The effects of hyperthermia and hypoxia on ventilation during low intensity steady-state exercise

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Running Head: “Core Temperature, Hypoxia and Ventilation”

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Abstract

This study assessed if the elevated sensitivity of ventilation to hypoxia during exercise is accounted for by an elevation of esophageal temperature (T_es). Eleven males volunteered for 2 exercise sessions on an underwater, head-out cycle ergometer at a steady-state rate of oxygen consumption (\( \dot{V}O_2 \)) of \(~0.87\ \text{L}\cdot\text{min}^{-1}\) (SD 0.07). In one exercise session 31.5°C (1.4) water held T_es at a normothermic level of \(~37.1°C\) and in the other exercise session water at 38.2°C (0.1) water maintained a hyperthermic T_es of \(~38.5°C\). Following a 30-min rest and 20-min warm-up, exercising participants inhaled air for 10 min (Euoxia 1 (E1)), an isocapnic hypoxic gas mixture with 12 % O_2 in N_2 (H1) for the next 10 min and air again (Euoxia 2 (E2)) for the last 10 min. A significant increase in \( \dot{V}_E \) during all hyperthermia conditions (0.01<\(P\) < 0.048) was evident, however, during hyperthermic hypoxia there was a disproportionate and significant (\(P = 0.017\)) increase in \( \dot{V}_E \) relative to normothermic hypoxia. This was the main explanation for a significant esophageal temperature and gas type interaction (\(P = 0.012\)) for \( \dot{V}_E \). Significant effects of hyperthermia, isocapnic hypoxic and their positive interaction remained evident after removing the influence of \( \dot{V}O_2 \) on \( \dot{V}_E \). Serum lactate and potassium concentrations, as well as hemoglobin oxygen saturation, were each not significantly different between normothermia and hyperthermic hypoxic conditions. In conclusion, the elevated sensitivity of exercise ventilation to hypoxia during exertion appears to be modulated by elevations in esophageal temperature, potentially due to a temperature mediated stimulation of the peripheral chemoreceptors.
Introduction

There have been several proposed mechanisms for the hyperpnea that occurs during exercise (16, 25, 37). A neurogenic hypothesis (16) implicates core temperature as a central mediating stimulus in the control of pulmonary ventilation during both actively and passively induced hyperthermia (2, 37). It suggests that increases in core temperature could increase pulmonary ventilation by several mechanisms. One proposed mechanism suggests an increase in core temperature is associated with an increase in carbon dioxide sensitivity (30), while another suggests a direct physical effect of increased temperature in the respiratory control center and the peripheral chemoreceptors thereby enhancing the reactivity to their normal stimuli (5). This increased sensitivity to carbon dioxide (CO₂) appears to be evident during exercise (35) and during post exercise hyperthermia (28). Another hypothesis suggests a direct effect of an increase in core temperature causing a change in the equilibrium constants of the CO₂ buffer system resulting in a diminished capacity to buffer CO₂ by body fluids (32). Pulmonary ventilation is then elevated after hydrogen ion (H⁺) concentration is increased in the regions of the central respiratory centres in the medulla oblongata.

Hypoxia is another well-established modulator of pulmonary ventilation. Low inspired O₂ partial pressure is detected by the peripheral chemoreceptors stimulating ventilation (6). Exercise enhances the hypoxic ventilatory response (HVR) and the effect becomes marked as the severity of exercise increases (35). The response to hypoxia has also been shown to depend on the end-tidal partial pressure of carbon dioxide (P_{\text{ET}}CO₂) (27). Hyperthermia in resting mice elevates their HVR (14) but what has not been examined in humans is if the concomitant increase in core temperature evident with exercise has an influence on the ventilatory response to hypoxia. To this end we have implemented an underwater exercise method similar to that by Park and
colleagues (24) to prevent increases in core temperature during exercise. As such, this allowed
an assessment for an interaction between esophageal temperature, employed as an index of
central blood temperature (10), and isocapnic hypoxia on exercise ventilation. We hypothesized
a greater exercise ventilation would be evident due to an increased sensitivity of the peripheral
chemoreceptors to hypoxia during a low intensity ‘hyperthermic’ exercise relative to a low
intensity ‘normothermic’ exercise when esophageal temperature was clamped at resting levels.
Materials and Methods

Participants

Eleven healthy male participants of a mean age of 23.7 (SD 4.4) years volunteered to participate in the study. Their physical characteristics included that they weighed 74.1 (9.0) kg, stood 1.77 (0.06) m in height and had a mean body surface area of 1.9 (0.1) m². All participants were non-smokers, non-asthmatics and refrained from caffeine as well as from alcohol consumption for 12 h prior to each test. Participants were also required to fast, avoid exercise and refrain from drinking any warm beverages for a minimum of 5 h prior each experimental session. Participants did not have any form of altitude habituation and resided at or close to sea-level. They were also informed of the potential risks associated with the protocol and after a 24 h reflection period gave their written, informed consent to participate. These experiments were approved by the SFU Office of Research Ethics. All experimental sessions started within ± 60 min of each other on a given day and that was between 10 am and 1 pm. Participants were clad in shorts and kayak boots during the experiments.

Instrumentation

Pulmonary ventilation (\( V_\text{E} \)) and its components of tidal volume (\( V_\text{T} \)) and ventilation frequency (\( f_\text{v} \)) are expressed in units adjusted to Barometric Pressure and Temperature Saturated (BTPS). Rates of oxygen consumption (\( V_\text{O}_2 \)) and carbon dioxide (\( V_\text{CO}_2 \)) production are expressed in Standard Temperature and Pressure Dry (STPD). Pulmonary ventilation, \( V_\text{O}_2 \) and \( V_\text{CO}_2 \) values were measured and calculated (15) with a breath-by-breath metabolic cart (Model \( V_{\text{max}} 229d \), Sensormedics, Yorba Linda, CA, USA). Participants wore a nose clip and were fitted with a mouthpiece connected to a Mass Flow Sensor. The mouthpiece was connected to a two-way flow sensor housing, which was connected to a two-way non-rebreathing valve (NRB 2700,
Hans Rudolph Inc, Kansas Cit, MO, USA) that was connected with 3.8 cm diameter corrugated Collins tubing to a 350 L Tissot spirometer. Breath-by-breath end-tidal gas samples were drawn from the inspired and expired air to the metabolic cart at a rate of 600 ml·min⁻¹. Tidal volume was determined from each breath as a difference from end-expiratory lung volume to maximum inspiratory lung volume. Carbon dioxide partial pressure was measured using non-dispersive infrared spectroscopy and oxygen concentration was measured using a paramagnetic sensor. A premixed hypoxic gas of 12 % O₂ in nitrogen (N₂) from a compressed gas bottle was used to fill the Tissot spirometer for the hypoxic condition. If the PETCO₂ fell below resting water-immersed values, 100 % CO₂ was manually titrated into the inspirate via a non-re-breathing demand valve apparatus to bring the PETCO₂ back to resting, water-immersed values (31). The resting water-immersed PETCO₂ (3) was determined during the 5-min rest session immediately prior to commencing the exercise session.

Arterial hemoglobin oxygen saturation (SₐO₂) and heart rate (HR) were continuously measured with a pulse oximeter (Masimo Radical, Irvine, CA, USA) that was positioned on the participants’ left ear lobe. Esophageal temperature (Tₑs) was measured by placing a paediatric size temperature thermocouple probe of approximately 2 mm in diameter through the participants’ nostrils, while they were asked to sip water through a straw. The location of the tip of the probe in the oesophagus was past the nares, at the T8/T9 level, a position bounded by the left ventricle and aorta. This position is based on the equation of Mekjavic and Rempel (20) for standing height. The choice of the esophageal temperature was also based on the demonstration with a Swan-Ganz catheter (10) that it closely tracts cardiac temperature. This temperature was assumed to be similar to the temperature of the chemoreceptors in carotid bodies. The participant was then immersed to the level of the shoulders in a water-filled tub and sat on the seat of a
hydraulically braked, underwater cycle ergometer. As discussed below, water temperature ($T_w$) was chosen to maintain $T_{es}$ in either a normothermic or hyperthermic state.

**Water temperature calculations**

During the preliminary testing session skinfold measurements were taken at 10 different sites with the Harpenden skinfold calliper (British Indicators, St. Albans, UK) using methods described by Veicsteinas and Rennie (34). The skinfold values (mean= 88.1 (SD 28.5 mm)) were used to determine the participant’s weighted mean subcutaneous fat thickness ($MFT_w$) (34). The $MFT_w$ values for each participant were used to predict their overall body insulation at rest ($I_{rest}$) by a regression equation derived from Park and colleagues study (24). These $I_{rest}$ values of 0.126 (SD 0.031) °C • m⁻² • W⁻¹ were used to calculate the water temperature for both the hyperthermic and normothermic sessions by using a re-arrangement of Park et al.’s (24) body insulation equation:

$$T_w = T_{es} - (I_{ex}*(0.92 \ M \pm S))$$

Where $T_w$ is the desired water temperature for the exercise session, $T_{es}$ is the desired core temperature measured by an esophageal probe, $I_{ex}$ is the overall body insulation during exercise (for healthy male participants, BSA ~ 1.9 m², exercising at a rate that produces a constant metabolic heat production of 145 W·m⁻², $I_{ex}$ was found to be ~40% of $I_{rest}$ (24)), $M$ is the metabolic heat production, $S$ is the rate of heat storage. For the normothermic condition $S$ is negligible and 0.92 is a weighting factor determined by the prediction of respiratory heat loss at rest and during exercise to be ~8% (24). For the hyperthermic condition at a $T_{es}$ of ~ 38.5°C, $S$ was empirically determined during pilot testing to be ~140 W·m⁻². This value was used as an estimated standard for the participant pool that was of similar physique to the pilot participant.
Core Temperature, Hypoxia and Ventilation

The mean water temperature for the normothermic condition was 31.5°C (SD 1.4) and for the
hyperthermic condition was 38.2°C (SD 0.1).

Protocol

All participants completed 2 separate exercise-testing sessions, with each session
separated by at least one week. Half of the participants were randomly chosen to start with the
hyperthermic session and the other half started with the normothermic session. After
instrumentation each protocol began with a 30-min rest period in room air to establish a stable
resting $T_{es}$. The exercise was preceded by a 5-min rest period with the participant seated on a
stationary underwater bicycle ergometer in water up to his shoulder level and instrumented with a
weight belt to avoid floatation. A metronome was used to maintain the pedalling cadence and the
participant was monitored continuously to assure adherence.

The work rate employed was determined based on the equation derived from Park et al.’s
(24) study as the ideal level amongst the participant population that would produce a $\dot{V}O_2$ of
approximately 0.8 to 1.0 L·min$^{-1}$ while cycling in a 30°C water-filled tub. A $\dot{V}O_2$ of 0.8 to 1.0
L·min$^{-1}$ was shown by Park et al. (24) to correspond with a metabolic heat production of ~145
W·m$^{-2}$ in a healthy male participant with a body surface area (BSA) of ~1.9 m$^2$. This metabolic
heat production rate was chosen as the exercise intensity to produce a steady-state normothermic
core temperature in thermoneutral water as shown in Park et al.’s (24) study. The same work rate
was used for the hyperthermic condition.

Each exercise session was performed at a constant work rate and consisted of a 20-min
warm-up period where a stable $\dot{V}_E$ and $T_{es}$ were achieved and then a 30-min testing period. Both
the warm-up and testing period were completed at the same work rate and cadence and there
Core Temperature, Hypoxia and Ventilation

were no rest phases between each period. The 30-min testing period was divided into 3 consecutive 10-min steady state exercise phases: a 10-min euoxic exercise period (E1) where the participant breathed room air, a 10-min hypoxic exercise period (H1) where the participant breathed a 12% O₂ hypoxic gas in N₂ with CO₂ bled into the inspirate to maintain P_{ET}CO₂ at resting, immersed, pre-exercise values, and a 10-min euoxic recovery exercise period (E2) when the participant again breathed room air. All participants followed this protocol in the same order for all sessions. The durations of each period in the protocol were each determined in the pilot study to ensure steady states were achieved for the cardio-respiratory variables.

Blood samples were drawn in 4 ml increments from a vein in the antecubital fossa at rest, and at 5 min of the E1, H1 and E2 steady-state exercise phases. The catheter was flushed with saline between each sample to assure heterogeneity of samples. Blood was collected into collection tubes containing the anti-coagulant lithium heparin (BD Vacutainers, Franklin Lakes, NJ, USA). Samples were immediately placed on ice and centrifuged within 30 minutes of being drawn at 4°C and a speed of 3500 rpm. Plasma was removed after centrifugation and allocated into in 1.5 ml eppendorf tubes. There were 2 alloquots from each sample, for 2 different analyses (Lactate and K⁺). The eppendorf tubes were stored at -80°C until the analyses, which was carried out within 3 months of the sampling date.

Plasma K⁺ concentrations were determined using an ion-selective electrode (Cole Parmer, Vernon Hills, Ill., USA). Samples of 100 µL plasma were diluted (100 x) to 10 ml with distilled water and the electrode was submerged in the 21°C solution. Electrode potential readings (mV) correspond to the concentration of K⁺ in the sample (mM). Lactate concentration in plasma samples was determined using a colorimetric, enzymatic diagnostic kit (Pointe Scientific, Lincoln
Core Temperature, Hypoxia and Ventilation

Park, Michigan) as previously described by Lin et al. (17). A volume of 10 µL of plasma was used for each determination of lactate.

**Calibrations and Analysis**

Ventilatory parameters, $T_{es}$, $S_aO_2$, lactate and $K^+$ for the steady-state exercise phases were analyzed using a two-way ANOVA for repeated measures. The factors were Esophageal Temperature (Levels: normothermic and hyperthermic) and Gas Type (Levels: euoxia (E1), hypoxia (H1), and euoxic recovery (E2)). Dependent $t$-tests with the Bonferroni correction for multiple comparisons of were used to compare the means. After the assumptions between conditions were met for homogeneity of regression, homogeneity of variances and normality of the distributions for both $V_E$ and $\bar{V}O_2$, an ANCOVA was employed to assess changes in $V_E$ after removing the variance due to $\bar{V}O_2$. This method of normalization accounts for the allometry of the $V_E$ to $\bar{V}O_2$ relationship and avoids spurious conclusions from the use of ratios or percentages as described by Packard and Boardman (23). A $P$ value < 0.05 was considered significant. For comparisons values are expressed as the mean and Standard Deviation (SD).
Results

Figure 1 indicates for a single participant the Gas Type phases used for analysis and shows the typical time course responses of $\dot{V}_E$, $\dot{V}O_2$, $P_{ET}CO_2$, $S_aO_2$ and $T_{es}$ during the normothermic and hyperthermic conditions. Prior to the commencement of the normothermic or hyperthermic exercise sessions the mean resting $T_{es}$ was between 37.20 and 37.30°C (Fig. 2). For the normothermic exercise condition participants’ mean $T_{es}$ was maintained at ~37.1°C during E1, H1 and E2 respectively. For the hyperthermic exercise condition $T_{es}$ increased steadily from rest and gradually approached a plateau at ~38.5°C after the completion of the warm-up exercise period. The mean $T_{es}$ during all steady-state exercise phases of the hyperthermic condition were significantly increased above the normothermic values by between ~1.3°C in E1 and 1.7°C in E2 (Fig. 2).

The ventilatory responses (Fig. 3) obtained during steady-state exercise in E1, H1, E2 during the normothermic condition indicated $\dot{V}_E$ significantly increased from 22.8 L·min$^{-1}$ (SD 2.7) in E1 to 34.5 L·min$^{-1}$ (SD 4.1) in H1 and returned to 22.7 L·min$^{-1}$ (SD 2.8) during E2 that was at the same rate ($P = 1.000$) as that in E1. During the hyperthermic condition $\dot{V}_E$ also increased from E1 at 24.9 L·min$^{-1}$ (SD 2.8) to H1 at 44.6 L·min$^{-1}$ (SD 10.6) and returned to 27.9 L·min$^{-1}$ (SD 9.3) during E2 that was also not significantly different ($P = 0.691$) from that in E1. For the hyperthermic compared to the normothermic condition, $\dot{V}_E$ increased by 2.0 L·min$^{-1}$ (SD 2.1) in E1 ($P = 0.010$), by 10.2 L·min$^{-1}$ (SD 9.0) in H1 ($P = 0.004$) and by 5.2 L·min$^{-1}$ (SD 7.7) in E2 ($P = 0.048$).

There was no significant main effect of Esophageal Temperature on $V_T$ ($P = 0.801$). During the normothermic condition $V_T$ (Fig. 3B) increased from E1 at ~1.1 L (SD 0.21) to H1 at
Core Temperature, Hypoxia and Ventilation

~1.6 L ($P = 0.001$) and returned to a value of ~1.1 L during E2, a value that was not different from that in E1 ($P = 0.159$). During the hyperthermic condition $V_T$ increased significantly from E1 at ~1.1 L to H1 at ~1.70 L ($P = 0.001$). Tidal volume during E2 decreased ($P = 0.026$) below the previous steady-state E1 values.

During the normothermic condition $f_v$ (Fig. 3.3C) showed no significant changes between E1, H1 and E2 with values remaining at ~21 to 22 breaths·min$^{-1}$. During the hyperthermic condition $f_v$ ranged from ~24 to 28 breaths·min$^{-1}$ and showed no changes from E1 to H1 to E2. Ventilation frequency was significantly elevated for all hyperthermic vs. normothermic steady-state exercise by 2.2 breaths·min$^{-1}$ (SD 3.1) in E1 ($P = 0.043$), by 5.8 breaths·min$^{-1}$ (SD 6.7) in H1 ($P = 0.017$) and by 5.7 breaths·min$^{-1}$ (SD 5.8) in E2 ($P = 0.008$).

A significant Esophageal Temperature and Gas Type interaction (Fig. 4A) was evident for $V_E$ ($F = 5.8$, $P = 0.012$) and a trend (Fig. 4B) for the same interaction was evident for $f_v$ ($F = 3.4$, $P = 0.076$). Between normothermic and hyperthermic conditions the increase of $V_E$ in H1 was significantly greater ($F = 8.2$, $P = 0.017$) than for the same increase in E1. Elevations of $V_E$ between normothermic and hyperthermic conditions were not significantly different in E1 and E2 ($P = 0.226$) (Fig. 4A). The $f_v$ did not increase from the normothermic to hyperthermic condition in both H1 ($P = 0.099$) and E2 ($P = 0.062$) as compared to E1 (Fig. 4B).

Oxygen saturation (Fig. 5A) significantly decreased during H1 to 85.6 % (SD 5.7) ($P = 0.001$) in the normothermic condition and to 83.5 % (SD 5.7) ($P = 0.001$) in the hyperthermic condition. Both decreases were by ~14.5% from the E1 and E2 values of ~98 to ~99%. An Esophageal Temperature effect was also indicated as $S_{aO_2}$ values decreased significantly during the hyperthermic condition from the normothermic degree of saturation during E1 by 2.0 % (SD 0.8) ($P = 0.001$) and during E2 by 2.5 % (SD 1.1). During H1, there was no significant
difference \( (P = 0.368) \) for \( S_aO_2 \) between the hyperthermic and normothermic condition. An isocapnic hypoxia was achieved (Fig. 5B), as \( P_{ET}CO_2 \) was maintained constant across both the normothermic and hyperthermic conditions during each of the 3 gas phases.

For \( \dot{V}O_2 \) (Fig. 6A) there were significant main effects of Gas Type \( (F = 107.1, P = 0.001) \) and Esophageal Temperature \( (F = 10.3, P = 0.009) \). During hyperthermic relative to normothermic exercise, \( \dot{V}O_2 \) was not different in E1 \( (P = 0.079) \) and significantly elevated in both H1 by 0.12 L·min\(^{-1}\) \((SD 0.09)\) \((P = 0.001)\) and in E2 by 0.09 L·min\(^{-1}\) \((SD 0.13)\) \((P = 0.034)\) (Fig. 5.2A).

For the Respiratory Exchange Ratio (RER) there was a significant main effect of Gas Type \( (F = 91.6, P = 0.001) \) and no significant main effect of Esophageal Temperature \( (F = 2.8, P = 0.123) \) (Fig. 6B). The pooled mean RER values between Esophageal Temperature conditions increased significantly from E1 at 0.83 \((SD 0.05)\) to H1 at 1.11 \((SD 0.11)\) and decreased below E1 values \((P = 0.001)\) on return to euoxic breathing during E2 at 0.78 \((SD 0.05)\).

For HR there were significant main effects of Gas Type \( (F = 130.0, P = 0.001) \) and Esophageal Temperature \( (F = 51.9, P = 0.001) \) as well as (Fig. 6C) a significant positive interaction between these factors \( (F = 4.8, P = 0.019) \). The interaction was explained by a smaller increase in HR of 12.9 beats·min\(^{-1}\) for the normothermic condition from E1 to H1 relative to that of 17.0 beats·min\(^{-1}\) \((SD 4.3)\) for the hyperthermic condition. During the hyperthermic condition relative to the normothermic condition HR was significantly \((P = 0.001)\) elevated by between \(-23\) and \(-29\) beats·min\(^{-1}\).

Comparisons of \( \dot{V}_E \) responses after accounting for the covariate \( \dot{V}O_2 \) with an ANCOVA are given in Figure 7. These \( \dot{V}O_2 \) adjusted ventilatory values gave main effects of Gas Type \( (F=36.8, p<0.0001) \), Esophageal Temperature \( (F=14.3, p=0.003) \) and a significant positive
interaction between these two main effects (F=4.3, P =0.028). During the normothermic condition $\dot{V}_E$ increased from 24.3 L·min$^{-1}$ (SD 2.3) in E1 to 31.7 L·min$^{-1}$ (SD 4.4) in H1 ($P = 0.001$). The normothermic $\dot{V}_E$ returned towards a steady-state during E2 at 23.9 L·min$^{-1}$ (SD 2.1) with a trend for a hypoxic ventilatory depression relative to E1 ($P = 0.053$). During the hyperthermic condition $\dot{V}O_2$ adjusted $\dot{V}_E$ significantly increased ($P = 0.01$) from E1 at 28.0 L·min$^{-1}$ (SD 1.6) to H1 at 40.9 L·min$^{-1}$ (SD 8.9). The hyperthermic $\dot{V}_E$ also returned towards a steady-state rate of 28.9 L·min$^{-1}$ (SD 7.4) in E2 and the value was not greater than during E1 ($P = 0.08$). For the hyperthermic condition $\dot{V}O_2$ adjusted $\dot{V}_E$ was significantly elevated in all steady-state exercise phases as compared to the normothermic condition (Fig. 7). The positive interaction between Gas Type and Esophageal Temperature was explained by the larger increase in $\dot{V}_E$ from E1 to H1 in the hyperthermic relative to the normothermic exercise condition (i.e. 12.9 L·min$^{-1}$ vs 7.4 L·min$^{-1}$).

Analysis of blood borne metabolites (Fig. 8) indicated there was no significant main effect of Gas Type for lactate ($F = 2.3, P = 0.121$) or for $K^+$ ($F = 2.1, P = 0.119$). Similarly there was no significant main effect of Esophageal Temperature for lactate ($F = 0.8, P = 0.395$) or for $K^+$ ($F = 1.0, P = 0.352$).
Discussion

The main finding in this study was that the increase in $\dot{V}_E$ observed during hypoxia was significantly greater during steady-state hyperthermic exercise as compared to steady-state normothermic exercise (Fig. 3A). The $T_{es}$-induced increase in hypoxic $\dot{V}_E$ appears to be related to a significant increase in $f_v$ (Fig. 3C) since $V_T$ (Fig. 3B) during hypoxia was not significantly influenced by the elevation of $T_{es}$. A hyperthermic-induced hyperpnea was also observed at E1 and E2 independent of changes to inspired gas composition (Fig. 3A) and this hyperpnea remained after using ANCOVA to account for increases in $\dot{V}_E$ due to $\dot{VO}_2$. Together these results supported that the sensitivity of exercise ventilation to hypoxia is elevated during hyperthermia and that hyperthermia per se increases ventilation (2, 37).

The HVR observed during low intensity exercise (Fig. 3A) is in agreement with Weil and colleagues results (35). Mean $\dot{V}_E$ increased significantly during both hypoxic conditions, however the hyperthermic hypoxia-induced increase in $\dot{V}_E$ (Fig. 3A) was almost twice that of the normothermic hypoxia-induced increase in $\dot{V}_E$. There was no significant difference in steady-state $\dot{V}_E$ during the normothermic condition between E1 and E2, which supported the absence of an order effect of hypoxia between the three phases of exercise (E1, H1 and E2). The HVR during normothermic exercise was mediated completely by $V_T$ (Fig. 3B) with no significant influence from $f_v$ (Fig. 3C). This result differed slightly from those of Savourey et al. (29) who showed that only at rest was the HVR a result of an increased $V_T$ and during moderate exercise it was a result of a both an increased $V_T$ and $f_v$. The difference from Savourey et al.’s study (29) was that $T_{es}$ was currently maintained at resting values throughout the hypoxic exercise and not allowed to increase. During the hyperthermic hypoxic exercise condition $V_T$ increased in a relatively equal magnitude as during the normothermic hypoxic condition, yet the HVR was
enhanced. This can be attributed primarily to the elevated \( f_v \) as a result of the increased \( T_{es} \), which has been described as a thermal tachypnea (2, 22). This supports the suggestion that an elevated \( T_{es} \) influences the sensitivity of the peripheral chemoreceptors and helps explain the elevated HVR during hyperthermic exercise (Fig. 3A).

The hyperthermic-induced hyperpnea during isocapnic euoxia (Fig. 3) is in agreement with results from previous studies (2, 25). Petersen and Vejby-Christensen (25) suggested that a core temperature threshold for ventilation existed around 38°C above which a significant hyperpnea was evident. These core temperature thresholds were subsequently defined for passively or actively-induced hyperthermia (2, 37) and above these thresholds ventilation increased proportionately to core temperatures (2, 37). We reasoned this proportionality between core temperature and ventilation accounts for the higher \( V_E \) in the hyperthermic exercise during E1 and E2 relative to that during normothermia (Fig. 2).

A probable mechanism for the observed thermal tachypnea (Fig. 3C) would be a direct temperature effect on the peripheral chemoreceptors that increased their sensitivity to arterial O2. Firing rates of the isolated peripheral chemoreceptors are known to increase proportionately to their temperatures (7, 8) suggesting either an additive or multiplicative influence of temperature on the afferent output from these carotid bodies to the integrative areas for pulmonary ventilation in the medulla oblongata.

The increase in \( \dot{V}_E \) during hyperthermic hypoxia relative to hyperthermic euoxia was greater than the same increase in normothermic hypoxia relative to normothermic euoxia (Fig. 3A). This supports that the observed \( \dot{V}_E \) enhancement during hyperthermic hypoxia was a peripheral response if it is accepted decreased arterial PO2 is sensed peripherally. Cunningham and O’Riordan (5) and Petersen and Vejby-Christensen (26) have previously suggested a similar
hypothesis in studies on passive hyperthermia and hypoxia and Weil et al. (35) showed the HVR becomes enhanced with increasing exercise intensity. Higher intensities of exercise are associated with an increasing core temperature (16, 21) and this suggests a temperature-induced enhancement of the HVR. Furthermore, during the hypoxic hyperthermic phase it would be expected that pH may increase in response to the hypoxic hyperventilation, however, PETCO2 was clamped at isocapnic value (Fig. 5) which should have prevented increases in pH (25). This last suggestion, however, needs to be expressed with the reservation that CO2 buffering capacity may also be diminished and that pH may decrease during hyperthermia (32). Future studies focused on the resolution of the mechanisms underlying this temperature-induced hyperventilation need to consider changes in CO2 buffering capacity.

Independent of hypoxia the mechanism of thermal-induced tachypnea in panting animals has been shown to be mediated by the hypothalamus (13) and/or the ventral surface of the medulla oblongata (4). In mice after surgical isolation of the brain stem, local heating directly modified the respiratory neural activity in the ventral respiratory group and this increased \( f_v \) (33). This would agree with previous studies in humans, which suggested that the thermal tachypnea observed during exercise may be a direct effect of temperature on the cells of the respiratory control centres in the medulla (5, 19). MacDougall et al. (18) suggested increasing concentration of H\(^+\) as a possible modulator acting at the peripheral chemoreceptors or central chemosensitive areas during hyperthermic exercise. However, during short term low intensity exercise arterial and cerebrospinal fluid pH are not thought to change (36). As such, the mechanism of the thermal tachypnea remains to be established in humans.

The metabolic cost of euoxic and hypoxic hyperthermia appeared also to contribute to the observed increases in exercise ventilation. The rate of oxygen consumption was elevated from
normothermia to hyperthermia in H1 and this was coupled with an elevation in RER (Fig. 6). Normally an RER greater than unity would suggest a non-metabolic simulation on ventilation, however, this conclusion is difficult to make currently since an isocapnia was maintained these exercise trials. Heart rate was elevated across all hyperthermia exercise phases and this supported a global increase in metabolic stress was contributing to the exercise ventilation. However, after this positive influence of $\dot{V}O_2$ on $\dot{V}E$ was removed (Fig. 7), with the analysis of covariance (23), the effect of $T_{es}$ remained significant across all conditions. In addition, we (2), and others (9, 25), have shown an elevated core temperature increases $\dot{V}E$ disproportionately to $\dot{V}O_2$. This lends further support to the view of an independent influence of $T_{es}$ on ventilation during hyperthermia that is in addition to a $Q_{10}$ effect.

During hyperthermic hypoxia an increase in body temperature shifts the oxy-hemoglobin dissociation curve to the right causing a reduction in the $O_2$ affinity for hemoglobin. This was evident to a small degree as $S_aO_2$ was slightly reduced during the hyperthermic condition by ~2% in E1 and E2 (Fig. 5A). This would have little effect during the euoxic conditions as the $S_aO_2$ was still at ~98 to 99% for both E1 and E2, which was not low enough to influence $\dot{V}E$ significantly.

Other possible influences on $\dot{V}E$ between temperature conditions would be the changes in blood borne metabolites known to influence pulmonary ventilation, however, both serum lactate and potassium were at similar concentrations across the two temperature conditions (Fig. 8). Also since decreases in central blood volume augment the HVR (12), an increase in central blood volume due to immersion (1) may reduce the HVR. Finally, Group III and IV afferents in skeletal muscle increase their firing rates due to increases in their temperature and this is another possible influence on $\dot{V}E$ in the hyperthermic condition (11).
Conclusion

In conclusion, in support of previous work, $\dot{V}_E$ was significantly increased by a hyperthermic as compared to a normothermic esophageal temperature during low intensity euoxic exercise. The hyperthermic-induced hyperpnea appears to be mediated solely by an increase in $f_v$, supporting the existence of a thermal-induced tachypnea. During low intensity exercise there was an enhancement of the hypoxic ventilatory response that was mediated primarily by $f_v$, since no significant temperature-induced changes were evident for $V_T$. The study supported the hypothesis that an increased esophageal temperature increases peripheral chemoreceptor sensitivity and the hypoxic ventilatory response during exercise.
Acknowledgements

The authors would like to thank Julia P.H. Christensen, Duncan Milne and Darryl Whitney for tireless help during this study. Special thanks are also given to the Vancouver Airevac Paramedics who provided medical supervision during the study.
Grants

This work was supported by grants from Natural Science and Engineering Research Council of Canada and the Canadian Foundation for Innovation.
Core Temperature, Hypoxia and Ventilation

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Figure Legends

**Figure 1.** Time course of the rate of pulmonary ventilation ($V_{E}$), the rate of oxygen consumption ($\dot{V}_O_2$), end-tidal CO$_2$ ($P_{ET}CO_2$), arterial oxygen saturation ($S_aO_2$) and esophageal temperature ($T_{es}$) for a typical participant (#5) during the normothermic condition. R1 represents rest out of water; R2 represents rest in-water; Warm-up is the warm-up exercise period; E1 represents the first steady-state euoxic exercise period; H1 represents the steady-state hypoxic exercise period; E2 represents the second steady-state euoxic exercise period. ■, normothermic condition; □, hyperthermic condition.

**Figure 2.** Esophageal temperature ($T_{es}$) for pre-immersion rest and each exercise phase. Rest period represents the 30-min pre-immersion period, E1 represents the 1st 10-min euoxic exercise period, H1 represents the 10-min hypoxic period, and E2 represents the 2nd 10-min euoxic period. Values are means for 11 participants; error bars indicate the SD. **significant at $P < 0.01$, NS non-significant. ■, normothermic condition; □, hyperthermic condition.

**Figure 3.** Mean rate of pulmonary ventilation ($\dot{V}_E$), tidal volume ($V_T$) and ventilation frequency ($f_v$) for each exercise phase. E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. Values are means for 11 participants; error bars represent the SD. *significant at $P < 0.05$, **significant at $P < 0.01$, ‡ significant from E1 at $P < 0.01$, NS non-significant. ■, normothermic condition; □, hyperthermic condition.

**Figure 4.** Interaction plots for rate of pulmonary ventilation ($\dot{V}_E$) and ventilation frequency ($f_v$). Values represent the mean increase from the normothermic to hyperthermic condition for each exercise phase. E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. Values are means for 11 participants; Error bars represent the SD. *significant at $P < 0.05$, NS non-significant.
Figure 5. Mean arterial hemoglobin oxygen saturation ($S_aO_2$) and end-tidal CO$_2$ ($P_{ET}CO_2$) for each exercise phase. E1, euoxic exercise phase; H1, hypoxic exercise phase; E2, recovery euoxic exercise phase. Rest represents the mean of the 5 min in-water resting period. Values are means for 11 participants; error bars indicate the SD. **significant at $P < 0.01$, NS non-significant, ‡ significant from E1 at $P < 0.01$. □, normothermic condition; ■, hyperthermic condition.

Figure 6. Mean rate of oxygen consumption ($\dot{V}O_2$), respiratory exchange ratio (RER) and heart rate (HR) for rest, euoxic exercise (E1), hypoxic exercise (H1) and recovery euoxic exercise (E2). Values are means for 11 participants; Error bars indicate the SD (**significant between temperature conditions at $P < 0.01$, ‡ significant from E1 at $P < 0.01$, NS non-significant). □, normothermic condition; ■, hyperthermic condition.

Figure 7. Increases in the rate of pulmonary ventilation ($\dot{V}_E$) from the normothermic to hyperthermic condition during euoxic exercise (E1), isocapnic hypoxic exercise (H1) and recovery euoxic exercise (E2). An ANCOVA (23) was employed to remove the variability in $\dot{V}_E$ due to the rate oxygen consumption ($\dot{V}O_2$). Values are means for 11 participants; Error bars indicate the SD (**significant between temperature conditions at $P < 0.01$, * at $P < 0.05$; ‡ significant from E1 at $P < 0.01$); □, normothermic condition; ■, hyperthermic condition.

Figure 8. Mean serum lactate and potassium ($K^+$) concentration for rest, euoxic exercise (E1), hypoxic exercise (H1), and recovery euoxic exercise (E2). Values are means for 11 participants; Error bars indicate the SD. NS non-significant. □, normothermic condition; ■, hyperthermic condition.
Figure 1

![Graph depicting various metrics over time](image)

- $\dot{V}O_2$ (L/min)
- $\dot{V}CO_2$ (L/min)
- $PrCO_2$ (kPa)
- $S_aO_2$ (%)
- $T_a$ (°C)

**Axes:**
- Time (min) from 0 to 85
- Y-axis values for each metric

**Legend:**
- R1, R2, Warm-up, E1, H1, E2
Figure 2
Figure 4

A

\( \dot{V}_{\text{E}} \) (L·min\(^{-1}\))

E1  H1  E2

B

\( \nu \) (breaths·min\(^{-1}\))

E1  H1  E2

---

NG

\( P = 0.062 \)

\( P = 0.099 \)
Figure 6

A  

\[ \text{Vo}_{2} \text{ (mL/min) } \]

B  

\[ \text{RER} \]

C  

\[ \text{HR (bpm)} \]
Figure 7
Figure 8

![Graph](image)

**A**

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**B**

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