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

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2 **Effect of food intake on the ventilatory response to increasing core**
3 **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,

34 food intake does not affect ventilatory parameters during exercise, despite elevation of
35 both body temperature and metabolism. Thus, with the exception of an early transient
36 effect on V_T , ventilatory sensitivity to rising core temperature is not affected by food
37 intake.

38

39 Keywords: diet-induced thermogenesis, postprandial thermogenesis, body temperature,
40 ventilation

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42 **Introduction**

43 During exercise in the heat, body temperature rises, and minute ventilation ($\dot{V}_E$)
44 increases in proportion to the rise in body temperature (Fujii et al. 2008, Hayashi et al.
45 2006, 2011, 2012, Nybo and Nielsen 2001, Tsuji et al. 2012, 2016). When expressed as
46 a function of esophageal temperature (T_{es}), $\dot{V}_E$ reportedly increases 5-12 l/min per 1°C
47 rise in T_{es} during prolonged exercise at moderate intensity (Fujii et al. 2008, Hayashi et
48 al. 2006, 2011, 2012, Tsuji et al. 2012, 2016). This hyperthermia-induced
49 hyperventilation enhances alveolar gas exchange, leading to a reduction in arterial CO₂
50 pressure (P_{aCO_2}). Because P_{aCO_2} influences ventilatory responses via the chemoreflex
51 (West 2012b), we previously examined the effect of CO₂ on ventilatory sensitivity to
52 rising body temperature (slope of the regression line relating $\dot{V}_E$ to T_{es}) during exercise
53 in the heat (Hayashi et al. 2011). We found that inhaling CO₂-enriched air to mitigate
54 hypocapnia otherwise caused by hyperthermia-induced hyperventilation, increased
55 ventilatory sensitivity to rising body temperature from 8.9 l·min⁻¹·°C⁻¹ (with inhaling
56 room air) to 19.8 l·min⁻¹·°C⁻¹ (with inhaling CO₂-enriched air), which suggests P_{aCO_2}
57 greatly influences ventilatory sensitivity to rising body temperature.

58 It is also well known that food intake increases metabolism and raises body
59 temperature. This is the so-called postprandial or diet-induced thermogenesis (Bergman

60 and Brooks 1999, Hayashi et al. 2014, Hill et al. 1985, Nielsen 1987, Welle 1984). We
61 previously observed that food intake increases end-tidal CO₂ pressure (PET_{CO2})
62 (Hayashi et al. 2014). Although the size of the increase in PET_{CO2} caused by food intake
63 was only 2 mmHg, it is reasonable to suggest the higher PET_{CO2} stimulates ventilation
64 during exercise. It is also well established that food intake leads to increased oxygen
65 uptake ($\dot{V}_{O_2}$) and carbon dioxide elimination ($\dot{V}_{CO_2}$) during rest (Hayashi et al. 2014,
66 Nielsen 1987, Welle 1984). It is possible that elevation of $\dot{V}_{CO_2}$ leads to increases in the
67 H⁺ concentration. Peripheral chemoreceptors also respond to elevated H⁺ (West 2012b),
68 suggesting that food intake may lead to an increase in $\dot{V}_E$ via chemoreceptor activity.
69 Consistent with that idea, increases in body temperature reportedly augment respiratory
70 chemosensitivity (Baker et al. 1996, Natalino et al. 1977), suggesting postprandial
71 thermogenesis may also augment respiratory chemosensitivity. It is thus likely that food
72 intake itself is the cause of augmented postprandial ventilatory responses.

73 On the other hand, it is possible that the rise in body temperature caused by
74 food intake leads to hyperventilation-induced hypocapnia (respiratory alkalosis), which
75 may suppress ventilatory responses, as hyperthermia exerts a greater stimulatory effect
76 on ventilation than does an elevation in metabolism (Fujii et al. 2008, Hayashi et al.
77 2006). Consequently, it remains unclear whether elevations in body temperature and

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

82

83 **Materials and methods**

84 *Participants*

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

92

93 $\dot{V}_{O_{2peak}}$ test

94 Initially, $\dot{V}_{O_{2peak}}$ was determined during an incremental exercise test performed on
95 a cycle ergometer (model 828E, Monark) to volitional fatigue. The exercise was started

96 at 60 W, after which the load was increased at a rate of 15 W/min throughout the entire
97 exercise period. Subjects pedaled at 60 rpm, and volitional fatigue was defined as an
98 inability to pedal at more than 50 rpm. During the exercise, the subjects wore a nose
99 clip and breathed into a mouthpiece containing a two-way valve. A mass-flow sensor
100 (hot-wire type) and a gas-sampling tube were connected to the mouthpiece, and the
101 expired volume and gases were analyzed using a metabolic cart (Vmax 29, Sensor
102 Medics, USA) with a mixing chamber set-up. The metabolic cart was calibrated with
103 the aid of an appurtenant calibration syringe that blew a fixed volume (3 L) of air. The
104 $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ sensors were calibrated using reference gases of known concentration. $\dot{V}_{O_2}$
105 and $\dot{V}_{CO_2}$ were calculated at 60-s intervals. $\dot{V}_{O_{2peak}}$ was taken as the highest value of $\dot{V}_{O_2}$
106 achieved by a given subject, as some subjects did not achieve a plateau (even though
107 respiratory exchange rate exceeded 1.1 when $\dot{V}_{O_2}$ reached a peak value). The $\dot{V}_{O_{2peak}}$ test
108 was carried out in an experimental laboratory maintained at 25°C and 40-60% relative
109 humidity.

110

111 *Test meal*

112 Test meals were designed for each subject. After estimating the basal metabolic
113 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 $3,097 \pm 235$ kJ.

120

121 *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

132 sitting in a chair to adjust the starting time of the experiment. During this period, a
133 thermocouple was inserted via the nasal passage to record T_{es} . This thermocouple was
134 inserted to a distance equivalent to one-fourth of the subject's height (Wenger and
135 Roberts 1980). The subject then voided urine, was weighed, and sat in a chair to rest for
136 another 30 min while a heart rate (HR) monitor and thermocouples for recording skin
137 temperature were attached. The subject then put on a water-perfused jacket. Because it
138 was difficult to finely control room temperature and humidity, we asked subjects to
139 wear a water-perfused suit, which gave us precise control over the temperature to which
140 the subjects were exposed. After that, subjects seated on a bike. A mass-flow sensor and
141 a gas-sampling tube were connected to the mask just before the measurements were
142 begun, and the jacket was perfused with water at 35°C.

143 The subjects performed the cycle exercise at 50% $\dot{V}_{O_{2peak}}$. At the onset of the
144 exercise, the temperature of the water perfusion was increased to 45°C, and the exercise
145 was continued for 45 min. No fluid was provided during any session. The experiments
146 were carried out in an experimental laboratory maintained at 25°C and 40-60% relative
147 humidity.

148

149 *Measurements*

150 During the exercise sessions, T_{es} and skin temperature data were collected via
151 copper constantan thermocouples, which were sampled every 1 s using a data logger
152 system (WE7000, Yokogawa, Japan) and averaged over 30-s periods. Skin temperatures
153 were collected at four sites (chest, upper arm, thigh and calf) and used to calculate the
154 weighted mean skin temperature ($\dot{T}_{sk}$) (Ramanathan 1964). The mean body temperature
155 ($\dot{T}_b$) was calculated as: $\dot{T}_b = 0.9T_{es} + 0.1\dot{T}_{sk}$ (Gagge and Nishi 1977). HR was recorded
156 every 5 s using a HR monitor (S810i, Polar, Finland) and averaged over 30-s periods.
157 The expired gas was measured breath-by-breath using the same analyzers used in the
158 $\dot{V}_{O_{2peak}}$ test (see above).

159

160 *Data analysis*

161 Baseline values were obtained from data averaged over the 5 min just before
162 exercise. Data obtained during exercise were averaged over every 5 min of the exercise.
163 We estimated dead space as 150 ml (West 2012a) and alveolar ventilation ($\dot{V}_A$) was
164 calculated by multiplying the value obtained by subtracting estimated dead space from
165 V_T by respiratory frequency (f_R). $\dot{V}_E$, V_T , f_R , ventilatory equivalents for oxygen uptake
166 ($\dot{V}_E/\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_E/\dot{V}_{CO_2}$) measured during the exercise sessions

167 were plotted as functions of T_{es} , and we took the slopes of the linear regression lines
168 calculated by the method of least squares as indices of the ventilatory response to the
169 increase in body temperature. To exclude the fast component of $\dot{V}_E$ kinetics, only data
170 collected after the 5th min of exercise were analyzed. Further, we confirmed that the
171 effects of exercise time and skin temperature on the ventilatory responses to the increase
172 in T_{es} was negligible (Hayashi et al. 2006).

173

174 *Statistical analysis*

175 The ventilatory sensitivities of $\dot{V}_E$, V_T , and f_R to rising core temperature (slope
176 of the regression lines relating the ventilatory parameters to T_{es}) were selected as
177 important indices. To compare their means, minimum sample sizes were calculated on
178 the basis of 80% power and a significance level of 0.05. We used standard deviations for
179 the ventilatory sensitivities to rising core temperature from our pilot experiments.
180 Sample sizes enabling detection of food intake-related differences of $4.0 \text{ L} \cdot \text{min}^{-1} \cdot ^\circ\text{C}^{-1}$
181 for the slope of the regression line relating $\dot{V}_E$ and T_{es} , $50 \text{ ml}/^\circ\text{C}$ for the slope of the
182 regression line relating V_T and T_{es} , and $3 \text{ breaths} \cdot \text{min}^{-1} \cdot ^\circ\text{C}^{-1}$ for the slope of the
183 regression line relating f_R and T_{es} were estimated to be 9, 8 and 9, respectively (Hayashi
184 et al. 2012). Therefore, our sample size of 9 subjects was adequate for our analysis.

185 All values are reported as means $\pm$ SD. Statistical analyses were performed
186 using IBM SPSS Statistics (version 19.0; SPSS Inc., USA). Two-way ANOVA with
187 repeated measures was conducted using time (levels: 0, 5, 10, 15, 20, 25, 30, and 35
188 min) and food intake (levels: with food intake and without food intake) as factors.
189 Times at which the number of subjects was reduced (40 and 45 min) were not analyzed.
190 Because a thermocouple measuring skin temperature peeled off of one subject, we
191 analyzed only 0-30 min of the $\dot{T}_{sk}$ and $\dot{T}_b$ data for that subject. After the significant
192 interaction and simple main effects were identified, pairwise differences were identified
193 using Bonferroni's post hoc procedure. Paired t -tests were also used to compare the
194 "with food intake" and "without food intake" sessions with respect to the baseline
195 values of the physiological parameters (Table 1), and the slopes and intercepts of their
196 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
197 functions of T_{es} (Table 2). Values of $P < 0.05$ were considered significant.

198

199 **Results**

200 *Baseline comparisons*

201 Baseline $\dot{T}_{sk}$, $\dot{T}_b$, HR, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, respiratory exchange ratio (RER), $\dot{V}_E$, $\dot{V}_A$, and
202 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_{CO_2} 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_{O_2}) did not significantly differ between sessions.

Comparisons during exercise

Figure 1 shows the changes in T_{es} , $\dot{T}_{sk}$ and $\dot{T}_b$ during exercise. T_{es} rose during exercise, reaching $38.6 \pm 0.4^\circ\text{C}$ at the end of the exercise during sessions with food intake and $38.4 \pm 0.2^\circ\text{C}$ 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 $\dot{T}_{sk}$ and $\dot{T}_b$ also increased during exercise. There were significant main effects of food intake on $\dot{T}_{sk}$ ($F = 5.51$, $P < 0.05$) and $\dot{T}_b$ ($F = 6.68$, $P < 0.05$) and of exercise time on $\dot{T}_{sk}$ ($F = 456.42$, $P < 0.01$) and $\dot{T}_b$ ($F = 104.13$, $P < 0.01$). On the other hand, there was no significant interaction effect on $\dot{T}_{sk}$ ($F = 1.694$, $P > 0.2$) or $\dot{T}_b$ ($F = 1.46$, $P > 0.2$). Both $\dot{T}_{sk}$ and $\dot{T}_b$

220 $\dot{V}_{O_2}$ were significantly higher at minutes 0-30 during sessions with food intake than
221 without food intake.

222 Figure 2 shows the changes in HR, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ during exercise. There were
223 significant main effects of food intake ($F = 6.40$, $P < 0.05$) and exercise time ($F =$
224 258.70 , $P < 0.01$) on HR. However, there was no significant interaction ($F = 2.52$, $P >$
225 0.07). The HR values were significantly higher at minutes 0-35 during the session with
226 food intake than without food intake. Although there was a significant main effect of
227 exercise time on $\dot{V}_{O_2}$ ($F = 278.97$, $P < 0.01$), there was no significant main effect of
228 food intake on $\dot{V}_{O_2}$ ($F = 0.74$, $P > 0.4$) and no significant interaction ($F = 0.70$, $P > 0.6$).
229 On the other hand, there were significant main effects of food intake ($F = 11.85$, $P <$
230 0.05) and exercise time ($F = 266.15$, $P < 0.01$) on $\dot{V}_{CO_2}$, but there was no significant
231 interaction between food intake and exercise time ($F = 0.43$, $P > 0.8$).

232 Figure 3 shows the changes in $\dot{V}_E$, $\dot{V}_A$, f_R , and V_T during the exercise sessions.
233 Although there were significant main effects of exercise time on $\dot{V}_E$ ($F = 143.94$, $P <$
234 0.01), $\dot{V}_A$ ($F = 153.12$, $P < 0.01$), f_R ($F = 37.26$, $P < 0.01$), and V_T ($F = 104.94$, $P <$
235 0.01), there were no significant main effects of food intake on $\dot{V}_E$ ($F = 4.64$, $P = 0.06$),
236 $\dot{V}_A$ ($F = 4.44$, $P = 0.07$), or f_R ($F = 0.02$, $P > 0.8$) or V_T ($F = 3.67$, $P = 0.09$). Moreover,
237 there was no significant interaction between food intake and exercise time affecting $\dot{V}_E$

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

242 Figure 4 shows the changes in $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$ and PET_{CO_2} during the exercise
243 sessions. $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ declined sharply after the onset of exercise, then
244 increased gradually during the remainder of the exercise session. Although there was no
245 significant main effect of food intake on $\dot{V}_E/\dot{V}_{O_2}$ ($F = 0.25$, $P > 0.6$), there was a
246 significant main effect of exercise time on $\dot{V}_E/\dot{V}_{O_2}$ ($F = 4.79$, $P < 0.05$). There was no
247 significant interaction between food intake and exercise time affecting $\dot{V}_E/\dot{V}_{O_2}$ ($F = 0.65$,
248 $P > 0.6$). On the other hand, there were significant main effects of food intake ($F = 5.41$,
249 $P < 0.05$) and of exercise time ($F = 19.18$, $P < 0.01$) on $\dot{V}_E/\dot{V}_{CO_2}$. Furthermore, there
250 was a significant interaction effect ($F = 4.25$, $P < 0.01$). $\dot{V}_E/\dot{V}_{CO_2}$ was significantly
251 higher at minute 0 during the session with food intake than without food intake. By
252 contrast, PET_{CO_2} increased sharply after the onset of exercise, then gradually declined
253 during the remainder of the session. There were significant main effects of food intake
254 ($F = 5.43$, $P < 0.05$) and exercise time ($F = 14.47$, $P < 0.01$) on PET_{CO_2} , but there was

no significant interaction ($F = 1.76$, $P > 0.1$). PET_{CO_2} was significantly higher at minutes 0-35 during the session with food intake than without food intake.

257

T_{es}-dependent changes in ventilatory responses

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).

267

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, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, RER, $\dot{V}_E$, $\dot{V}_A$, and V_T were all higher after food intake, which is consistent with earlier studies (Fronck and Stahlgren 1968, Hirai et al. 1991, Kelbæk et al. 1987, Nielsen 1987, Segal et al. 1987, Sue et al. 1989, Welle 1984). PET_{CO_2} 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

289 suggests that two-thirds of the observed increase in HR is explained by a rise in body
290 temperature.

291 To a large extent, ventilation is controlled by respiratory chemoreflexes, with
292 higher P_{aCO_2} stimulating increases in ventilation (Duffin et al. 2000, West 2012b).
293 Duffin et al. (2000) reported that there are two ventilatory recruitment thresholds for
294 P_{CO_2} ; with a P_{O_2} of 100 mmHg, the first breakpoint is around a P_{CO_2} of 45 mmHg, while
295 the second breakpoint is about 52 mmHg. Just above the first breakpoint, increases in
296 $\dot{V}_E$ are caused mainly by increases in V_T . However, the ventilatory recruitment threshold
297 for CO_2 reportedly varies depending on the altitude at which one lives, so that the
298 threshold in highlanders (altitude, 4550 m) is more than 10 mmHg lower than in
299 lowlanders (Slessarev et al. 2010). In the present study, all participants were lowlanders
300 and PET_{CO_2} was 40-45 mmHg before and during exercise, which suggests PET_{CO_2} values
301 were around the first ventilatory recruitment threshold or lower than that. Furthermore,
302 Duffin et al. (2000) also reported that, with P_{O_2} at 100 mmHg, just above the first
303 ventilatory recruitment threshold $\dot{V}_E$ increased $3.7 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and V_T increased
304 160 ml/mmHg. In the present study, the difference in PET_{CO_2} was 2 mmHg at rest,
305 which is equivalent to 7.4 l/min in $\dot{V}_E$ and 320 ml in V_T , which differs substantially
306 from the actual increase in $\dot{V}_E$ (1.5 l/min) and V_T (85 ml). Because respiratory

307 chemosensitivity is reportedly enhanced by increases in body temperature (Baker et al.
308 1996, Natalino et al. 1977), it is possible that increased chemosensitivity also
309 contributed to the elevations in $\dot{V}_E$ and V_T at rest. However, the ventilatory recruitment
310 threshold for P_{CO_2} is reportedly not affected by changes in body temperature (Baker et al.
311 1996). Similarly, when we recently examined the effects of increased body temperature
312 on respiratory chemosensitivity, we observed that increasing body temperature by
313 $<0.7^\circ\text{C}$ did not affect hypercapnic chemosensitivity (Hayashi et al. 2015). Taken
314 together, these findings make it difficult to attribute the observed elevation in $\dot{V}_E$ and V_T
315 at rest to the ventilatory recruitment threshold or the sensitivity of the hypercapnia
316 ventilatory response.

317 Peripheral chemoreceptors also respond to H^+ ions (West 2012b). $\dot{V}_{CO_2}$ was
318 elevated by food intake, suggesting H^+ ions were also elevated. It is therefore possible
319 that elevation of H^+ ions contributed to increasing $\dot{V}_E$ via peripheral chemoreceptors.
320 Because a rise in body temperature is one factor that can increase ventilation (Hayashi
321 et al. 2006, Tsuji et al. 2016), it is also possible that increases in ventilatory parameters
322 are induced by postprandial thermogenesis. On the other hand, we previously reported
323 that there is a core temperature threshold for hyperpnea at around 38°C in resting
324 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 .

337

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, $\dot{V}_{\text{CO}_2}$ and PET_{CO_2} 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

343 when T_{es} is $>37^{\circ}\text{C}$ (Fujii et al. 2008; Hayashi et al. 2006, 2011, 2012; Tsuji et al. 2012,
344 2016). In the present study, $\dot{V}_E$ increased about 7 l/min per 1°C rise in T_{es} , and the
345 difference in T_{es} during exercise was 0.2°C , which is equivalent to only 1.4 l/min. This
346 suggests the rise in T_{es} caused by food intake was not sufficient to elicit a significant
347 change in $\dot{V}_E$. We previously examined the effect of CO_2 on ventilatory responses
348 during exercise and reported that elevated P_{CO_2} leads to increases in $\dot{V}_E$ and V_T (Hayashi
349 et al. 2011). We suggest that one of reasons for the discrepancy between the present
350 study and our earlier one is the magnitude of the difference between P_{CO_2} in sessions
351 with or without food intake. The difference was 2-5 mmHg in our earlier study but was
352 only 0.5-2 mmHg in the present study. It is thus possible that increased CO_2 production
353 caused by food intake was not a strong enough stimulus to increase $\dot{V}_E$ and V_T during
354 exercise. Sue et al. (1989) compared respiratory responses during low intensity exercise
355 after eating a low-carbohydrate, high-fat meal (10% of calories from carbohydrate) or a
356 high-carbohydrate, low-fat meal (70% of calories from carbohydrate) to examine the
357 effect of the proportion of dietary fat and carbohydrate on respiratory responses during
358 exercise. They reported that $\dot{V}_{\text{CO}_2}$ was higher in the high-carbohydrate session than in
359 the low-carbohydrate session before and during exercise, but $\dot{V}_E$ did not differ between
360 the low- and high-carbohydrate sessions. In that study, the difference in $\dot{V}_{\text{CO}_2}$ between

361 resting and exercising was only 70 ml/min, and PET_{CO_2} did not differ, suggesting the
362 increase in CO_2 production caused by the high-carbohydrate meal was not a strong
363 enough stimulus to augment $\dot{V}_E$. Another possibility is that the chemoreflex effect on $\dot{V}_E$
364 was influenced by exercise or by a synergetic effect of exercise plus food intake. When
365 Weil et al. (1972) examined the effect of exercise on respiratory chemosensitivity and
366 estimated chemosensitivity at rest and during exercise at 19%, 26%, and 34% of
367 maximal oxygen uptake ($\dot{V}_{O_{2max}}$), they observed that chemosensitivity to CO_2 was
368 increased by exercise at more than 19% of $\dot{V}_{O_{2max}}$. In the present study, subjects
369 exercised at 50% of $\dot{V}_{O_{2peak}}$, making it likely their chemosensitivity to CO_2 was
370 increased by exercise. It is therefore possible that food intake or the combination of
371 exercise and food intake suppresses chemosensitivity to CO_2 . Durand et al. (1981)
372 examined the effect of feeding on respiratory responses in the newborn infant and
373 reported that feeding suppresses ventilatory chemosensitivity to CO_2 . To our knowledge,
374 however, there have been no studies examining the effect of food intake on respiratory
375 chemosensitivity in adults. A future study will be necessary to clarify this issue.

376 As mentioned, food intake increases sympathetic nervous system activity, leading
377 to elevation in plasma noradrenaline, which stimulates $\dot{V}_E$. Moderate intensity exercise
378 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 $\dot{V}_E$ 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 $\dot{V}_E$ is smaller than the summed $\dot{V}_E$ response imposed separately (Ward 2014). Consequently, $\dot{V}_E$ and V_T may have remained steady across sessions as a result of redundancy, even though both body temperature and CO₂ 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

397 slope and intercept of the V_T - T_{es} relationship. We suggest this higher V_T early during
398 exercise in the food intake session reflected the relatively slow adjustment of V_T . Bell
399 and Duffin (2006) examined changes in respiratory parameters that accompany the
400 transition from rest to exercise, and from passive to active exercise. They showed that
401 $\dot{V}_E$ and f_R change rapidly in response to changes in conditions, but changes in V_T are
402 slower than those in $\dot{V}_E$ and f_R . Consequently, V_T would be increased by ventilatory
403 drive induced by CO_2 production and elevated plasma noradrenaline and then remain
404 higher early during the exercise. However, this remains to be confirmed.

405 406 *Limitations and perspectives*

407 The increase in CO_2 production caused by food intake was not sufficient to
408 change $\dot{V}_E$ during exercise. We designed test meals to provide 25-30% of estimated total
409 energy expenditure with 60-65% of calories from carbohydrate. Sue et al. (1989) also
410 showed that differences in $\dot{V}_{CO_2}$ between high and low carbohydrate meals was only 70
411 ml/min both before and during exercise, which is consistent with our results. Total
412 energy content of the meals in the study from Sue et al. was comparable to our test
413 meals. Subjects then exercised 90 min after food intake in the present study, while the
414 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), $\dot{V}_{\text{CO}_2}$ and PET_{CO_2} 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 $\dot{V}_{\text{CO}_2}$, 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_{CO_2} 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_{CO_2} was small, the present study showed that Pa_{CO_2} 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.

433

434 **Conclusion**

435 In summary, the present study shows that food intake increases baseline body
436 temperature and augments cardiorespiratory responses at rest, and that the increases in
437 body temperature and HR persist during exercise started 90 min after food intake.
438 P_{ETCO_2} at rest was not affected by food intake, but was increased during exercise.
439 However, differences in ventilatory parameters were diminished soon after the onset
440 exercise, suggesting that the increases in body temperature and P_{ETCO_2} do not affect
441 ventilatory responses during exercise. Only V_T was elevated early during the exercise
442 after food intake, and this change influenced ventilatory sensitivity to rising core
443 temperature.

444

445 **Author Contribution Statement**

446 KH, YI, and YS conceived and designed research. NI and YI designed and
447 prepared test meals. KH and NI conducted experiments. KH and NI analyzed data. KH
448 drafted the manuscript. KH and YS edited and revised manuscript. All authors read and
449 approved final version of manuscript.

450

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455

456 **Compliance with ethical standards**

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460

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596

597 Table 1. *Baseline levels of the measured parameters*

	With food intake	Without food intake
T_{es} , °C	37.1 ± 0.2	36.9 ± 0.2 ($P < 0.09$)
$\bar{T}_{sk}$, °C	35.3 ± 0.6	35.0 ± 0.5 *
$\bar{T}_b$, °C	36.9 ± 0.2	36.7 ± 0.3 *
HR, beats/min	75 ± 11	66 ± 8 *
$\dot{V}_{O_2}$, ml/min	408 ± 60	354 ± 50 *
$\dot{V}_{CO_2}$, ml/min	359 ± 56	287 ± 36 *
RER, unit	0.88 ± 0.03	0.81 ± 0.04 *
$\dot{V}_E$, l/min	12.1 ± 1.7	10.6 ± 1.3 *
$\dot{V}_A$, l/min	9.8 ± 1.3	8.2 ± 1.0 *
f_R , breaths/min	17 ± 2	17 ± 2
V_T , ml	723 ± 80	638 ± 64 *
$\dot{V}_E/\dot{V}_{O_2}$, unit	29.9 ± 2.0	30.4 ± 2.2
$\dot{V}_E/\dot{V}_{CO_2}$, unit	34.1 ± 2.1	37.3 ± 2.3 *
PET _{O₂} , mmHg	108 ± 4	109 ± 4
PET _{CO₂} , mmHg	40 ± 2	38 ± 3 ($P < 0.06$)

598 Values are means $\pm$ SD. * $P < 0.05$ with food intake vs. without food intake.

599

600 Table 2. *Slopes and intercepts of regression lines calculated after plotting the indicated*
601 *ventilatory parameter against esophageal temperature*

	With food intake	Without food intake
$\dot{V}_E - T_{es}$		
Slope, l·min ⁻¹ ·°C ⁻¹	6.8 ± 3.6	6.9 ± 6.4
Intercept, l/min	-206.4 ± 128.0	-210.1 ± 235.7
$f_R - T_{es}$		
Slope, breaths·min ⁻¹ ·°C ⁻¹	7.8 ± 3.8	6.9 ± 6.3
Intercept, breaths/min	-259.6 ± 137.6	-222.8 ± 230.6
$V_T - T_{es}$		
Slope, ml/°C	-97 ± 83	-43 ± 87 *
Intercept, ml	5127 ± 3261	3028 ± 3293 *
$\dot{V}_E/\dot{V}_{O_2} - T_{es}$		
Slope, unit/°C	1.57 ± 0.95	1.30 ± 1.86
Intercept, unit	-32.53 ± 35.44	-22.21 ± 67.89
$\dot{V}_E/\dot{V}_{CO_2} - T_{es}$		
Slope, unit/°C	2.53 ± 1.00	2.34 ± 1.88
Intercept, unit	-68.13 ± 37.30	-59.71 ± 68.66

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

603

604 **Figure legends**

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

612

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

616

617 **Figure 3.** Time-dependent changes in minute ventilation (*top*), alveolar ventilation
618 (*second*), respiratory frequency (*third*) and tidal volume (*bottom*) during exercise
619 sessions with (solid circles) and without (open circles) food intake. *P < 0.05 with vs.
620 without food intake.

621

622 **Figure 4.** Time-dependent changes in ventilatory equivalents for oxygen uptake
623 ($\dot{V}_E/\dot{V}_{O_2}$) (*top*), ventilatory equivalents for carbon dioxide output ($\dot{V}_E/\dot{V}_{CO_2}$) (middle)
624 and end-tidal P_{CO_2} (P_{ETCO_2}) (*bottom*) during exercise sessions with (solid circle) and
625 without (open circle) food intake. * $P < 0.05$ with vs. without food intake.

626
627 **Figure 5.** Esophageal temperature-dependent changes in minute ventilation (*top*),
628 respiratory frequency (middle) and tidal volume (*bottom*) during exercise sessions with
629 (solid circle and black line) and without (open circle and gray line) food intake.

630
631 **Figure 6.** Esophageal temperature-dependent changes in $\dot{V}_E/\dot{V}_{O_2}$ (*top*) and $\dot{V}_E/\dot{V}_{CO_2}$
632 (*bottom*) during exercise sessions with (solid circle and black line) and without (open
633 circle and gray line) food intake.

634

Esophageal Temperature (°C)