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Effect of food intake on the ventilatory response to increasing core temperature during exercise

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Abstract

Food intake increases metabolism and body temperature, which may in turn influence ventilatory responses. Our aim was to assess the effect of food intake on ventilatory sensitivity to rising core temperature during exercise. Nine healthy male subjects exercised on a cycle ergometer at 50% of peak oxygen uptake in sessions with and without prior food intake. Ventilatory sensitivity to rising core temperature was defined by the slopes of regression lines relating ventilatory parameters to core temperature.

Mean skin temperature, mean body temperature (calculated from esophageal temperature and mean skin temperature), oxygen uptake, carbon dioxide elimination, minute ventilation, alveolar ventilation, and tidal volume ($V_T$) were all significantly higher at baseline in sessions with food intake than without food intake. During exercise, esophageal temperature, mean skin temperature, mean body temperature, carbon dioxide elimination, and end-tidal $CO_2$ pressure were all significantly higher in sessions with food intake than without it. By contrast, ventilatory parameters did not differ between sessions with and without food intake, with the exception of $V_T$ during the first 5 min of exercise. The ventilatory sensitivities to rising core temperature also did not differ, with the exception of an early transient effect on $V_T$. Food intake increases body temperature before and during exercise. Other than during the first 5 min of exercise,
food intake does not affect ventilatory parameters during exercise, despite elevation of both body temperature and metabolism. Thus, with the exception of an early transient effect on $V_T$, ventilatory sensitivity to rising core temperature is not affected by food intake.

Keywords: diet-induced thermogenesis, postprandial thermogenesis, body temperature, ventilation
**Introduction**

During exercise in the heat, body temperature rises, and minute ventilation ($V_E$) increases in proportion to the rise in body temperature (Fujii et al. 2008, Hayashi et al. 2006, 2011, 2012, Nybo and Nielsen 2001, Tsuji et al. 2012, 2016). When expressed as a function of esophageal temperature ($T_{es}$), $V_E$ reportedly increases 5-12 l/min per 1°C rise in $T_{es}$ during prolonged exercise at moderate intensity (Fujii et al. 2008, Hayashi et al. 2006, 2011, 2012, Tsuji et al. 2012, 2016). This hyperthermia-induced hyperventilation enhances alveolar gas exchange, leading to a reduction in arterial $CO_2$ pressure ($Pa_{CO_2}$). Because $Pa_{CO_2}$ influences ventilatory responses via the chemoreflex (West 2012b), we previously examined the effect of CO$_2$ on ventilatory sensitivity to rising body temperature (slope of the regression line relating $V_E$ to $T_{es}$) during exercise in the heat (Hayashi et al. 2011). We found that inhaling CO$_2$-enriched air to mitigate hypocapnia otherwise caused by hyperthermia-induced hyperventilation, increased ventilatory sensitivity to rising body temperature from 8.9 l·min$^{-1}$·°C$^{-1}$ (with inhaling room air) to 19.8 l·min$^{-1}$·°C$^{-1}$ (with inhaling CO$_2$-enriched air), which suggests $Pa_{CO_2}$ greatly influences ventilatory sensitivity to rising body temperature.

It is also well known that food intake increases metabolism and raises body temperature. This is the so-called postprandial or diet-induced thermogenesis (Bergman...
and Brooks 1999, Hayashi et al. 2014, Hill et al. 1985, Nielsen 1987, Welle 1984). We previously observed that food intake increases end-tidal CO$_2$ pressure (P$_{ET\text{CO}_2}$) (Hayashi et al. 2014). Although the size of the increase in P$_{ET\text{CO}_2}$ caused by food intake was only 2 mmHg, it is reasonable to suggest the higher P$_{ET\text{CO}_2}$ stimulates ventilation during exercise. It is also well established that food intake leads to increased oxygen uptake (V$_{O_2}$) and carbon dioxide elimination (V$_{CO_2}$) during rest (Hayashi et al. 2014, Nielsen 1987, Welle 1984). It is possible that elevation of V$_{CO_2}$ leads to increases in the H$^+$ concentration. Peripheral chemoreceptors also respond to elevated H$^+$ (West 2012b), suggesting that food intake may lead to an increase in V$_E$ via chemoreceptor activity. Consistent with that idea, increases in body temperature reportedly augment respiratory chemosensitivity (Baker et al. 1996, Natalino et al. 1977), suggesting postprandial thermogenesis may also augment respiratory chemosensitivity. It is thus likely that food intake itself is the cause of augmented postprandial ventilatory responses.

On the other hand, it is possible that the rise in body temperature caused by food intake leads to hyperventilation-induced hypocapnia (respiratory alkalosis), which may suppress ventilatory responses, as hyperthermia exerts a greater stimulatory effect on ventilation than does an elevation in metabolism (Fujii et al. 2008, Hayashi et al. 2006). Consequently, it remains unclear whether elevations in body temperature and


CO₂ production caused by food intake augment ventilatory responses or suppress them due to hypocapnia caused by hyperthermia-induced hyperventilation during exercise. To address this issue, we compared ventilatory sensitivity to rising core temperature measured during exercise with and without food intake before the exercise.

**Materials and methods**

**Participants**

Nine healthy male subjects [mean age = 23 ± 2 (SD) yr; height = 174.3 ± 5.4 cm; weight = 64.8 ± 11.8 kg; peak oxygen uptake (\(\dot{V}_{\text{O}_2\text{peak}}\)) = 42.4 ± 5.7 ml·kg⁻¹·min⁻¹] participated in the study, which was approved by the Human Subjects Committee of the University of Shizuoka. All participants provided written informed consent. Before any data were collected, the subjects were allowed to practice the cycle ergometer exercise they would be asked to perform during the experiments until they were accustomed to its style.

**\(\dot{V}_{\text{O}_2\text{peak}}\) test**

Initially, \(\dot{V}_{\text{O}_2\text{peak}}\) was determined during an incremental exercise test performed on a cycle ergometer (model 828E, Monark) to volitional fatigue. The exercise was started
at 60 W, after which the load was increased at a rate of 15 W/min throughout the entire
exercise period. Subjects pedaled at 60 rpm, and volitional fatigue was defined as an
inability to pedal at more than 50 rpm. During the exercise, the subjects wore a nose
clip and breathed into a mouthpiece containing a two-way valve. A mass-flow sensor
(hot-wire type) and a gas-sampling tube were connected to the mouthpiece, and the
expired volume and gases were analyzed using a metabolic cart (Vmax 29, Sensor
Medics, USA) with a mixing chamber set-up. The metabolic cart was calibrated with
the aid of an appurtenant calibration syringe that blew a fixed volume (3 L) of air. The
O₂ and CO₂ sensors were calibrated using reference gases of known concentration. \( \dot{V}_{O_2} \)
and \( \dot{V}_{CO_2} \) were calculated at 60-s intervals. \( \dot{V}_{O_2\text{peak}} \) was taken as the highest value of \( \dot{V}_{O_2} \)
achieved by a given subject, as some subjects did not achieve a plateau (even though
respiratory exchange rate exceeded 1.1 when \( \dot{V}_{O_2} \) reached a peak value). The \( \dot{V}_{O_2\text{peak}} \) test
was carried out in an experimental laboratory maintained at 25°C and 40-60% relative
humidity.

\textit{Test meal}

Test meals were designed for each subject. After estimating the basal metabolic
rate for each subject using the equation of Ganpule et al. (2007), we estimated the total
energy expenditure by multiplying the estimated basal metabolic rate by the estimated average physical activity level (1.75) (Westerterp 2003). The amounts of carbohydrate (target amount was 50-65%), protein (13-20%) and fat (20-30%) were based on the Dietary Reference Intake for the Japanese (Ministry of Health, Labour and Welfare 2014). As a result, test meals contained 115.9 ± 9.0 g of carbohydrate, 22.4 ± 0.6 g of protein, and 20.5 ± 2.6 g of fat with a total energy content of 3,097 ± 235 kJ.

Experimental design

In a pilot study, body temperature measured at least 90 min after eating was still higher than before eating. We therefore scheduled the start-time for the exercise to be 90 min after eating (Hayashi et al. 2014). Each subject completed two exercise sessions (after a test meal and after a 12 h fast) separated by at least 5 days in random order. The subjects were all asked to consume the same diet (not including the test meal) during the 24 h before the exercise sessions, and to abstain from strenuous exercise, alcohol and caffeine during the same period. They were also asked to drink 10 mL water/kg body weight the night before the experiment and then again on the morning of the experiment. The test meal was consumed in the laboratory office. After consuming the test meal or remaining in a fasted state, each subject came to the laboratory and rested for 30-60 min.
sitting in a chair to adjust the starting time of the experiment. During this period, a thermocouple was inserted via the nasal passage to record $T_{es}$. This thermocouple was inserted to a distance equivalent to one-fourth of the subject’s height (Wenger and Roberts 1980). The subject then voided urine, was weighed, and sat in a chair to rest for another 30 min while a heart rate (HR) monitor and thermocouples for recording skin temperature were attached. The subject then put on a water-perfused jacket. Because it was difficult to finely control room temperature and humidity, we asked subjects to wear a water-perfused suit, which gave us precise control over the temperature to which the subjects were exposed. After that, subjects seated on a bike. A mass-flow sensor and a gas-sampling tube were connected to the mask just before the measurements were begun, and the jacket was perfused with water at 35°C.

The subjects performed the cycle exercise at 50% $V_{\text{O2peak}}$. At the onset of the exercise, the temperature of the water perfusion was increased to 45°C, and the exercise was continued for 45 min. No fluid was provided during any session. The experiments were carried out in an experimental laboratory maintained at 25°C and 40-60% relative humidity.
Measurements

During the exercise sessions, $T_{es}$ and skin temperature data were collected via copper constantan thermocouples, which were sampled every 1 s using a data logger system (WE7000, Yokogawa, Japan) and averaged over 30-s periods. Skin temperatures were collected at four sites (chest, upper arm, thigh and calf) and used to calculate the weighted mean skin temperature ($T_{sk}$) (Ramanathan 1964). The mean body temperature ($T_{b}$) was calculated as: $T_{b} = 0.9T_{es} + 0.1T_{sk}$ (Gagge and Nishi 1977). HR was recorded every 5 s using a HR monitor (S810i, Polar, Finland) and averaged over 30-s periods.

The expired gas was measured breath-by-breath using the same analyzers used in the $V_{O2peak}$ test (see above).

Data analysis

Baseline values were obtained from data averaged over the 5 min just before exercise. Data obtained during exercise were averaged over every 5 min of the exercise.

We estimated dead space as 150 ml (West 2012a) and alveolar ventilation ($\dot{V}_A$) was calculated by multiplying the value obtained by subtracting estimated dead space from $V_T$ by respiratory frequency ($f_R$). $\dot{V}_E$, $V_T$, $f_R$, ventilatory equivalents for oxygen uptake ($\dot{V}_E/\dot{V}_{O2}$) and carbon dioxide output ($\dot{V}_E/\dot{V}_{CO2}$) measured during the exercise sessions.
were plotted as functions of $T_{es}$, and we took the slopes of the linear regression lines calculated by the method of least squares as indices of the ventilatory response to the increase in body temperature. To exclude the fast component of $V_E$ kinetics, only data collected after the 5th min of exercise were analyzed. Further, we confirmed that the effects of exercise time and skin temperature on the ventilatory responses to the increase in $T_{es}$ was negligible (Hayashi et al. 2006).

**Statistical analysis**

The ventilatory sensitivities of $V_E$, $V_T$, and $f_R$ to rising core temperature (slope of the regression lines relating the ventilatory parameters to $T_{es}$) were selected as important indices. To compare their means, minimum sample sizes were calculated on the basis of 80% power and a significance level of 0.05. We used standard deviations for the ventilatory sensitivities to rising core temperature from our pilot experiments.

Sample sizes enabling detection of food intake-related differences of 4.0 L·min$^{-1}$.°C$^{-1}$ for the slope of the regression line relating $V_E$ and $T_{es}$, 50 ml/°C for the slope of the regression line relating $V_T$ and $T_{es}$, and 3 breaths·min$^{-1}$.°C$^{-1}$ for the slope of the regression line relating $f_R$ and $T_{es}$ were estimated to be 9, 8 and 9, respectively (Hayashi et al. 2012). Therefore, our sample size of 9 subjects was adequate for our analysis.
All values are reported as means ± SD. Statistical analyses were performed using IBM SPSS Statistics (version 19.0; SPSS Inc., USA). Two-way ANOVA with repeated measures was conducted using time (levels: 0, 5, 10, 15, 20, 25, 30, and 35 min) and food intake (levels: with food intake and without food intake) as factors. Times at which the number of subjects was reduced (40 and 45 min) were not analyzed. Because a thermocouple measuring skin temperature peeled off of one subject, we analyzed only 0-30 min of the $T_{sk}$ and $T_{b}$ data for that subject. After the significant interaction and simple main effects were identified, pairwise differences were identified using Bonferroni’s post hoc procedure. Paired $t$-tests were also used to compare the “with food intake” and “without food intake” sessions with respect to the baseline values of the physiological parameters (Table 1), and the slopes and intercepts of their linear regression lines calculated after $\dot{V}_E$, $V_T$, $f_R$, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$ were plotted as functions of $T_{es}$ (Table 2). Values of $P < 0.05$ were considered significant.

**Results**

**Baseline comparisons**

Baseline $T_{sk}$, $T_b$, HR, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, respiratory exchange ratio (RER), $\dot{V}_E$, $\dot{V}_A$, and $V_T$ were all significantly higher during the session with food intake (Table 1). On the
other hand, baseline $\dot{V}_E/\dot{V}_{CO_2}$ was significantly lower with food intake. Baseline PET$_{CO2}$ did not significantly differ between sessions, though there was a tendency toward a difference (P < 0.06). Baseline $T_{es}$, $f_R$, $\dot{V}_E/\dot{V}_{O_2}$, and end-tidal O$_2$ pressure (PET$_{O2}$) did not significantly differ between sessions.

Comparisons during exercise

Figure 1 shows the changes in $T_{es}$, $T_{sk}$ and $T_b$ during exercise. $T_{es}$ rose during exercise, reaching 38.6 ± 0.4°C at the end of the exercise during sessions with food intake and 38.4 ± 0.2°C during sessions without food intake. There were significant main effects of food intake ($F = 7.98$, $P < 0.05$) and exercise time ($F = 92.98$, $P < 0.01$) on $T_{es}$. On the other hand, there was no significant interaction between food intake and exercise time ($F = 1.20$, $P > 0.3$). $T_{es}$ values were significantly higher at minutes 0-35 during sessions with food intake than without food intake. Both $T_{sk}$ and $T_b$ also increased during exercise. There were significant main effects of food intake on $T_{sk}$ ($F = 5.51$, $P < 0.05$) and $T_b$ ($F = 6.68$, $P < 0.05$) and of exercise time on $T_{sk}$ ($F = 456.42$, $P < 0.01$) and $T_b$ ($F = 104.13$, $P < 0.01$). On the other hand, there was no significant interaction effect on $T_{sk}$ ($F = 1.694$, $P > 0.2$) or $T_b$ ($F = 1.46$, $P > 0.2$). Both $T_{sk}$ and $T_b$
were significantly higher at minutes 0-30 during sessions with food intake than without food intake.

Figure 2 shows the changes in HR, $\dot{V}_{O2}$, and $\dot{V}_{CO2}$ during exercise. There were significant main effects of food intake ($F = 6.40, P < 0.05$) and exercise time ($F = 258.70, P < 0.01$) on HR. However, there was no significant interaction ($F = 2.52, P > 0.07$). The HR values were significantly higher at minutes 0-35 during the session with food intake than without food intake. Although there was a significant main effect of exercise time on $\dot{V}_{O2}$ ($F = 278.97, P < 0.01$), there was no significant main effect of food intake on $\dot{V}_{O2}$ ($F = 0.74, P > 0.4$) and no significant interaction ($F = 0.70, P > 0.6$). On the other hand, there were significant main effects of food intake ($F = 11.85, P < 0.05$) and exercise time ($F = 266.15, P < 0.01$) on $\dot{V}_{CO2}$, but there was no significant interaction between food intake and exercise time ($F = 0.43, P > 0.8$).

Figure 3 shows the changes in $\dot{V}_E$, $\dot{V}_A$, $f_R$, and $V_T$ during the exercise sessions. Although there were significant main effects of exercise time on $\dot{V}_E$ ($F = 143.94, P < 0.01$), $\dot{V}_A$ ($F = 153.12, P < 0.01$), $f_R$ ($F = 37.26, P < 0.01$), and $V_T$ ($F = 104.94, P < 0.01$), there were no significant main effects of food intake on $\dot{V}_E$ ($F = 4.64, P = 0.06$), $\dot{V}_A$ ($F = 4.44, P = 0.07$), or $f_R$ ($F = 0.02, P > 0.8$) or $V_T$ ($F = 3.67, P = 0.09$). Moreover, there was no significant interaction between food intake and exercise time affecting $\dot{V}_E$. 

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(\(F = 0.70, P > 0.6\)), \(V_A (F = 1.25, P > 0.2)\), or \(f_R (F = 1.39, P > 0.2)\). On the other hand, there was a significant interaction effect on \(V_T (F = 3.54, P < 0.01)\). The \(V_T\) values were significantly higher at minutes 0 and 5 during the session with food intake than without food intake.

Figure 4 shows the changes in \(\dot{V}_E/\dot{V}_{O_2}\), \(\dot{V}_E/\dot{V}_{CO_2}\) and \(P_{ETCO_2}\) during the exercise sessions. \(\dot{V}_E/\dot{V}_{O_2}\) and \(\dot{V}_E/\dot{V}_{CO_2}\) declined sharply after the onset of exercise, then increased gradually during the remainder of the exercise session. Although there was no significant main effect of food intake on \(\dot{V}_E/\dot{V}_{O_2} (F = 0.25, P > 0.6)\), there was a significant main effect of exercise time on \(\dot{V}_E/\dot{V}_{O_2} (F = 4.79, P < 0.05)\). There was no significant interaction between food intake and exercise time affecting \(\dot{V}_E/\dot{V}_{O_2} (F = 0.65, P > 0.6)\). On the other hand, there were significant main effects of food intake \((F = 5.41, P < 0.05)\) and of exercise time \((F = 19.18, P < 0.01)\) on \(\dot{V}_E/\dot{V}_{CO_2}\). Furthermore, there was a significant interaction effect \((F = 4.25, P < 0.01)\). \(\dot{V}_E/\dot{V}_{CO_2}\) was significantly higher at minute 0 during the session with food intake than without food intake. By contrast, \(P_{ETCO_2}\) increased sharply after the onset of exercise, then gradually declined during the remainder of the session. There were significant main effects of food intake \((F = 5.43, P < 0.05)\) and exercise time \((F = 14.47, P < 0.01)\) on \(P_{ETCO_2}\), but there was
no significant interaction ($F = 1.76, P > 0.1$). $\text{PETCO}_2$ was significantly higher at minutes 0-35 during the session with food intake than without food intake.

To assess the effect of food intake on the relation between ventilatory responses and core temperature, we plotted $\dot{V}_E, f_R, V_T, \dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ against $T_{es}$ (Figures 5 and 6). We found that $\dot{V}_E, f_R, \dot{V}_E/\dot{V}_{O_2}$, and $\dot{V}_E/\dot{V}_{CO_2}$ all increased with increases in $T_{es}$ during exercise in both the sessions with and without food intake. On the other hand, $V_T$ declined slightly with increases in $T_{es}$. Although there were no significant food intake-related differences in the slopes or intercepts for $\dot{V}_E, f_R, \dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$, there was a significant between-session difference in the slope and intercept for $V_T$ (Table 2).

**Discussion**

The major findings of the present study are that 1) differences in ventilatory parameters at rest caused by food intake are diminished during exercise, and 2) the sensitivities of ventilatory parameters to rising core temperature during exercise were
not influenced by food intake, with the exception of $V_T$ (slope of regression line relating $V_T$ to $T_{es}$).

Effect of food intake in the resting state

We observed that before exercise, body temperature, HR, $\dot{V}_{O2}$, $\dot{V}_{CO2}$, RER, $\dot{V}_E$, $\dot{V}_A$, and $V_T$ were all higher after food intake, which is consistent with earlier studies (Fronek and Stahlgren 1968, Hirai et al. 1991, Kelbæk et al. 1987, Nielsen 1987, Segal et al. 1987, Sue et al. 1989, Welle 1984). $P_{ETCO2}$ also tended to be higher after food intake ($P < 0.06$). Previous studies showed that the thermic effects of food, as well as postprandial increases in HR and metabolism, persist for at least 4-5 hours (Nielsen 1987, Segal et al. 1987, Welle 1984). Kelbæk et al. (1987) examined the effect of autonomic nervous control on postprandial hemodynamic changes and suggested the increase in HR is caused by vagal withdrawal or other effects independent of autonomic nervous function. Because it was reported that a 1°C increase in core temperature elicits an increase in HR of about 30 beats/min (Johnson and Proppe 1996), we suggest that increased body temperature is a likely contributor to the increase in HR. In resting subjects, the postprandial increase in $T_{es}$ was 0.2°C, which is equivalent to 6 beats/min in HR and
suggests that two-thirds of the observed increase in HR is explained by a rise in body
temperature.

To a large extent, ventilation is controlled by respiratory chemoreflexes, with
higher Pa\textsubscript{CO\textsubscript{2}} stimulating increases in ventilation (Duffin et al. 2000, West 2012b).

Duffin et al. (2000) reported that there are two ventilatory recruitment thresholds for
P\textsubscript{CO\textsubscript{2}}; with a P\textsubscript{O\textsubscript{2}} of 100 mmHg, the first breakpoint is around a P\textsubscript{CO\textsubscript{2}} of 45 mmHg, while
the second breakpoint is about 52 mmHg. Just above the first breakpoint, increases in
\dot{V}_E are caused mainly by increases in V\textsubscript{T}. However, the ventilatory recruitment threshold
for CO\textsubscript{2} reportedly varies depending on the altitude at which one lives, so that the
threshold in highlanders (altitude, 4550 m) is more than 10 mmHg lower than in
lowlanders (Slessarev et al. 2010). In the present study, all participants were lowlanders
and P\textsubscript{ET\textsubscript{CO\textsubscript{2}}} was 40-45 mmHg before and during exercise, which suggests P\textsubscript{ET\textsubscript{CO\textsubscript{2}}} values
were around the first ventilatory recruitment threshold or lower than that. Furthermore,
Duffin et al. (2000) also reported that, with P\textsubscript{O\textsubscript{2}} at 100 mmHg, just above the first
ventilatory recruitment threshold \dot{V}_E increased 3.7 l min\textsuperscript{-1} mmHg\textsuperscript{-1} and V\textsubscript{T} increased
160 ml/mmHg. In the present study, the difference in P\textsubscript{ET\textsubscript{CO\textsubscript{2}}} was 2 mmHg at rest,
which is equivalent to 7.4 l/min in \dot{V}_E and 320 ml in V\textsubscript{T}, which is differs substantially
from the actual increase in \dot{V}_E (1.5 l/min) and V\textsubscript{T} (85 ml). Because respiratory
chemosensitivity is reportedly enhanced by increases in body temperature (Baker et al. 1996, Natalino et al. 1977), it is possible that increased chemosensitivity also contributed to the elevations in $\dot{V}_E$ and $V_T$ at rest. However, the ventilatory recruitment threshold for $P_{CO_2}$ is reportedly not affected by changes in body temperature (Baker et al. 1996). Similarly, when we recently examined the effects of increased body temperature on respiratory chemosensitivity, we observed that increasing body temperature by $<0.7^\circ C$ did not affect hypercapnic chemosensitivity (Hayashi et al. 2015). Taken together, these findings make it difficult to attribute the observed elevation in $\dot{V}_E$ and $V_T$ at rest to the ventilatory recruitment threshold or the sensitivity of the hypercapnia ventilatory response.

Peripheral chemoreceptors also respond to $H^+$ ions (West 2012b). $\dot{V}_{CO_2}$ was elevated by food intake, suggesting $H^+$ ions were also elevated. It is therefore possible that elevation of $H^+$ ions contributed to increasing $\dot{V}_E$ via peripheral chemoreceptors. Because a rise in body temperature is one factor that can increase ventilation (Hayashi et al. 2006, Tsuji et al. 2016), it is also possible that increases in ventilatory parameters are induced by postprandial thermogenesis. On the other hand, we previously reported that there is a core temperature threshold for hyperpnea at around $38^\circ C$ in resting subjects (Fujii et al. 2008), which suggests the increase in $\dot{V}_E$ after food intake is not
caused by the rise in body temperature. Alternatively, it is possible that noradrenaline
acted on peripheral chemoreceptors to increased $\dot{V}_E$ and $V_T$ (Whelan and Young 1953),
as plasma noradrenaline is reportedly elevated after food intake (Welle 1995). It is
thought that the elevation in plasma noradrenaline is caused by increased muscle
sympathetic nerve activity, which is in turn thought to be a result of baroreflex-induced
counteraction to a fall blood pressure caused by vasodilation in the splanchnic
vasculature (Berne et al. 1989). We therefore suggest the increases in $\dot{V}_E$ and $V_T$
observed before exercise are caused by higher CO$_2$ production and elevation in
circulating noradrenaline levels caused by increased muscle sympathetic nerve activity.
However, we did not measure plasma noradrenaline concentrations. Further study will
be necessary to determine whether increases in plasma noradrenaline caused by food
intake contributes to the observed increases in $\dot{V}_E$ and $V_T$.

**Effect of food intake on ventilatory responses during exercise**

The changes in $\dot{V}_E$ and $V_T$ elicited by food intake were diminished after
exercise started, though body temperature, $\dot{V}_{CO2}$ and $PET_{CO2}$ were all increased. We
therefore suggest that hyperventilation-induced hypocapnia was not caused by the rise
in core temperature. $\dot{V}_E$ increases linearly with rising core temperature during exercise.
when $T_{es}$ is $>37^\circ C$ (Fujii et al. 2008; Hayashi et al. 2006, 2011, 2012; Tsuji et al. 2012, 2016). In the present study, $V_E$ increased about 7 l/min per 1°C rise in $T_{es}$, and the difference in $T_{es}$ during exercise was 0.2°C, which is equivalent to only 1.4 l/min. This suggests the rise in $T_{es}$ caused by food intake was not sufficient to elicit a significant change in $V_E$. We previously examined the effect of CO$_2$ on ventilatory responses during exercise and reported that elevated P$_{CO2}$ leads to increases in $V_E$ and V$_T$ (Hayashi et al. 2011). We suggest that one of reasons for the discrepancy between the present study and our earlier one is the magnitude of the difference between P$_{CO2}$ in sessions with or without food intake. The difference was 2-5 mmHg in our earlier study but was only 0.5-2 mmHg in the present study. It is thus possible that increased CO$_2$ production caused by food intake was not a strong enough stimulus to increase $V_E$ and V$_T$ during exercise. Sue et al. (1989) compared respiratory responses during low intensity exercise after eating a low-carbohydrate, high-fat meal (10% of calories from carbohydrate) or a high-carbohydrate, low-fat meal (70% of calories from carbohydrate) to examine the effect of the proportion of dietary fat and carbohydrate on respiratory responses during exercise. They reported that $V_{CO2}$ was higher in the high-carbohydrate session than in the low-carbohydrate session before and during exercise, but $V_E$ did not differ between the low- and high-carbohydrate sessions. In that study, the difference in $V_{CO2}$ between
resting and exercising was only 70 ml/min, and \( \text{PET}_{\text{CO}_2} \) did not differ, suggesting the increase in \( \text{CO}_2 \) production caused by the high-carbohydrate meal was not a strong enough stimulus to augment \( \dot{V}_E \). Another possibility is that the chemoreflex effect on \( \dot{V}_E \) was influenced by exercise or by a synergetic effect of exercise plus food intake. When Weil et al. (1972) examined the effect of exercise on respiratory chemosensitivity and estimated chemosensitivity at rest and during exercise at 19%, 26%, and 34% of maximal oxygen uptake (\( \dot{V}_{\text{O}_2\text{max}} \)), they observed that chemosensitivity to \( \text{CO}_2 \) was increased by exercise at more than 19% of \( \dot{V}_{\text{O}_2\text{max}} \). In the present study, subjects exercised at 50% of \( \dot{V}_{\text{O}_2\text{peak}} \), making it likely their chemosensitivity to \( \text{CO}_2 \) was increased by exercise. It is therefore possible that food intake or the combination of exercise and food intake suppresses chemosensitivity to \( \text{CO}_2 \). Durand et al. (1981) examined the effect of feeding on respiratory responses in the newborn infant and reported that feeding suppresses ventilatory chemosensitivity to \( \text{CO}_2 \). To our knowledge, however, there have been no studies examining the effect of food intake on respiratory chemosensitivity in adults. A future study will be necessary to clarify this issue.

As mentioned, food intake increases sympathetic nervous system activity, leading to elevation in plasma noradrenaline, which stimulates \( \dot{V}_E \). Moderate intensity exercise also leads to increased muscle sympathetic nerve activity (Ichinose et al. 2008), which
also increases linearly with increases in core temperature (Shiraki et al. 1995). This suggests plasma noradrenaline levels were higher in the session with food intake than without food intake. However, exercise intensity did not differ between the two session, and the difference in core temperature was only about 0.2°C. Respiration is also reportedly influenced by a variety of other factors during exercise. For example, central command and/or inputs from muscle via group III and IV muscle afferents, among others (Ward 2014). This suggests \( V_E \) during exercise is not simply explained by the chemoreflex. Breathing responses during exercise are complex and well-modulated. When several stimuli are imposed, the magnitude of the change in \( V_E \) is smaller than the summed \( V_E \) response imposed separately (Ward 2014). Consequently, \( V_E \) and \( V_T \) may have remained steady across sessions as a result of redundancy, even though both body temperature and CO\(_2\) production were increased and sympathetic nervous system activity may have also been increased by food intake.

On the other hand, we observed that the slope and intercept of the \( V_T-T_{es} \) relationship were increased by food intake. To calculate the slopes and intercepts of regression lines relating ventilatory parameters to \( T_{es} \), we began collecting data after 5 min of exercise. The elevation in \( V_T \) was maintained for 5 min after the start of the exercise, which means the increase in \( V_T \) influenced the food-induced changes in the
slope and intercept of the $V_T-T_{es}$ relationship. We suggest this higher $V_T$ early during exercise in the food intake session reflected the relatively slow adjustment of $V_T$. Bell and Duffin (2006) examined changes in respiratory parameters that accompany the transition from rest to exercise, and from passive to active exercise. They showed that $V_E$ and $f_R$ change rapidly in response to changes in conditions, but changes in $V_T$ are slower than those in $V_E$ and $f_R$. Consequently, $V_T$ would be increased by ventilatory drive induced by CO$_2$ production and elevated plasma noradrenaline and then remain higher early during the exercise. However, this remains to be confirmed.

**Limitations and perspectives**

The increase in CO$_2$ production caused by food intake was not sufficient to change $V_E$ during exercise. We designed test meals to provide 25-30% of estimated total energy expenditure with 60-65% of calories from carbohydrate. Sue et al. (1989) also showed that differences in $V_{CO2}$ between high and low carbohydrate meals was only 70 ml/min both before and during exercise, which is consistent with our results. Total energy content of the meals in the study from Sue et al. was comparable to our test meals. Subjects then exercised 90 min after food intake in the present study, while the subjects in Sue et al. exercised 120 min after food intake. Because it is possible that
CO₂ production reaches a peak 30-60 min after intake of carbohydrate (Claessens et al. 2007), V̇\textsubscript{CO₂} and PET\textsubscript{CO₂} may not greatly differ between sessions in the present study. Furthermore, with regard to the effect of food intake on CO₂ production, Talpers et al. (1992) reported that differences in carbohydrate content (isocaloric with 40-75% of calories from carbohydrate) did not influence V̇\textsubscript{CO₂}, but changes in total energy content did. This suggests increasing the total energy content – i.e. increasing the amount of carbohydrate – induces higher CO₂ production.

Reductions in Pa\textsubscript{CO₂} caused by hyperthermic hyperventilation induce cerebral hypoperfusion (Hayashi et al. 2011, Nybo and Nielsen 2001), which in turn leads to increased brain temperature (Nybo et al. 2002). Although the difference in the absolute level of Pa\textsubscript{CO₂} was small, the present study showed that Pa\textsubscript{CO₂} is maintained at a higher level for at least 2 hours after food intake. This suggests the possibility that some foods or drinks can increase CO₂ production to a greater degree than others. For example, foods composed largely of carbohydrate may mitigate the reduction in cerebral blood flow during exercise in the heat. On the other hand, gastrointestinal blood flow is also increased to support digestion and/or absorption (Fara 1984), which can impact blood flow to other areas, including the brain. Future studies will be required to determine whether food intake affects cerebral blood flow during exercise.
Conclusion

In summary, the present study shows that food intake increases baseline body temperature and augments cardiorespiratory responses at rest, and that the increases in body temperature and HR persist during exercise started 90 min after food intake. 

PET_{CO2} at rest was not affected by food intake, but was increased during exercise. 

However, differences in ventilatory parameters were diminished soon after the onset of exercise, suggesting that the increases in body temperature and PET_{CO2} do not affect ventilatory responses during exercise. Only V_{T} was elevated early during the exercise after food intake, and this change influenced ventilatory sensitivity to rising core temperature.

Author Contribution Statement

KH, YI, and YS conceived and designed research. NI and YI designed and prepared test meals. KH and NI conducted experiments. KH and NI analyzed data. KH drafted the manuscript. KH and YS edited and revised manuscript. All authors read and approved final version of manuscript.
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Compliance with ethical standards

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Conflict of interest: The authors declare no conflicts of interest, financial or otherwise.
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Table 1. Baseline levels of the measured parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With food intake</th>
<th>Without food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{es}$, °C</td>
<td>37.1 ± 0.2</td>
<td>36.9 ± 0.2 (P &lt; 0.09)</td>
</tr>
<tr>
<td>$T_{sk}$, °C</td>
<td>35.3 ± 0.6</td>
<td>35.0 ± 0.5 *</td>
</tr>
<tr>
<td>$T_{b}$, °C</td>
<td>36.9 ± 0.2</td>
<td>36.7 ± 0.3 *</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>75 ± 11</td>
<td>66 ± 8 *</td>
</tr>
<tr>
<td>$V_{O2}$, ml/min</td>
<td>408 ± 60</td>
<td>354 ± 50 *</td>
</tr>
<tr>
<td>$V_{CO2}$, ml/min</td>
<td>359 ± 56</td>
<td>287 ± 36 *</td>
</tr>
<tr>
<td>RER, unit</td>
<td>0.88 ± 0.03</td>
<td>0.81 ± 0.04 *</td>
</tr>
<tr>
<td>$V_{E}$, l/min</td>
<td>12.1 ± 1.7</td>
<td>10.6 ± 1.3 *</td>
</tr>
<tr>
<td>$V_{A}$, l/min</td>
<td>9.8 ± 1.3</td>
<td>8.2 ± 1.0 *</td>
</tr>
<tr>
<td>$f_R$, breaths/min</td>
<td>17 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>$V_T$, ml</td>
<td>723 ± 80</td>
<td>638 ± 64 *</td>
</tr>
<tr>
<td>$V_{E}/V_{O2}$, unit</td>
<td>29.9 ± 2.0</td>
<td>30.4 ± 2.2</td>
</tr>
<tr>
<td>$V_{E}/V_{CO2}$, unit</td>
<td>34.1 ± 2.1</td>
<td>37.3 ± 2.3 *</td>
</tr>
<tr>
<td>PET$_{O2}$, mmHg</td>
<td>108 ± 4</td>
<td>109 ± 4</td>
</tr>
<tr>
<td>PET$_{CO2}$, mmHg</td>
<td>40 ± 2</td>
<td>38 ± 3 (P &lt; 0.06)</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 with food intake vs. without food intake.
Table 2. *Slopes and intercepts of regression lines calculated after plotting the indicated ventilatory parameter against esophageal temperature*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With food intake</th>
<th>Without food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E - T_{es}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, l·min$^{-1}$·°C$^{-1}$</td>
<td>6.8 ± 3.6</td>
<td>6.9 ± 6.4</td>
</tr>
<tr>
<td>Intercept, l/min</td>
<td>-206.4 ± 128.0</td>
<td>-210.1 ± 235.7</td>
</tr>
<tr>
<td>$f_R - T_{es}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, breaths·min$^{-1}$·°C$^{-1}$</td>
<td>7.8 ± 3.8</td>
<td>6.9 ± 6.3</td>
</tr>
<tr>
<td>Intercept, breaths/min</td>
<td>-259.6 ± 137.6</td>
<td>-222.8 ± 230.6</td>
</tr>
<tr>
<td>$V_T - T_{es}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, ml/°C</td>
<td>-97 ± 83</td>
<td>-43 ± 87 *</td>
</tr>
<tr>
<td>Intercept, ml</td>
<td>5127 ± 3261</td>
<td>3028 ± 3293 *</td>
</tr>
<tr>
<td>$V_E/V_{O2} - T_{es}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, unit/°C</td>
<td>1.57 ± 0.95</td>
<td>1.30 ± 1.86</td>
</tr>
<tr>
<td>Intercept, unit</td>
<td>-32.53 ± 35.44</td>
<td>-22.21 ± 67.89</td>
</tr>
<tr>
<td>$V_E/V_{CO2} - T_{es}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope, unit/°C</td>
<td>2.53 ± 1.00</td>
<td>2.34 ± 1.88</td>
</tr>
<tr>
<td>Intercept, unit</td>
<td>-68.13 ± 37.30</td>
<td>-59.71 ± 68.66</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 with food intake vs. without food intake.
Figure legends

Figure 1. Time-dependent changes in esophageal temperature (top), mean skin temperature (middle) and mean body temperature (bottom) during exercise sessions with (solid circle) and without (open circle) food intake. The numbers adjacent to the symbols in the graph of esophageal temperature indicate the number of subjects still exercising at the corresponding time, while the numbers adjacent to the symbols in the graph of mean skin temperature indicate the number of subjects whose skin temperature we were able to measure. *P < 0.05 with vs. without food intake.

Figure 2. Time-dependent changes in heart rate (top), oxygen uptake (middle) and carbon dioxide output (bottom) during exercise sessions with (solid circle) and without (open circle) food intake. *P < 0.05 with vs. without food intake.

Figure 3. Time-dependent changes in minute ventilation (top), alveolar ventilation (second), respiratory frequency (third) and tidal volume (bottom) during exercise sessions with (solid circles) and without (open circles) food intake. *P < 0.05 with vs. without food intake.
Figure 4. Time-dependent changes in ventilatory equivalents for oxygen uptake ($\dot{V}_E/\dot{V}_{O_2}$) (top), ventilatory equivalents for carbon dioxide output ($\dot{V}_E/\dot{V}_{CO_2}$) (middle) and end-tidal $P_{CO_2}$ ($PET_{CO_2}$) (bottom) during exercise sessions with (solid circle) and without (open circle) food intake. *$P < 0.05$ with vs. without food intake.

Figure 5. Esophageal temperature-dependent changes in minute ventilation (top), respiratory frequency (middle) and tidal volume (bottom) during exercise sessions with (solid circle and black line) and without (open circle and gray line) food intake.

Figure 6. Esophageal temperature-dependent changes in $\dot{V}_E/\dot{V}_{O_2}$ (top) and $\dot{V}_E/\dot{V}_{CO_2}$ (bottom) during exercise sessions with (solid circle and black line) and without (open circle and gray line) food intake.