Ventilatory response to increasing body temperature: Characteristics and effect on central fatigue

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Abstract More than a hundred years ago, it was first reported that increases in body temperature stimulate minute ventilation. Since then, the characteristics, mechanisms and physiological meaning of this ventilatory response to increasing body temperature, so-called hyperthermia-induced hyperventilation, have gradually been uncovered. For example, it is now known that hyperthermia-induced hyperventilation has a core temperature threshold, like heat-dissipating responses (sweating and cutaneous vasodilation); but several factors affecting heat-dissipating responses do not influence the ventilatory response to increasing body temperature. On the other hand, evidence from several studies suggests there may be some relation between hyperthermia-induced hyperventilation and heat-dissipating responses. In addition, more recent evidence indicates that hyperthermia-induced hyperventilation may be related to central fatigue, which is considered to be one of the reasons exercise performance is diminished in heat. In fact, it has been suggested that hyperthermia-induced hyperventilation causes cerebral blood perfusion to be reduced, which decreases cerebral oxygenation and heat removal. This review presents an overview of the characteristics of the ventilatory response to increasing body temperature and its effect on central fatigue.

Keywords: hyperthermia, heat stress, thermoregulation, hyperpnea, panting

Introduction

In 1905, Haldane\(^1\) reported that when air temperature is high, body temperature, heart rate and respiration all increase. This suggested that a hot environment causes hyperventilation – i.e., increases in body temperature stimulate ventilation. To our knowledge, that was the first study examining the ventilatory response to increasing body temperature in humans, so-called hyperthermia-induced hyperventilation. Thereafter, research on the subject continued, and the characteristics of hyperthermia-induced hyperventilation, its mechanism and physiological meaning are gradually being elucidated. At present, there are two hypotheses as to the function of hyperthermia-induced hyperventilation in humans. One is that it acts to selectively cool the brain, while the other is that it causes central fatigue\(^2\). In recent years, we have been investigating the relationship between body temperature and ventilatory responses. This review focuses on the characteristics of hyperthermia-induced hyperventilation and its effect on central fatigue.

Characteristics of hyperthermia-induced hyperventilation

Threshold and sensitivity. In subjects at rest and during prolonged exercise, ventilation increases linearly with increasing body temperature (Fig. 1A, B). However, there are several ways in which the increases in ventilation seen in resting subjects differ from those seen during exercise. At rest, ventilation does not increase until esophageal temperature (Tes) exceeds 38.0-38.5 °C\(^4\)\(^-\)\(^6\). Above this Tes threshold, minute ventilation (V\(_E\)), tidal volume and respiratory frequency all increase in proportion to the increase in Tes\(^5\)\(^,\)\(^6\). Above this Tes threshold, minute ventilation (V\(_E\)), tidal volume and respiratory frequency all increase in proportion to the increase in Tes\(^5\)\(^,\)\(^6\). On the other hand, White and Cabanac\(^7\) reported that during incremental exercise, there is a core temperature threshold for hyperventilation around a tympanic temperature of 37.0-37.7 °C or a Tes of 37.5-37.9 °C, while Beaudin et al.\(^8\) and Sancheti and White\(^9\) reported the Tes threshold for hyperventilation during incremental exercise to be around 37.1-38.2 °C. In addition, after pre-cooling subjects in cold water (18°C) to decrease body temperature enough to cause a 1°C drop in Tes, Tsuji et al.\(^10\) found that there is a Tes threshold for hyperventilation around 37°C during prolonged steady-state light and moderate intensity exercise (25% and 50% of peak oxygen uptake [V\(_{\text{O}2\text{peak}}\)], respectively). Above this threshold, V\(_E\) and respiratory frequency increased in proportion to the increase in Tes\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^10\) (Fig. 2), though no increases in tidal volume were seen. It thus appears that the range within which the core temperature threshold for hyperventilation during exercise can fall is somewhat wide. Nonetheless, in all cases, the core temperature threshold
Table 1. Summary of thresholds and slopes of hyperthermia-induced hyperventilation.

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>n</th>
<th>Exercise intensity</th>
<th>Rest Threshold (°C)</th>
<th>Exercise Threshold (°C)</th>
<th>Sensitivity (1 min⁻¹ °C⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaudin et al. (2009)⁸</td>
<td>8</td>
<td>Incremental exercise (heat acclimation)</td>
<td>38.1 (Tₚ)</td>
<td>37.9 - 38.2 (Tₑ)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>(control)</td>
<td>38.5 (Tₑ)</td>
<td>37.1 - 37.3 (Tₑ)</td>
<td>-</td>
</tr>
<tr>
<td>Cabanac &amp; White (1995)⁹</td>
<td>7</td>
<td>-</td>
<td>38.1 (Tₚ)</td>
<td>37.8 (Tₑ)</td>
<td>-</td>
</tr>
<tr>
<td>Fujii et al. (2008)⁵</td>
<td>19</td>
<td>50%VO₂peak</td>
<td>37.8 (Tₑ)</td>
<td>26.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Fujii et al. (2008)¹¹</td>
<td>13</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>8.8 (control)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>(heat acclimation)</td>
<td>-</td>
<td>-</td>
<td>7.7 - 8.0</td>
</tr>
<tr>
<td>Fujii et al. (2012)¹²</td>
<td>10</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>7.0 - 8.2</td>
</tr>
<tr>
<td>Hayashi et al. (2006)³</td>
<td>13</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>5.5 - 6.1</td>
</tr>
<tr>
<td>Hayashi et al. (2009)¹³</td>
<td>18</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>7.2</td>
</tr>
<tr>
<td>Hayashi et al. (2011)¹⁴</td>
<td>13</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>8.9 (room air)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>(heat acclimation)</td>
<td>-</td>
<td>-</td>
<td>19.8 (CO₂-enriched air)</td>
</tr>
<tr>
<td>Hayashi et al. (2012)¹⁵</td>
<td>10</td>
<td>50%VO₂peak</td>
<td>-</td>
<td>-</td>
<td>7.7 (follicular phase)</td>
</tr>
<tr>
<td>Sancheti &amp; White (2006)⁹</td>
<td>7</td>
<td>Incremental exercise</td>
<td>37.1 (Tₚ)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tsuji et al. (2012)⁶</td>
<td>12</td>
<td>25 and 50%VO₂peak</td>
<td>38.3 (Tₑ)</td>
<td>37.1 (Tₑ) (precooling)</td>
<td>10.4 (25%VO₂peak) (25%VO₂peak)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>50%VO₂peak</td>
<td>36.9 (Tₑ)</td>
<td>36.9 (Tₑ)</td>
<td>8.7 (50%VO₂peak)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Incremental exercise</td>
<td>37.0 - 37.7 (Tₑ)</td>
<td>37.1 (Tₑ) (precooling)</td>
<td>10.6 (precooling)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Incremental exercise</td>
<td>37.5 - 37.9 (Tₑ)</td>
<td>37.1 (Tₑ) (precooling)</td>
<td>10.6 (precooling)</td>
</tr>
</tbody>
</table>

Tₚ and Tₑ represent tympanic and esophageal temperature. n = sample size.
for hyperventilation was lower in subjects during exercise than at rest.

We also evaluated the ventilatory sensitivity to increasing body temperature (slope of the regression line between $V_E$ and $T_e$) and found that the sensitivity is higher at rest than during exercise, and that the sensitivity is not influenced by exercise intensity (25% vs. 50% of VO$_{2peak}$). Table 1 summarizes the findings for threshold and sensitivity of hyperthermia-induced hyperventilation.

Hyperventilation induced by increases in body temperature leads to excessive elimination of CO$_2$ and a decrease of arterial PCO$_2$ (PaCO$_2$) both at rest and during prolonged exercise (Fig. 1C). Given that changes in PaCO$_2$ influence $V_E$ via chemoreceptors, and that there is a positive linear relationship between $V_E$ and PaCO$_2$, it seems likely that this hypocapnia suppresses the increase in $V_E$. To investigate the effect of hypocapnia on hyperthermia-induced hyperventilation, we examined the ventilatory response to increasing body temperature in subjects breathing CO$_2$-enriched air to maintain PaCO$_2$ at the eucapnic level at rest and during exercise. We found that $V_E$ is unchanged at rest, but that during prolonged exercise at 50% of VO$_{2peak}$, the ventilatory sensitivity to increasing body temperature is 2-3 times greater in CO$_2$-enriched air than in room air (hypocapnic condition) (Table 1), and that this augmentation is caused by increases in tidal volume and respiratory frequency. We suggested that the reason $V_E$ did not change was that the resting PaCO$_2$ level was lower than the PaCO$_2$ threshold for an increase in $V_E$, which is reportedly 40-50 mmHg. However, the eucapnic level during exercise was nearly the same as at rest, and $V_E$ was augmented by breathing CO$_2$-enriched air during exercise. We therefore suggested the PaCO$_2$ threshold may be lower during exercise than at rest. Nonetheless, these observations suggest that increases in body temperature strongly stimulate $V_E$ dur-
ing prolonged exercise, and that the characteristics of hyperthermia-induced hyperventilation differ somewhat, depending on whether a subject is resting or exercising.

Comparison of hyperthermia-induced hyperventilation with thermoregulatory response. Like hyperthermia-induced hyperventilation, heat-dissipating responses (e.g., cutaneous vasodilation and sweating) have a core temperature threshold. Moreover, heat-dissipating responses are also influenced by skin temperature – i.e., higher skin temperatures decrease the core temperature threshold for cutaneous vasodilation and sweating\(^21\). By contrast, our findings suggest that changes in skin temperature do not influence ventilation during light intensity exercise. And, whereas hypohydration attenuates temperature do not influence ventilation during light intensity exercise\(^3\). Similarly, Greiner et al.\(^2\) reported that changes in skin temperature do not influence ventilation during light intensity exercise. And, whereas hypohydration attenuates the cutaneous vasodilatory response and sweating\(^24\), we found that hypohydration (2.5% of body weight) does not influence hyperthermia-induced hyperventilation, though the Tes threshold for cutaneous vasodilation is increased, and the sensitivity of cutaneous vasodilatation is reduced\(^1\). Furthermore, when Fujii et al.\(^3\) examined the effect of exercise-heat acclimation on the ventilatory response to increasing body temperature and the cutaneous vasodilatory response, they found that 6 days of exercise-heat acclimation lowers the Tes threshold for cutaneous vasodilatation and augments the sensitivity of cutaneous vasodilatation, but has no effect on hyperthermia-induced hyperventilation. Finally, over the course of the menstrual cycle, the core temperature threshold for cutaneous vasodilatation and sweating is higher during the luteal phase than the follicular phase\(^26,27\). When we examined the effect of the menstrual cycle phase on the ventilatory response to increasing body temperature during prolonged exercise, we found that \(\dot{V}E\) is higher in the luteal phase than the follicular phase during mild hyperthermia (\(\text{T}_{\text{es}} \approx 38^\circ\text{C}\)), but menstrual cycle phase does not influence the slope or intercept of the regression line relating \(\dot{V}E\) to \(\text{T}_{\text{es}}\).\(^5\) Collectively, these findings indicate that the characteristics of hyperthermia-induced hyperventilation differ from those of heat-dissipating responses.

Nonetheless, several studies have suggested that hyperthermia-induced hyperventilation may be in some way connected to heat-dissipating responses. Wilsmore et al.\(^26\) compared the ventilatory responses to increasing body temperature in subjects with and without spinal cord injury, and reported that the rate at which breathing frequency increases with rising body temperature in subjects with a spinal cord injury (C4-L5) is more than twice that of able bodied subjects. In addition, Totel\(^29\) reported that ectodermal dysplasic subjects and quadriplegic subjects (C5-8) with impaired ability to sweat show greater increases in \(\dot{V}E\) and respiratory frequency during heating at rest. It is noteworthy that primates with stronger sweating responses show weaker ventilatory responses to increases in body temperature (i.e., thermal hyperpnea) in the heat\(^20\), and that humans exhibit the strongest sweating response during heat stress and the smallest thermal hyperpnea. It thus appears that the ventilatory response to increasing body temperature is augmented to some degree in compensation for lower heat dissipating capacity. When we examined relationships among the ventilatory sensitivity to increasing body temperature, \(\dot{V}O_{\text{peak}}\) and the cutaneous vasodilatory response, we found that ventilatory sensitivity to increasing body temperature has a significant negative relationship with \(\dot{V}O_{\text{peak}}\) and the sensitivity of cutaneous vasodilatory response (Fig. 3)\(^3\), which is consistent with the compensation hypothesis. On the other hand, Fujii et al.\(^31\) recently examined the effect of voluntary hypocapnic hyperventilation on heat-dissipating responses and reported that hypocapnia increases the Tes threshold for cutaneous vasodilation and reduces the sensitivity of the cutaneous vasodilatory response. Because hyperthermia-induced hyperventilation causes hypocapnia, it is plausible that the greater ventilatory sensitivity to increasing body temperature causes a greater drop in \(\text{PaCO}_2\). The results from Fujii et al.\(^31\) may therefore explain, in part, the negative relationship between ventilatory sensitivity to increasing body temperature and the cutaneous vasodilatory response.

**Mechanism of hyperthermia-induced hyperventilation**

The mechanism underlying hyperthermia-induced hyperventilation in humans is not fully understood. However, it is likely that a rise in the temperature of the medulla oblongata stimulates ventilation. Chai and Lin\(^32\) observed that heating the spinal cord and medulla oblongata induces hyperpnea, and that cooling them slows respiration. Further, Tryba and Ramirez\(^33,34\) reported that a rise in the temperature of the ventral respiratory group, in medullary brain slices from mice, increases the activity...
of the ventral respiratory group. It is also likely that chemoreceptors influence hyperthermia-induced hyperventilation. It is known, for example, that central and peripheral chemosensitivities increase with increases in body temperature\cite{43, 44}. In addition, when Fujii et al.\cite{17} examined the effect of peripheral chemoreflexes on hyperthermic hyperventilation in passively-heated humans, they found that breathing 100% O\textsubscript{2} reduces \(V_E\), and that the magnitude of the reduction gradually increases with rising \(T_{es}\). This suggests that chemoreceptor ventilatory O\textsubscript{2} drive contributes to hyperthermia-induced hyperventilation.

As mentioned, hyperthermia-induced hyperventilation causes hypocapnia, which, in turn, can cause a reduction in cerebral blood flow (see below). Recently, Ogoh et al.\cite{42} suggested that the reduced cerebral blood flow may reduce the rate of CO\textsubscript{2} elimination from the brain, thereby stimulating ventilation via the respiratory chemoreflex. It was further suggested that reductions in blood pH caused by increases in blood temperature\cite{38} and increases in noradrenalin levels caused by hyperthermia-induced stimulation of sympathetic activity\cite{39, 40} lead to increases in peripheral chemoreceptor activity. More recently, Fujii et al.\cite{41} reported that there is a negative relationship between changes in arterial blood pressure and changes in \(V_E\) elicited by passive heating. Because baroreceptor unloading reportedly increases ventilation in resting normothermic dogs\cite{45}, and the increases in plasma angiotensin II levels caused by reductions in blood pressure also increase ventilation in resting normothermic dogs\cite{43, 44}, they suggested that the reduction in arterial blood pressure seen during hyperthermia contributes to the increase in \(V_E\).

During exercise, output from central command and input from muscle mechanoreceptors and metaboreceptors via group III and IV muscle afferents also modulate \(V_E\)\cite{46-48}, and it is thought these factors could contribute to hyperthermia-induced hyperventilation. Taking the rating of perceived exertion (RPE) as an index of central command, it appears that the signal from central command is enhanced by a rise in body temperature\cite{4, 10, 18-20}, and that the increase in the signaling is induced by central fatigue caused by hyperthermia (see below). Furthermore, the activities of group III and IV muscle afferents are apparently increased by hyperthermia\cite{51, 52}. Although these factors are all thought to be involved in hyperthermia-induced hyperventilation, the extent to which they are involved remains unclear.

**Effect of hyperthermia-induced hyperventilation on central fatigue**

It is well known that a high ambient temperature impairs one’s ability to perform endurance exercise. And it has been hypothesized that one of the factors influencing exercise performance in heat is an increase in brain temperature. By independently manipulating hypothalamic and trunk temperatures in goats, Caputa et al.\cite{53} clearly showed that running speed is reduced by increases in hypothalamic temperature, even when trunk temperature is held constant. Moreover, when Nybo and Nielsen\cite{54} evaluated sustained maximal voluntary contraction (MVC) over a 2-min period in hyperthermic (\(T_{es} = 40^\circ\text{C}\)) and normothermic (\(T_{es} = 38^\circ\text{C}\)) humans, they found that the reduction in MVC over time is larger in hyperthermia than normothermia. Nonetheless, the sustained maximal force elicited by electrical stimulation did not differ between trials, which suggests the reduction is caused by a central factor. Morrison et al.\cite{55} examined the effect of passive heating (from 37.4°C to 39.4°C of rectal temperature) and rapid skin cooling during hyperthermia on a 10-s MVC knee extension. They showed that a 2°C increase in rectal temperature reduces MVC by 13%, and that rapid skin cooling during hyperthermia does not restore MVC, suggesting core temperature elevation is the primary factor contributing to the reduction in MVC. Consistent with this idea, Nielsen et al.\cite{56} reported that brain activity decreases in proportion to rising \(T_{es}\) during exercise in the heat.

During prolonged exercise in the heat, \(V_E\) increases in proportion to rising body temperature, and it has been suggested that this hyperthermia-induced hyperventilation is related to reduced brain activity. Rasmussen et al.\cite{57} estimated the cerebral mitochondrial oxygen tension as an index of cerebral oxygenation during exercise in heat, and reported that both cerebral blood flow and cerebral mitochondrial oxygen tension are lower in hyperthermic than normothermic subjects. Because cerebral blood flow is strongly influenced by PaCO\textsubscript{2}\textsuperscript{14, 16, 18, 57, 58}, reduced cerebral blood flow most likely reflects the hypocapnia caused by hyperthermia-induced hyperventilation\textsuperscript{14, 16, 18}. Rasmussen et al.\cite{59} suggested reduced cerebral oxygenation is caused by the combination of reduced cerebral blood flow and an increased cerebral metabolic rate for oxygen, and they showed that RPE increased with decreasing cerebral mitochondrial oxygen tension. Although it may be difficult to see RPE as an index of central fatigue, RPE has a significant linear relationship with changes in brain activity\textsuperscript{59}. These data therefore suggest that reductions in cerebral blood flow caused by hyperthermic hyperventilation lead to decreases in cerebral oxygenation, resulting in reduced brain activity.

It has also been suggested that hyperthermia-induced hyperventilation reinforces the increase in brain temperature. Nybo et al.\cite{59} measured esophageal, tympanic, arterial and jugular venous temperatures during prolonged exercise under thermoneutral and hyperthermic conditions, and observed that jugular venous temperature (an index of average brain temperature) was higher than the other temperatures measured during the experiment, and that the jugular venous temperature was consistently higher than the arterial temperature (an index of core temperature), with or without hyperthermia. Nybo et al.\cite{59} also found that cerebral blood flow and heat removal via jugular
venous blood were both reduced by hyperthermia, resulting in increased storage of heat in the brain. These results suggest that hyperthermia-induced hyperventilation does not cool the brain; instead, it may reinforce the increase in brain temperature.

Conclusions

An increase in body temperature is a potent stimulus for increasing V\textsubscript{E}. During passive heating or exercising in heat, the body temperature increases, and V\textsubscript{E} increases along with it. There is a body core temperature threshold for hyperventilation, above which V\textsubscript{E} increases in proportion to the increase in body core temperature. The characteristics of hyperthermia-induced hyperventilation are different from those of heat-dissipating responses, although it may be that hyperthermia-induced hyperventilation has some connection to heat dissipation. A clear difference from thermal panting in animals is that hyperthermia-induced hyperventilation in humans causes a reduction in PaCO\textsubscript{2} that is proportional to the increase in V\textsubscript{E}. Consequently, cerebral perfusion decreases, which reduces cerebral oxygenation and reinforces the increase in brain temperature. It is suggested that these changes in brain conditions lead to central fatigue during hyperthermia.

Conflict of Interests

The author declare that there is no conflict of interests regarding the publication of this article.

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