Fueling shivering thermogenesis during passive hypothermic recovery

François Haman,1 Chris G. Scott,2 and Glen P. Kenny2
1Faculty of Health Sciences and 2School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada

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Haman F, Scott CG, Kenny GP. Fueling shivering thermogenesis during passive hypothermic recovery. J Appl Physiol 103: 1346–1351, 2007. First published July 19, 2007; doi:10.1152/japplphysiol.00931.2006.—In humans, the relative importance of oxidative fuels for sustaining shivering during passive hypothermic recovery or rewarming is still unclear. The main goals of this study were 1) to quantify the respective contributions of lipids and carbohydrates (CHO) during passive rewarming and 2) to determine the effects of precooling exercise on the pattern of fuel utilization. With indirect calorimetry methodologies, changes in fuel metabolism were quantified in nonacclimatized adult men shivering to rewarm from moderate hypothermia (core temperature ~34.5°C) not following (Con) or following a precooling exercise at 75% VO2max for 15 min (Pre-CE). As hypothermic individuals shiver to normothermia, results showed that CHO dominate at all shivering intensities above 50% Shivpeak, while lipids were preferred at lower intensities. This change in the relative importance of CHO and lipids to total heat production was dictated entirely by modulating CHO oxidation rate, which decreased by as much as 10-fold from the beginning to the end of rewarming (from 1,611 ± 396 to 141 ± 361 mg/min for Con and 1,555 ± 230 to 207 ± 261 mg/min for Pre-CE). In contrast, lipid oxidation rate remained constant and low (relatively to maximal rates at exercise) throughout rewarming, averaging 183 ± 141 for Con and 207 ± 118 mg lipids/min for Pre-CE. In addition, this pattern of fuel selection remained the same between treatments. We concluded that fuel selection is regulated entirely by changes in CHO oxidation rate. Further research should focus on establishing the exact regulatory processes involved in achieving this large upregulation of CHO utilization rate following hypothermia.

IN COLD EXPOSED HUMANS, significant decreases in core temperature or hypothermia occur when increases in heat production are not sufficient to compensate for increases in heat loss. Following a hypothermic episode, shivering thermogenesis (ST) remains the only physiological process available for reestablishing core temperature in nonexercising, nonassisted individuals (15). Most studies during passive hypothermic recovery or passive rewarming focused on the efficiency of external warming methods (for example, warm water immersion, warm air breathing; Ref. 6) and, therefore, little is known about the metabolic requirements of ST following hypothermia. In the only study focusing on the energy demand of ST during passive rewarming, Neuner et al. (15) showed that core warming rate in nonacclimatized hypothermic men remained unaffected by glycogen depletion (0.61 vs. 0.71°C/h for control vs. glycogen depleted). However, the respective importance of CHO and lipids to total heat production (Hprod) still remains unknown because rates of oxidation have never been quantified. During sustained low and moderate shivering intensities, recent work has shown that the relative contribution of CHO to total Hprod increases progressively as shivering intensifies, while that of lipids and proteins decreases progressively (11). Most importantly, these changes in fuel selection occur entirely by upregulating rates of CHO utilization because lipid and protein oxidation rates remain unchanged. Whether this same pattern of fuel selection is found during passive rewarming remains to be established.

Therefore, the main goals of this study were 1) to determine the pattern of fuel selection during rewarming and 2) to investigate the potential effects of high-intensity, short-duration precooling exercise on changes in fuel utilization rates. More specifically, changes in CHO and lipid oxidation rates were quantified in nonacclimatized adult men following moderate hypothermia (core temperature ~34.5°C). These experiments were conducted either without performing precooling exercise (Con) or following a precooling exercise bout at 75% VO2max for 15 min on a cycle ergometer (Pre-CE). Based on the previously reported fuel selection pattern observed during low- and moderate-intensity shivering (11), we predict that the contribution of CHO to total heat production will be dominant at high shivering intensities, while lipids will be the preferred fuel at lower intensities. Second, assuming that the combination of cycling at 75% VO2max for 15 min is sufficient to induce neuromuscular fatigue and a reduction in CHO availability, we anticipate that CHO utilization rate will be decreased during rewarming following precooling exercise due to an overall reduction in the recruitment of type II, fatigable fibers, and/or CHO availability (9, 14, 22).

This study will also address another important issue. Previous shivering work indicates that maximal lipid oxidation rate seems to be already reached at low metabolic rates (~135 mg-lipids kg−1·h−1; Ref. 11); a value more than three times lower than the one reported for sustained exercise by Achten et al. (1). Physiological reasons for this limitation are still unknown because subsequent measurements during shivering were only performed at low (~2.5× resting metabolic rate (RMR)) or ~15% VO2max) and moderate intensities (~3.5× RMR or ~20% VO2max). In the present study, it is expected that shivering intensities during rewarming will exceed 3.5× RMR and may even reach maximal shivering intensity at ~5× RMR (5) due to the severity of the cold stress. Consequently, this study will allow us to determine if higher rates of lipid oxidation can be achieved during shivering.

METHODS

Subjects. Six healthy, physically active men with no history of cardiorespiratory disease or cold injuries volunteered for this study. The subject’s characteristics were as follows (mean ± SD); age: 30.5 ± 3.3 yrs.

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Address for reprint requests and other correspondence: F. Haman, Faculty of Health Sciences, Univ. of Ottawa, 125 Univ. St., Ottawa, Ontario, Canada K1N 6N5 (e-mail: fhman@uottawa.ca).
Experimental protocol. Each subject participated in two experimental trials: 1) rewarming without precooling exercise (Con) and 2) rewarming with precooling exercise (Pre-CE; described in more detail below). These experimental trials were randomized and conducted at the same time of the day after 48 h without heavy physical activity. Subjects were also instructed to abstain from consuming caffeine and alcohol for at least 12 h prior to each trial and to refrain from eating for at least 2 h before each experiment. Care was taken to minimize thermal stimuli between awakening and the start of the experiment (i.e., to avoid exposure to hot or cold temperatures and to avoid physical activity during transit from home to the laboratory). On their arrival in the laboratory, subjects were instrumented with thermal probes and asked to sit quietly for 1 h at 23°C (32% relative humidity). During this baseline period, temperature and indirect calorimetry measurements were collected in the last 30 min. Subjects were then asked to (J) remain resting for an additional 15 min (Con) or 2) perform 15 min of cycling at 75% VO2max (Pre-CE). Following the aforementioned treatment, subjects were immersed up to the clavicles in a circulated water bath at 7°C (simulating typical open water temperatures in early spring and late autumn in Canada) until their core temperature reached 34.5°C. Prior to this cold water immersion, subjects were fitted with neoprene mitts and socks to minimize the risk of developing nonfreezing cold injuries at the extremities. During the immersion period, the water temperature was monitored with a thermocouple and adjusted when necessary by the addition of ice. Once core temperature reached 34.5°C, subjects were helped out of the water bath, towel dried, and asked to remain seated in an upright position at room temperature (~23°C) until their core temperature had returned to baseline values (prior to cold exposure or precooling exercise). During cooling, time before reaching baseline values was also the same between treatments, averaging 40.0 ± 4.1 min for Con and 37.5 ± 7.6 min for Pre-CE.

Thermal response. Whole body heat loss (Hloss in kj/min) was estimated using the following equation:

\[ H_{\text{loss}} = (R + C) + H_{\text{cop}} \]  

where, R and C represent rates of radiative and convective heat loss and Hcop is the rate of evaporative and convective heat loss by ventilation. R and C were estimated using heat flux transducers (Concept Engineering, Old Saybrook, CT) placed on the surface of the skin at 11 sites (i.e., forehead, chest, biceps, forearm, abdomen, lower and upper back, front and back calf, quadriceps, hamstrings) and calculated using an area-weighed equation (3). Evaporative heat loss from the skin was assumed to be negligible at 23 and 10°C (16). Hcop was estimated using the following equation:

\[ H_{\text{cop}} = \rho \cdot V_e \cdot \left( (c_e + \gamma \cdot c_v) \cdot (T_e - T_s) + \rho \cdot V_e \cdot \lambda \cdot (\gamma_e - \gamma_i) \right) \]

where, ρ is the density of air (kg/m³), V_e the ventilation (l/min), λ is the latent heat vaporization (m²·s·K⁻¹), c is the specific heat (J·kg⁻¹·K⁻¹; subscripts a and v refer to air and vapor, respectively), T is temperature (°C or K) (subscripts e and I refer to the expired and inspired air, respectively), and γ is the humidity ratio.

Total heat production (Hprod) was calculated by indirect respiratory calorimetry corrected for protein oxidation (see percent). Shivering peak was determined by dividing VO₂ (ml·kg⁻¹·min⁻¹) values measured in the cold by the highest metabolic rate recorded postcooling for Con and Pre-CE. This maximal shivering rate (Shivpeak, in ml·kg⁻¹·min⁻¹) was not different from those calculated using the shivering peak estimated for each subject using the equation proposed by Eysöllfson et al. (5):

\[ \text{Shivpeak} = 30.5 + (0.348 \times \text{VO} \text{max}) - (0.909 \times \text{BMI}) - (0.233 \times \text{age}) \]  

where, VO2max is the maximal oxygen consumption (ml·kg⁻¹·min⁻¹), BMI is the body mass index (kg·m⁻²), and the age is in years.

Statistical analyses. Changes in Tskin, Tes, Hloss, and Hprod were assessed by two-way ANOVA for repeated measures. Differences in Hprod, fuel utilization for CHO (CHOox) and lipids (FATox) at baseline (23°C) as well as during exercise (only for the precooling exercise experiment) and cooling rewarming were determined using one-way ANOVA to verify the main effect of the treatment (Con vs. Pre-CE). Statistical differences were considered significant when P ≤ 0.05. The statistical power of the two-way ANOVA for repeated measures was calculated for CHOox and FATox and it reached 0.54 and 0.74, respectively. All values presented are means ± SD (n = 6) unless indicated otherwise.

RESULTS

Thermal responses. Changes in Tskin, Tes, Hprod, and Hloss measured prior to cooling, during precooling exercise (Pre-CE only), during cooling and postcooling for Con and Pre-CE are presented in Fig. 1. While postexercise values were significantly higher for Pre-CE, no difference between Con and Pre-CE were observed by the end of cooling and throughout rewarming. By the end of immersion, Tskin decreased from 31.9 ± 0.6°C at baseline to 12.2 ± 4.7°C prior to rewarming for Con and from 31.7 ± 0.9 to 11.2 ± 3.5°C for Pre-CE (Fig. 1). Tes decreased from 37.1 ± 0.3 to 34.1 ± 0.3°C for Con and from 37.1 ± 0.2°C to 34.5 ± 0.03°C for Pre-CE (Fig. 1). Hprod increased 3.7-fold for Con from 7.2 ± 1.1 to 26.5 ± 7.5 kJ/min and 3.9-fold for Pre-CE from 6.7 ± 1.2 to 25.1 ± 7.7 kJ/min (Fig. 1). For both Con and Pre-CE, metabolic rates reached by the beginning of rewarming was equivalent to maximal shiv-
ering intensity (5). $H_{\text{loss}}$ increased fourfold for Con from $7.4 \pm 0.9$ to $29.8 \pm 10.3$ kJ/min and for Pre-CE from $7.4 \pm 1.4$ to $29.7 \pm 13.8$ kJ/min (Fig. 1). By the end of rewarming, $T_{\text{skin}}$ and $T_{es}$ increased to $27.5 \pm 1.3$ and $36.2 \pm 0.3^\circ C$ for Con ($27.6 \pm 1.0$ and $36.2 \pm 0.2^\circ C$ for Pre-CE) while $H_{\text{prod}}$ and $H_{\text{loss}}$ increased to $10.8 \pm 3.4$ and $5.9 \pm 1.7$ kJ/min for Con ($14.5 \pm 9.4$ and $5.1 \pm 1.7^\circ C$ for Pre-CE).

Changes in rewarming rates and heat balance during rewarming are shown in Fig. 2. Rewarming rate and heat balance during rewarming were not different between Pre-CE and Con. Maximal rewarming rate was measured at 15 min and averaged $0.09 \pm 0.05^\circ C/\text{min}$ (Con) and $0.08 \pm 0.05^\circ C/\text{min}$ (Pre-CE). In addition, Fig. 3 illustrates changes in shivering intensity ($\%\text{Shiv}_{\text{peak}}$) as a function of changes in $T_{es}$ and $T_{\text{skin}}$ for Con and Pre-CE. Again, no difference was found between Con and Pre-CE.

**Fuel selection.** Changes in the absolute rates and relative contributions of CHO and lipids to total heat production as a function of percent shivering intensity ($\%\text{Shiv}_{\text{peak}}$) during rewarming are presented in Fig. 4. From the beginning to the end of rewarming, shivering intensity ranged from $97 \pm 0$ to $26 \pm 5.1\%\text{Shiv}_{\text{peak}}$ for Con and from $95 \pm 0$ to $27 \pm 7\%\text{Shiv}_{\text{peak}}$ for Pre-CE. Along this range of shivering intensities, no significant difference in absolute rates of oxidation and relative contribution to total $H_{\text{prod}}$ were observed between Con and Pre-CE. Absolute rates of CHO oxidation varied from $1,611 \pm 396$ to $141 \pm 360$ mg/min for Con and $1,555 \pm 237$ to $207 \pm 261$ mg/min for Pre-Ex. In contrast, absolute rates of

Fig. 1. Changes in mean skin ($T_{\text{skin}}$) and esophageal temperatures ($T_{es}$) as well as rates of heat production ($H_{\text{prod}}$) and heat loss ($H_{\text{loss}}$) measured in men recovering from moderate hypothermia not following (Con) and following precooling exercise at 75% $V_{\text{O2max}}$ for 15 min (Pre-CE). Average values measured at baseline (B), at the end of exercise (PE), end of cold-water immersion (PC), and at the after-drop level (AD, the lowest post-cooling $T_{es}$) are also shown. Values are presented for the longest rewarming period common to all subjects for each condition. *Immersion time averaged $56 \pm 21$ min for Con and $53 \pm 23$ min for Pre-CE.
lipid oxidation remained constant averaging 183 ± 141 mg/min for Con and 207 ± 118 mg/min for Pre-Ex. Relative contributions of CHO to total H\textsubscript{prod} decreased continuously from beginning to the end of rewarming from 79.3 ± 15.6 to 25.5 ± 13.2% H\textsubscript{prod} for Con and from 69.9 ± 9.9 to 37.7 ± 11.8% H\textsubscript{prod} for Pre-CE), whereas that of lipids increased from 16.7 ± 15.7 to 60.9 ± 13.2% H\textsubscript{prod} for Con and from 26.4 ± 10.3 to 48.4 ± 12.4% H\textsubscript{prod} for Pre-CE. The crossover point or point at which CHO and lipid provide equally to total heat production occurred at 50% (Con) and 60% Shiv\textsubscript{peak} (Pre-CE) and was not different between treatments. Table 1 summarizes total amounts of CHO and lipids used during rewarming in Con and Pre-CE, as well as the relative contributions of these fuels to total H\textsubscript{prod} averaged over the entire rewarming period. Again, no overall differences between Con and Pre-CE were found in the total amount of CHO or of lipid used to sustain shivering and in the relative contributions of these fuels to total H\textsubscript{prod} production when averaged over the entire rewarming period.

DISCUSSION

This study quantifies the contributions of CHO and lipids to total heat production during passive rewarming. It shows that as individuals shiver to normothermia, CHO dominate at all shivering intensities above 50% Shiv\textsubscript{peak}, while lipids are preferred at lower intensities (Fig. 4). This change in CHO and lipid utilization rate is achieved entirely by a modulation of CHO oxidation rate, which varies by as much as 10-fold from the beginning to the end of rewarming (Fig. 4). In contrast, over the entire range of shivering intensities, lipid oxidation rate remains stable and low (relative to maximal rates during exercise, see Oxidizing lipids). The pattern of fuel selection found here during rewarming is consistent with the one observed previously in men during sustained low- and moderate-intensity shivering (11; Fig. 5). Finally, pre-cooling exercise at 75% V\textsubscript{O2max} for 15 min is insufficient to cause the anticipated decrease in CHO utilization rate during rewarming (P = 0.20; Fig. 4 and Table 1).

Fuel selection during passive hypothermic recovery. The 7°C water immersion used in this study to induce hypothermia in nonacclimatized men resulted in decreases of ~3°C for T\textsubscript{es} and ~20°C for T\textsubscript{skin} by the end of cold exposure. Together these changes in deep and peripheral temperatures were sufficient to elicit maximal shivering by the beginning of warming [4–5 times resting metabolic rate or ~50% V\textsubscript{O2max}; Eyolfson et al. (5)]. As individuals shiver to normothermia, results show that absolute rates of CHO oxidation decrease by as much as 10-fold (from 1,611 ± 396 to 141 ± 361 mg/min for Con and 1,555 ± 230 to 207 ± 261 mg/min for Pre-CE), whereas lipid utilization rate remains constant (discussed later, see Oxidizing lipids; Fig. 4, A and B). In effect, the relative contribution of CHO decreases progressively (from ~80 to 25% H\textsubscript{prod} for Con and from ~70 to 38% H\textsubscript{prod} for Pre-CE), whereas that of lipids increases from ~17 to 61% H\textsubscript{prod} for Con (from ~26 to 48% H\textsubscript{prod} for Pre-CE) as shivering lessens in intensity and individuals approach normothermia (Fig. 4, C and D). The crossover point or the shivering intensity at which CHO and lipids contribute equally to total heat production occurs at ~50% Shiv\textsubscript{peak} when precooling exercise is not performed. This pattern of fuel oxidation rate is consistent with the one described recently during sustained shivering in nonhypothermic adult men exposed for 90 min to either 10°C [low-intensity shivering (L); or 5°C (moderate-intensity shivering (M); Ref. 11]. We compared patterns of fuel selection found previously

Table 1. H\textsubscript{prod} as well as absolute and relative contributions of CHO and lipids to H\textsubscript{prod} measured in men recovering from moderate hypothermia not following or following pre-CE

<table>
<thead>
<tr>
<th></th>
<th>Con</th>
<th>Pre-CE</th>
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<tbody>
<tr>
<td>H\textsubscript{prod}, kJ</td>
<td>806±213</td>
<td>797±289</td>
</tr>
<tr>
<td>CHO, g</td>
<td>28.9±7.4</td>
<td>25.6±10.5</td>
</tr>
<tr>
<td>%H\textsubscript{prod}</td>
<td>61.5±19.1</td>
<td>52.6±11.9</td>
</tr>
<tr>
<td>Lipids, g</td>
<td>7.0±5.5</td>
<td>8.1±3.8</td>
</tr>
<tr>
<td>%H\textsubscript{prod}</td>
<td>32.5±19.0</td>
<td>41.0±11.8</td>
</tr>
</tbody>
</table>

Values are means ± SD. H\textsubscript{peak}, total heat production; CHO, carbohydrates, Con, control [not following precooling exercise (Pre-CE)].
during sustained shivering in nonhypothermic men (11) and during passive rewarming in hypothermic men in the present study. This comparison is summarized in Fig. 5 and reveals that fuel selection patterns are identical between shivering conditions. As observed in the present study, rates of CHO oxidation increase from L to M intensified, whereas that of lipids remains unaffected (Fig. 5, top). In addition, the relative importance of CHO increases progressively as shivering intensifies during sustained shivering in nonhypothermic men while that of lipids decreases. These changes in the relative importance of CHO and lipids to total heat production also reveal the same crossover point found at ~50% Shiv peak. With an isotopic tracer method, this previous work has also shown that most of the increase in CHO oxidation rate from L to M is supported by a substantial increase in the mobilization of muscle glycogen reserves. In the present study, it is still unclear whether the 8- to 10-fold increase in CHO oxidation rate found during hypothermic recovery is also sustained primarily by an increase in muscle glycogen utilization rate.

On the basis of previous observations, a number of mechanisms could be responsible for the large increase in CHO oxidation observed here. Fuel selection is modified acutely in three ways: 1) by recruiting different metabolic pathways within the same fibers, 2) by recruiting specific subpopulations of fuel specific fibers within the same muscle, or 3) by recruiting muscles varying in fiber composition (20). In the cold, the first two mechanisms of fuel selection have been identified (7, 8). During low-intensity shivering (~2.5 times resting metabolic rate (RMR)), CHO-depleted and CHO-loaded individuals were able to sustain the same rate of heat production by recruiting different metabolic pathways within the same fibers (7). In contrast, during moderate shivering (~3.5 times RMR), alterations in fuel selection are achieved by recruiting subpopulations of fuel specific fibers within the same muscle (8). In view of the large range of shivering intensities found here during hypothermic recovery (up to 5 times RMR), we can speculate that the 8- to 10-fold increase in CHO utilization rate is achieved by proportionally increasing the specific recruitment of “CHO specific” fibers (i.e., type II glycolytic fibers) within shivering muscles; assuming that the same muscles were recruited throughout warming. Clearly, however, additional work is needed to identify the exact mechanisms responsible for this regulation in CHO oxidation rate.

**Oxidizing lipids.** During hypothermic recovery, the relative importance of lipids increases progressively as shivering intensity declines and individuals approach normothermia. However, this change is not achieved by upregulating lipid oxidation rate as it remains constant, averaging 183 ± 141 for Con and 207 ± 118 mg lipids/min for Pre-CE throughout rewarming (Fig. 4). Similarly, during sustained shivering in the cold, previous work has shown that lipid oxidation rate never exceeds ~165 mg lipids/min even when shivering intensity decreases from low to moderate (Fig. 5; Ref. 11). Together these findings indicate that maximal rates of lipid oxidation are already achieved at low shivering intensities. Clearly, however, we anticipated that much higher rates could be reached as shivering intensified from 3.5 to 5× RMR. To date, the highest RF ox values measured during shivering are still more than three times lower than reported for sustained exercise (1). What limits lipid utilization rate during shivering? Although the exact physiological reasons are unclear at best, we can speculate on a number of possible mechanisms that may limit RF ox during shivering. For example, cold exposure is associated with reduced peripheral blood flow, which may lead to impaired fatty acid supply to shivering muscles via the circulation. In addition, as shivering intensity increases, the progressive recruitment of proportionally more type II glycolytic fibers may occur, whereas the recruitment of type I lipolitic fibers remains constant. Finally, one may also consider the influence of cold exposure on other factors responsible for controlling fuel oxidation such as circulating hormones (e.g., catecholamines), trans-membrane transporters (fatty acid transporters), and a series of intracellular metabolites (acetyl-CoA, malonyl-CoA, Ca2+, ADP, AMP, Pπ, and AMPK). Future work in this field of research should attempt to better understand the relative importance of these factors on energy substrate regulation in the cold.

**Effect of precooling exercise.** The second objective of this study was to examine whether precooling exercise at 75% V̇O2 max for 15 min is sufficient to reduce CHO utilization rate by inducing neuromuscular fatigue and, thus, the recruitment of type II, fatigable muscle fibers. Recent work had shown that the recruitment of type II fatigable fibers was key in dictating fuel selection in the cold by modulating CHO oxidation rate (8). Based on previous observations during rewarming, we also
expected that such changes in fuel use could occur without significant alterations in rates of heat production and/or rewarming. For example, during sustained shivering in the cold, a growing body of evidence indicates that heat production rates can be sustained independently of 1) changes in the size of glycogen reserves (or fuel mixtures being used; Refs. 9, 14, 22) or 2) whether exhaustive exercise is performed prior to cold exposure (21). In addition, during passive rewarming in hypoc- thermic men, Neufer et al. (15) showed that rewarming rates remain unimpaired even when the size of muscle glycogen reserves are reduced prior to cooling. However, to date, the effects of precooling exercise on thermal responses and on oxidative fuel selection during rewarming had never been quantified. In the present study, results show that exercising at 75% \( \dot{V}O_2 \text{max} \) for 15 min prior to cooling has no significant effect on \( H_{\text{prod}} \) and rewarming rate (Figs. 1 and 2, Table 1). In addition, contrary to what was expected, absolute rates and relative contributions of CHO to total \( H_{\text{prod}} \) remained unchanged between Con and Pre-CE (Fig. 4, Table 1). It is likely that the precooling exercise intensity and duration selected in this study were insufficient to induce the expected neuromuscular fatigue and associated reduction in type II fiber recruitment and/or CHO availability. It still remains unclear whether more intense and longer duration exercise could modify thermal responses and the pattern of fuel selection during passive rewarming.

**Conclusion.** This study shows that both CHO and lipids play substantial roles in sustaining heat production during passive hypothermic recovery (CHO above and lipids below 50%ShivPeak); a pattern unaffected by precooling exercise (75% \( \dot{V}O_2 \text{max} \) for 15 min). More importantly, it indicates that this regulation in fuel selection is modulated entirely by precooling exercise and/or CHO availability. It still remains unclear whether more intense and longer duration exercise could modify thermal responses and the pattern of fuel selection during passive rewarming.

**REFERENCES**


