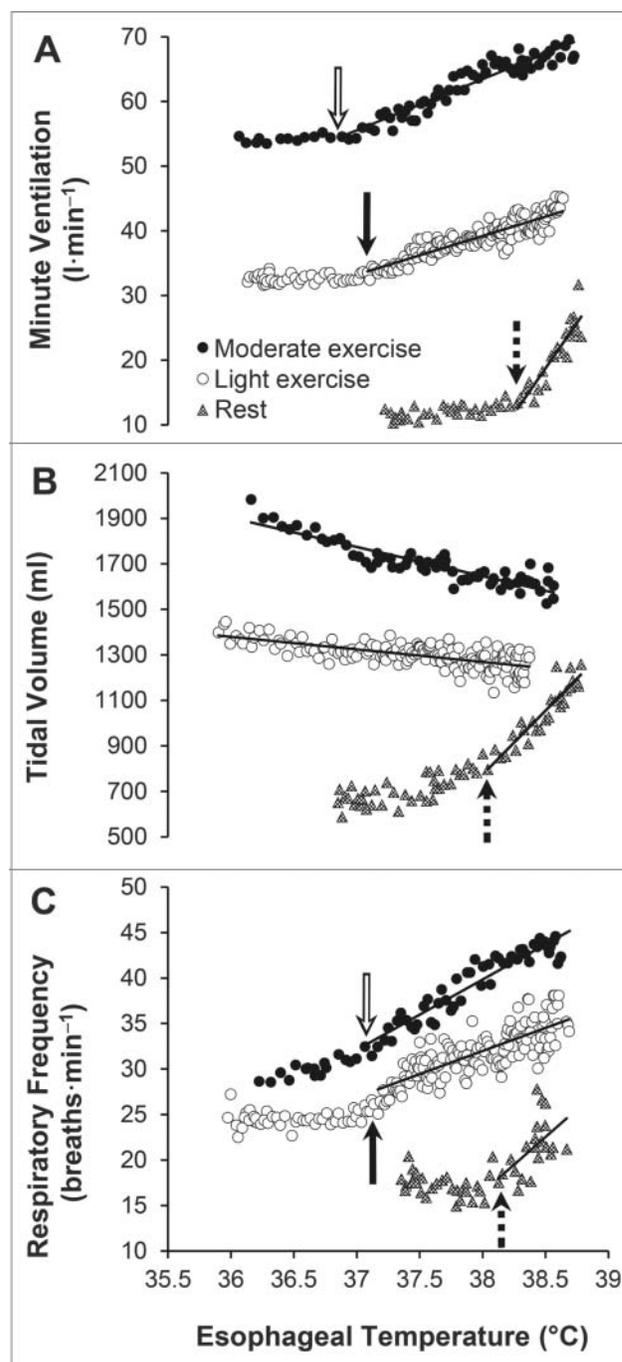


Figure 4. Body core (esophageal) temperature-dependent changes in minute ventilation (A), tidal volume (B) and respiratory frequency (C) during passive heating at rest (Rest), prolonged light exercise (25% of peak oxygen uptake) and moderate exercise (50% of peak oxygen uptake) in 9 subjects. Symbols show 30-s averaged data, and the symbols during exercise show data collected after 5 min of exercise. Arrows indicate the averaged thresholds. Note that the threshold and the sensitivity for minute ventilation were lower during passive heating than exercise, irrespective of exercise intensity, and that tidal volume has a threshold during passive heating but not during exercise (adapted from Tsuji *et al.*¹⁸).

sensitivity of the sweating response to rising body core temperature (esophageal temperature) without changing the body core temperature threshold.^{34,35} Similar increases in exercise intensity also elevate the temperature threshold for cutaneous vasodilation without changing sensitivity.^{34,49} On the other hand, we showed that hyperthermia-induced hyperventilation is unaffected by different exercise intensities, as neither the body core temperature threshold nor the sensitivity of hyperventilation to rising body core temperature differed between prolonged light and moderate exercise (25% and 50% of peak oxygen uptake, respectively).¹⁸ Whether exercise intensities outside that range also do not affect hyperventilatory responses is not yet known.

The respiratory patterns of hyperthermia-induced hyperventilation likely differ between passive heating at rest and exercise. The respiratory pattern during passive heating is not consistent among studies, as hyperthermia-induced hyperventilation sometimes reflects increases in only respiratory frequency,^{12,50,51} only tidal volume^{5,15,52} or both.^{1,28,17,18,53} The hyperventilation during hyperthermic exercise at a constant-workload was more consistent and reportedly due to an increase in respiratory frequency.^{17-20,47,54-57} By using the same subjects for both tests, we found that there are esophageal temperature thresholds for increases in both respiratory frequency and tidal volume during passive heating at rest, whereas there was a temperature threshold only for increases in respiratory frequency during prolonged light or moderate exercise; tidal volume decreased gradually with rising esophageal temperature (Fig. 4).^{17,18} Thus the respiratory pattern of hyperthermia-induced hyperventilation differs between resting and exercising subjects.

Hypohydration

Prolonged exercise or resting in the heat leads to profuse sweating. This can in turn lead to hypohydration accompanied with hypovolemia and hyperosmolality, which in humans may affect hyperthermia-induced hyperventilation. Senay & Christensen⁵⁸ investigated the effect of hypohydration on the ventilatory response in resting heated humans. In that study, subjects were exposed to 43°C for 12 h during rehydration and dehydration (body weight was progressively reduced by 5%). It was observed that both minute ventilation and plasma osmolality were increased in the

dehydration trial, but neither of those was increased in the rehydration trial. This suggests that increases in plasma osmolality can lead to increases in ventilation in resting heated humans. In that study, however, oral temperature was substantially higher during dehydration than rehydration (37.7 vs. 37.1°C). Fan *et al.*⁵¹ demonstrated that in resting humans, mild dehydration increases minute ventilation slightly. However, they also showed that baseline ventilation in normothermic conditions (before heating) was elevated, which means the higher ventilation associated with mild hypohydration could be simply due to a baseline shift, not enhanced hyperthermia-induced hyperventilation. Importantly, they did not evaluate the relationship between body core temperature and ventilation. In exercising humans, we showed that 2.5% dehydration does not influence the sensitivity of hyperventilation to rising esophageal temperature.⁴⁶ Whether hypohydration can affect body core temperature threshold for hyperventilation during exercise remains to be determined, however. In addition, it remains to be seen whether severe hypohydration (i.e., > 4% loss of body weight), which can reduce mean arterial pressure,⁵⁹ affects hyperthermia-induced hyperventilation. It has been shown that reductions in central blood volume and mean arterial pressure elicited by lower body negative pressure can increase ventilation under both normothermic^{60,61} and hyperthermic^{62,63} conditions. However, a reduction in mean arterial pressure of ~20 mmHg (induced by lower body negative pressure) is required to cause a noticeable increase in ventilation at presyncope.^{60,63} Importantly, even severe hypohydration (4.7% body weight loss) causes only a minimal reduction in mean arterial pressure during exercise in the heat (~5 mmHg).⁵⁹ Furthermore, another recent study showed that during passive heating at rest, increases in ventilation did not change, even when concomitant decreases in mean arterial pressure (~10 mmHg) were reversed by infusion of phenylephrine, a vasoconstrictor agent.⁶⁴ From these results, it appears that even when hypohydration is severe enough to reduce mean arterial pressure, it has little effect on ventilation.

Heat acclimation

It is well established that heat acclimation improves thermoregulatory cutaneous vasodilation and sweating such that cutaneous blood flow and sweat rate are

higher at a given body core temperature, but there is little understanding of the effect of heat acclimation on ventilatory responses during hyperthermia. For instance, Adam *et al.*⁶⁵ reported that heat acclimation achieved through hyperthermic exercise training consisting of 2 hours of exercise in a hot environment (~40–46°C) daily for 13 days resulted in a decrease in minute ventilation during exercise in the heat as compared to that prior to heat acclimation. This suggests heat acclimation attenuates hyperventilation during exercise in the heat. However, because they did not evaluate the relationship between body core temperature and minute ventilation, it remained uncertain whether the hyperventilatory response to rising body core temperature during exercise was affected by heat acclimation. Thereafter, Beaudin *et al.*⁶⁶ showed that passive heat acclimation achieved through repeated heat exposure for 10 days under resting conditions lowers body core temperature threshold for hyperventilation during incremental exercise from rest to exhaustion in parallel with a shift in the temperature threshold for sweating. The sensitivity of the hyperventilation to rising body core temperature did not change. Consistent with those findings, we observed that short-term exercise heat acclimation does not influence the sensitivity of hyperventilation to rising body core temperature during prolonged moderate exercise in the heat.⁵⁵ However, the effect of heat acclimation on body core temperature threshold for hyperventilation during the prolonged moderate exercise remains to be determined. In heated resting humans, we recently reported that body core temperature threshold for hyperventilation and sensitivity of the response during passive heating at rest are unaffected by heat acclimation achieved through short-term exercise training in the heat.⁶⁷ This suggests hyperthermia-induced hyperventilation at rest is unaffected by exercise-heat acclimation.

Concomitant hypocapnia

Hyperthermia-induced hyperventilation involving an increase in alveolar ventilation reduces arterial CO₂ pressure (hypocapnia). Because arterial CO₂ has significant effects on the control of breathing, it is plausible that the resultant hypocapnia reduces ventilatory drive, partially diminishing hyperthermia-induced hyperventilation. In that regard, earlier studies using passive heating at rest showed that temporary restoration of end-tidal CO₂ pressure to a normocapnic level

did not change,²⁷ increased^{52,68} or decreased⁶⁹ ventilation. There is thus no consensus on the effect of hypocapnia on hyperthermia-induced hyperventilation at rest. The reason(s) for the inconsistency remains unclear. By contrast, we reported that during prolonged moderate exercise in the heat, the sensitivity of hyperventilation to rising esophageal temperature was doubled by restoration of arterial CO₂ pressure to the normocapnic level, as compared to a condition in which arterial CO₂ pressure decreased due to hyperthermia-induced hyperventilation (19.8 vs. 8.9 L/min/°C)⁵⁶ (Fig. 5). This is consistent with results from studies in which hypocapnia attenuated the panting response during exercise in sheep.^{70,71} The reason why hypocapnia associated with hyperthermia-induced hyperventilation suppresses ventilation during exercise but not rest remains to be unknown, but one possible explanation is that exercise with heat stress lowers the arterial CO₂ pressure threshold for increases in ventilation, allowing hypocapnia to reduce ventilation. It is also likely that the different effects of hypocapnia are involved in the mechanism underpinning the 3 times lower sensitivity of hyperventilation to rising body core temperature during prolonged exercise than during rest.

Aerobic capacity

Increasing physical fitness (as reflected by increased peak oxygen uptake) through exercise training reportedly improves cutaneous vasodilation and sweating responses.^{44,72} Cross-sectional studies also showed that cutaneous vasodilation and sweating during exercise are greater in highly physically fit subjects than those who are less fit.^{73,74} We tested whether the magnitude of hyperthermia-induced hyperventilation during exercise is related to aerobic capacity using physically fit subjects who exhibited peak oxygen uptakes ranging widely from ~33 to 61 ml/kg/min. We found that the sensitivity of hyperventilation to rising esophageal temperature during exercise was negatively related to peak oxygen uptake.⁴⁷ This indicates that hyperthermia-induced hyperventilation is related to the aerobic capacity of the subject.

Heat dissipation capacity

We also reported that the sensitivity of hyperventilation to rising esophageal temperature during prolonged exercise was negatively related to the

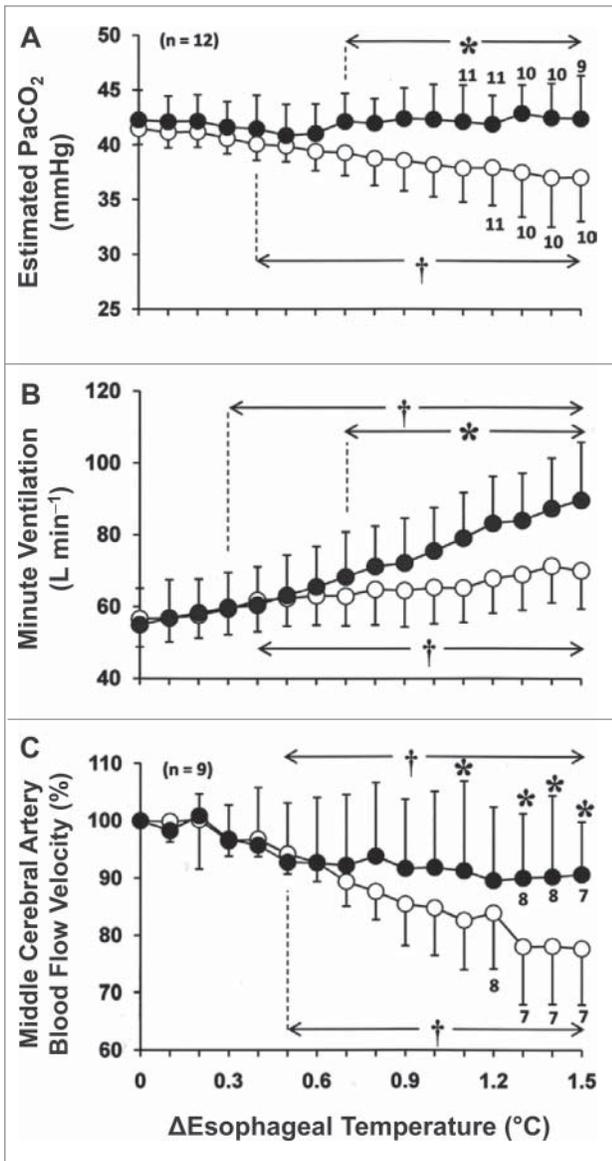


Figure 5. Body core (esophageal) temperature-dependent changes in estimated PaCO_2 ($\text{PaCO}_{2\text{estimated}}$; A), minute ventilation (B) and middle cerebral artery blood flow velocity (C) during prolonged moderate exercise (50% of peak oxygen uptake) in room air (open circles) and CO_2 -enriched air (filled circles). The CO_2 -enriched air was a mixture of room air and 100% CO_2 . We manually added 100% CO_2 to the inhaled air to maintain $\text{PaCO}_{2\text{estimated}}$ throughout the exercise. Changes in esophageal temperature (Δ) were measured from the start of inhalation of CO_2 -enriched air. The numbers adjacent to the symbols in A and C indicate the numbers of subjects still exercising at the corresponding temperature; the numbers in A also apply to B. * $P < 0.05$, room air vs. CO_2 -enriched air; † $P < 0.05$ vs. Δ esophageal temperature = 0°C . Note that when hyperthermic hyperventilation-induced hypocapnia was restored to normocapnic level, minute ventilation was increased and the cerebral blood flow velocity was largely restored to normocapnic level. Adapted from Hayashi *et al.*⁵⁶

cutaneous vasodilatory response to rising esophageal temperature.⁴⁷ This relationship does not necessarily indicate causality, though one could infer that breathing would tend to be augmented to a greater degree in subjects exhibiting less cutaneous vasodilation. Similar issues were addressed in studies examining hyperthermia-induced hyperventilation in individuals with a chronic disease impairing thermoregulatory heat loss. Total⁷⁵ reported that quadriplegic and ectodermal dysplastic men, who have an impaired sweating response, exhibited hyperventilation while resting in the heat at a level that did not cause hyperventilation in able-bodied subjects. Because Total⁷⁵ did not evaluate the relationship between body core temperature and ventilation, however, we cannot say whether the hyperventilation in those patient populations was due to altered sensitivity and/or body core temperature threshold for hyperthermia-induced hyperventilation, or simply to a greater increase in body core temperature resulting in greater ventilation without a change in threshold or sensitivity. In another study, Wilmore *et al.*⁷⁶ evaluated hyperthermia-induced hyperventilation in individuals with spinal-cord injuries. They showed that during passive heating at rest that caused mean body temperature (calculated based on esophageal and skin temperatures) to increase by 1.2 – 1.7°C , subjects with spinal-cord injuries, who are known to have impaired thermoregulatory responses, exhibited a detectable temperature threshold for hyperthermia-induced hyperventilation. By contrast, this heating was not enough to reveal the threshold in able-bodied subjects.⁷⁶ Thus hyperthermia-induced hyperventilation may be augmented in individuals with spinal-cord injury.

Sex

Because menstrual cycle modulates chemoreflex control of breathing, as evaluated based on the hypoxic and/or hypercapnic ventilatory response,⁷⁷⁻⁷⁹ it may also modulate hyperthermia-induced hyperventilation. We reported that, consistent with an earlier report,^{80,81} esophageal temperature at rest and during prolonged moderate exercise was higher during the luteal than follicular phase in young female subjects, and that minute ventilation was higher during the luteal phase in parallel with the temperature

changes.⁸² However, when evaluating the relationship between esophageal temperature and minute ventilation, we found that menstrual cycle phase does not modulate the sensitivity of hyperventilation to rising esophageal temperature during exercise.⁸² Instead, resting esophageal temperature was at a higher level during the luteal than follicular phase, and body core temperature threshold for hyperventilation may also be shifted to a higher level, though this requires direct testing.

Aging

Aging reportedly affects chemoreflex control of breathing such that it decreases the ventilatory response to hypoxia and hypercapnia at normothermia.⁸³⁻⁸⁵ On the other hand, there is little understanding of the effect of aging on ventilatory responses during hyperthermia. For instance, in a study of respiratory and cerebrovascular responses to passive heating at rest that elevated esophageal temperature by 0.5°C in young (29 years) and older (70 years) males, the increase in body core temperature induced no change in end-tidal CO₂ pressure in either subjects.⁸⁶ Furthermore, a preliminary study in which greater hyperthermia (1.4°C increase in esophageal temperature) was induced through passive exposure to 50°C ambient temperature showed that minute ventilation at the elevated body core temperature was similar between young (30 years, $n = 5$) and older (57 years, $n = 5$)⁸⁷ subjects. But although it appears that aging does not affect hyperthermia-induced hyperventilation during passive heating at rest in these few studies, further investigation is needed to clarify the effect of aging on hyperthermia-induced hyperventilation at rest and during exercise.

Consequences of hyperthermia-induced hyperventilation

Cerebral blood flow

It is generally accepted that cerebral blood flow is tightly regulated by arterial CO₂ pressure.⁸⁸⁻⁹⁰ It therefore seems plausible that hypocapnia associated with hyperthermia-induced hyperventilation causes a reduction in cerebral blood flow. In line with that, Nybo & Nielsen⁴⁸ found that hyperthermia occurring during prolonged exercise in the heat leads to decreases in middle cerebral artery blood flow velocity

(an index of anterior cerebral blood flow) with concomitant hyperventilation and hypocapnia. Moreover, Rasmussen *et al.*⁹¹ demonstrated that during prolonged exercise in the heat, relieving hypocapnia induced by hyperthermia-induced hyperventilation fully restored middle cerebral artery blood flow velocity, confirming the role of arterial CO₂ pressure in cerebral hypoperfusion that occurs during exercise in the heat. Similar results have also been reported by more recent studies involving exercise in the heat^{56,92} (Fig. 5).

Cerebral hypoperfusion also occurs during passive heating at rest.^{62,93} Examining changes in cerebral blood flow during hyperthermia and the underlying mechanisms is important because cerebral hypoperfusion during hyperthermia may be partially responsible for impaired orthostatic tolerance during hyperthermia,⁶² and could reportedly lead to increases in brain temperature,⁹⁴ as we will discuss later (see “Brain cooling effect?”). We found that by restoring arterial CO₂ pressure to the eucapnic level, middle cerebral artery blood flow velocity could be partially restored (30%).²⁷ This means although CO₂ contributes to cerebral hypoperfusion during passive heating at rest, a large portion of the reduction in flow is not attributable to CO₂-dependent mechanisms. Consistent with that idea, in a subsequent study, Brothers *et al.*⁹⁵ showed that CO₂ accounts for 50% of cerebral hypoperfusion during passive heating at rest. This reduction in flow may reflect sympathetic nerve-mediated cerebral vasoconstriction. Indeed, the role of cerebral sympathetic nerve activity in the modulation of cerebral blood flow was demonstrated in a human study showing that unilateral trigeminal ganglion stimulation reduced mean blood velocity in the middle cerebral artery at rest.⁹⁶ Moreover, hyperthermia is a potent activator of sympathetic nerve activity.⁹⁷ However, other studies found that arterial CO₂ pressure fully explains cerebral hypoperfusion during passive heating at rest.^{52,68} The reason underlying the between-study difference remains unclear.

Thermoregulatory heat loss response

Albert⁹⁸ and Robinson & King⁹⁹ found that voluntary hyperventilation-induced hypocapnia at rest in a hot environment reduced sweating and hand blood flow and increased rectal temperature as compared to normocapnia accompanied with hyperventilation.

Based on those findings, they suggested that hypocapnia induced by hyperthermia-induced hyperventilation could potentially affect thermoregulatory responses. A subsequent study found that increases in forearm skin blood flow during passive heating were diminished by voluntary hyperventilation-induced hypocapnia with a 0.6°C elevation in esophageal temperature, but not with a 1.0°C elevation.¹⁰⁰ Fujii *et al.*¹⁰¹ also reported that during exercise, hypocapnia induced by voluntary hyperventilation increased esophageal temperature threshold for cutaneous vasodilation and decreased sensitivity to rising esophageal temperature, whereas hypocapnia did not affect the sweating response, suggesting the cutaneous vasodilatory response to rising body core temperature during exercise is attenuated by hypocapnia. Whether hyperthermia-induced hyperventilation and the resultant hypocapnia diminish thermoregulatory heat loss responses during both resting and exercise remains to be determined, however.

Brain cooling effect?

Although heat loss from respiratory evaporation is relatively small in comparison to evaporative heat loss through sweating, if this respiratory evaporation selectively removed heat from the brain, the hyperthermia-induced hyperventilation could contribute to maintaining homeostasis through selective brain cooling.¹⁰²

This notion was first proposed by Cabanac *et al.*, who demonstrating that in heated resting¹⁰³ and exercising¹⁰⁴ humans, face fanning reduced tympanic temperature, which is thought to be an index of brain temperature. In addition, in postoperative neurosurgical patients, intense breathing through nose during mild passive warming reduced the temperature of the cribriform plate, near the base of the brain.¹⁰⁵ This suggests that increasing ventilation can reduce brain temperature. On the other hand, hyperthermia-induced hyperventilation can reduce cerebral perfusion, as mentioned above, which can in turn diminish heat removal and thus increase brain temperature.⁹⁴ It therefore remains debatable whether hyperthermia-induced hyperventilation is functionally important for controlling brain temperature during heat stress. More discussion of human cerebral brain cooling is found elsewhere¹⁰².

Summary and conclusion

Schematic overview of hyperthermia-induced hyperventilation in humans and its effect on physiological responses is presented in Figure 6. In summary, during passive heating at rest and prolonged exercise in the heat, elevation of body core temperature leads to increased ventilation independently of metabolic factors, resulting in a reduction in arterial CO_2 pressure (hypocapnia). The hyperthermia-induced

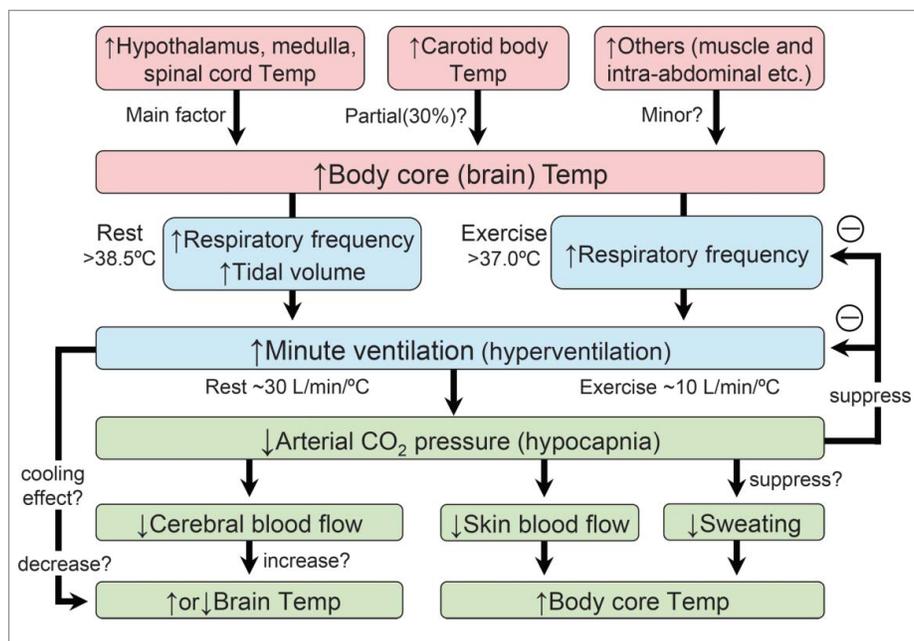


Figure 6. Schematic representation of the effects of hyperthermia-induced hyperventilation on physiological responses in humans.

hyperventilation is induced mainly by an increase in body core temperature in both resting and exercising humans. Increased temperatures in the hypothalamus, medulla oblongata and spinal cord are likely key factors driving hyperthermia-induced hyperventilation, though increasing the temperature of the carotid body chemoreceptors also contributes. The effects of increased muscle and intra-abdominal temperatures on ventilatory responses remain unknown in humans.

Hyperthermia-induced hyperventilation differs depending upon whether the subject is at rest or exercising. During passive heating at rest, hyperventilation is initiated when body core (esophageal) temperature reaches a critical threshold of $\sim 38.5^{\circ}\text{C}$, whereas the temperature threshold during prolonged submaximal exercise is $\sim 37^{\circ}\text{C}$. In addition, the degree to which hyperthermia-induced hyperventilation is reflected by the sensitivity of hyperventilation to rising body core temperature is 3 times smaller during exercise than at rest (~ 10 vs. ~ 30 L/min/ $^{\circ}\text{C}$), irrespective of whether the exercise intensity is light or moderate. The lower sensitivity of hyperventilation during exercise is attributable to the finding that hyperventilation-induced hypocapnia reduces sensitivity via central chemoreceptors during exercise. The sensitivity of hyperventilation to rising body core temperature during exercise is unaffected by hypohydration, menstrual cycle or heat acclimation achieved through exercise training in the heat. This means the control of hyperthermia-induced hyperventilation during exercise is likely robust, and differs from the control of sweating and cutaneous vasodilation. On the other hand, the sensitivity of ventilation is likely related to aerobic capacity, as there is a negative relationship between the sensitivity of hyperventilation to rising body core temperature and peak oxygen uptake.

It has been suggested that hyperthermia-induced hyperventilation contributes to cooling the brain in humans as in animals, but hyperventilation-induced hypocapnia reportedly leads to cerebral hypoperfusion, which can reduce heat removal from the brain, leading to increases in brain temperature. The physiological significance of hyperthermia-induced hyperventilation for selective cooling of brain in humans remains unclear. It also remains unclear whether hyperventilation-induced changes in arterial CO_2 pressure fully accounts for the cerebral hypoperfusion during passive heating, though it appears that hypoperfusion is mainly due to hyperventilation-induced

hypocapnia during prolonged exercise in the heat. Finally, hyperthermia-induced hyperventilation may affect other thermoregulatory heat loss responses, most notably cutaneous vasodilation, through hyperventilation-induced hypocapnia.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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About the authors

This Japanese research group has focused on human respiratory, thermal and cardiovascular regulation during acute and chronic (i.e., heat acclimation) heat stress. The group has revealed the characteristics and mechanisms of hyperthermia-induced hyperventilation and concomitant cerebral hypoperfusion experienced by exercising and resting humans in a hot environment. These findings provide insight into potential interventions aimed at preventing heat-related illness.



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