

**HIGHLIGHTED TOPIC** | *A Physiological Systems Approach to Human and Mammalian Thermoregulation*

## Shivering in the cold: from mechanisms of fuel selection to survival

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**Haman, François.** Shivering in the cold: from mechanisms of fuel selection to survival. *J Appl Physiol* 100: 1702–1708, 2006; doi:10.1152/jappphysiol.01088.2005.—In cold-exposed adult humans, significant or lethal decreases in body temperature are delayed by reducing heat loss via peripheral vasoconstriction and by increasing rates of heat production via shivering thermogenesis. This brief review focuses on the mechanisms of fuel selection responsible for sustaining long-term shivering thermogenesis. It provides evidence to explain large discrepancies in fuel selection measurements among shivering studies, and it proposes links between choices in fuel selection mechanism and human survival in the cold. Over the last decades, a number of studies have quantified the contributions of carbohydrate (CHO) and lipid to total heat generation. However, the exact contributions of these fuels still remain unclear because of large differences in fuel selection measurements even at the same metabolic rate. Recent advances on the mechanisms of fuel selection during shivering provide some plausible explanations for these discrepancies between shivering studies. This new evidence indicates that muscles can sustain shivering over several hours using a variety of fuel mixtures achieved by modifying diet (changing the size of CHO reserves) or by changing muscle fiber recruitment (increasing or decreasing the recruitment of type II fibers). From a practical perspective, how does the choice of fuel selection mechanism affect human survival in the cold? Based on a glycogen-depletion model, estimates of shivering endurance show that, whereas the oxidation of widely different fuel mixtures does not improve survival time, the selective recruitment of fuel-specific muscle fibers provides a substantial advantage for cold survival. By combining fundamental research on fuel metabolism and applied strategies to improve shivering endurance, future research in this area promises to yield important new information on what limits human survival in the cold.

energy metabolism; shivering thermogenesis; fuel selection; survival in the cold; thermoregulation

SURVIVAL IN COLD ENVIRONMENTS has been an ongoing challenge for humans over the ages. As furless endotherms, they are well adapted for dissipating heat in warm climates but particularly bad at retaining it in cold environments. Over the past decades, much emphasis from an engineering standpoint has been placed on the development of protective clothing and shelters to reduce excessive heat loss and allow long-term survival in cold environments. Today, these efforts have improved access to more extreme climates for occupational and recreational activities. However, this greater accessibility has also increased the risks for cold-related injuries and/or hypothermia. In cold-exposed adult humans, significant or lethal decreases in body temperature are delayed by reducing rates of heat loss via peripheral vasoconstriction and by increasing rates of heat production ( $\dot{H}_{\text{prod}}$ ) via shivering thermogenesis. This brief review focuses on the fuel selection mechanisms responsible

for sustaining shivering thermogenesis. It presents new evidence to explain large discrepancies in fuel selection measurements among shivering studies, and it proposes links between the choice of fuel selection mechanism and human survival in the cold.

**OXIDIZING FUELS TO STAY WARM**

Shivering is elicited by long-term exposure to cold air or water and in adult humans; it can reach intensities equivalent to ~40% of maximal oxygen consumption [or 5 times resting metabolic rate (RMR)] (2). Even though the exact physiological reasons for this upper limit are unknown, a number of studies have shown that shivering intensity is associated with cold exposure duration and severity as well as with the morphological characteristics of individuals (i.e., percent body fat, surface-to-volume ratio, blood flow) (2, 32, 43). The ATP required to sustain involuntary muscle contractions during shivering is supplied through the oxidization carbohydrates (CHO), lipids, and proteins. These substrates are provided to shivering muscles at appropriate times and rates from intra-

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muscular reserves and/or from other tissues via circulation (see Ref. 41 for review). It is generally assumed that shivering muscles are fuelled by CHO and lipids, whereas the contribution of proteins remains minimal (but see *Status of CHO reserves*). For this reason, most studies to date have only quantified the respective importance of CHO and lipids for sustaining thermogenic rates, and few have accounted for the contribution of proteins (10–12, 34, 39). Figure 1 summarizes the relative contributions of CHO and lipids to total  $\dot{H}_{\text{prod}}$  measured between 60 and 90 min of cold exposure in 16 shivering studies over the last two decades using the three experimental cooling methods [air exposure, water immersion, liquid-conditioned suit] (4, 5, 11, 12, 18, 21, 22, 26, 33–38, 39, 42). Values were calculated from nonprotein respiratory exchange ratios (25) and plotted, when possible, as a function of shivering intensity [expressed relatively to resting metabolic rate;  $\times$  RMR; low ( $<2.5 \times$  RMR), moderate ( $2.5\text{--}3.8 \times$  RMR), high ( $3.8\text{--}5 \times$  RMR) shivering intensity]. This analysis reveals substantial variations in fuel selection measurements among studies. During exercise, such divergence in substrate use is often explained by differences in intensity, but in Fig. 1 there is no apparent relationship between fuel selection and metabolic rate. Even for studies reporting values at the same relative shivering intensity ( $\sim 2 \times$  RMR), the respective contribution of CHO varies from 28 to 78%  $\dot{H}_{\text{prod}}$  (from 22 to 72%  $\dot{H}_{\text{prod}}$  for lipids). The reasons for such variability remain uncertain, but recent advances on the mechanisms of fuel selection during shivering may help shed some light on possible explanations.

#### MECHANISMS OF FUEL SELECTION IN THE COLD

Mechanisms of fuel selection have received a lot of attention during exercise, but few studies have investigated them during shivering (see Ref. 40 for review). To date, research has shown that fuel selection can be modified in three ways: 1) by recruiting different metabolic pathways within the same fibers, 2) by recruiting specific subpopulations of fibers within the

same muscle, or 3) by recruiting muscles varying in fiber composition. Even though no information is currently available on the effects of the selective recruitment of different muscles on fuel use during shivering, the first two mechanisms of fuel selection have recently been identified by Haman et al. (8, 9). In the context of this review, these two studies also provide an important basis for explaining large differences in oxidative fuel measurements between shivering experiments (Fig. 1). They show that such inconsistencies could be related to differences in the nutritional status of subjects (e.g., size of CHO reserves) (10, 21, 44) and/or to interindividual differences in shivering pattern (relative importance of bursts of high-intensity shivering and continuous low-intensity shivering) (9).

*Status of CHO reserves.* Prolonged/strenuous exercise and alterations in diet have important effects on the quantity and the quality of metabolic fuels reserves available for shivering. Of all metabolic fuels, CHO reserves are the most influenced by such changes in exercise and diet regimen; this fuel represents only  $\sim 1\%$  of total energy stores ( $\sim 95\%$  for lipids and  $\sim 4\%$  for proteins) but still supplies a large fraction of the substrate needed to sustain energy expenditure. More than a decade ago, researchers provided the first clues on the effects of changes in the size of CHO reserves on fuel metabolism during cold exposure. In two independent studies during moderate-intensity shivering, glycogen-depleted and glycogen-loaded men were shown to use drastically different fuels mixtures while having little (21) or no effect on thermogenic rate (44). However, the underlying mechanisms responsible for these large differences in fuel selection remained unknown because 1) changes in fiber recruitment had never been quantified in glycogen-depleted and glycogen-loaded individuals and 2) no information was available on the role played by proteins. More recently, Haman et al. (10) confirmed the findings of Young et al. (44) and Martineau and Jacobs (21) but also indicated that these large differences in oxidative fuel use are achieved by selectively recruiting different metabolic pathways within the same fibers (see the first mechanism of fuel

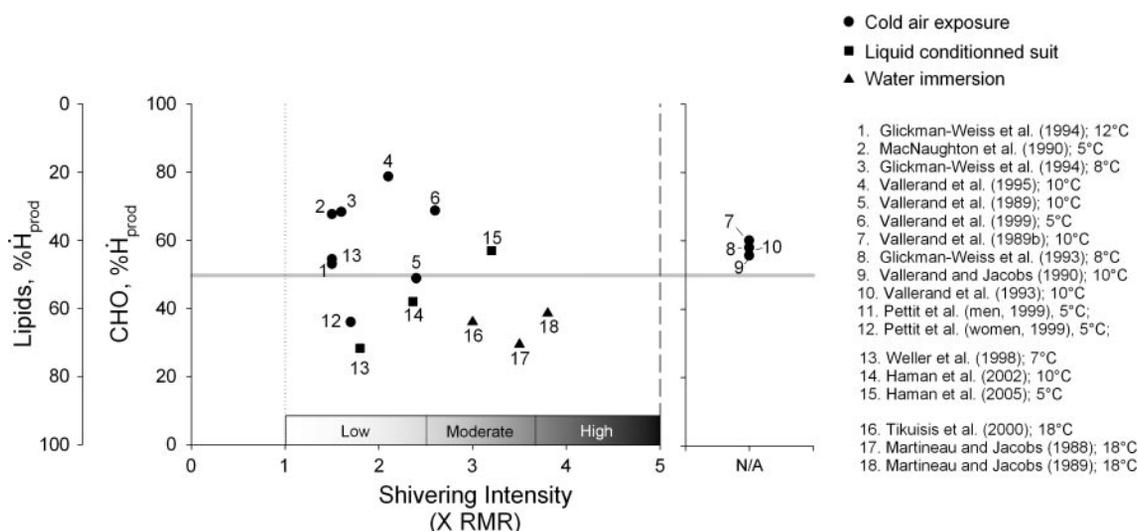


Fig. 1. Relative contribution of lipids and carbohydrates (CHO) to total heat production ( $\dot{H}_{\text{prod}}$ ) as a function of shivering intensity (expressed relatively to resting metabolic rate:  $\times$  RMR) reported in 16 studies between 60 and 90 min of cold exposure. All experiments were conducted in men with the exception of studies 12 and 16. ●, ▲, and ■, Studies where individuals were cooled in air, in water, and using a liquid-conditioned suit, respectively. Dotted line, 1 RMR; dashed line, estimated maximal shivering intensity (2). Low, Moderate, and High refer to the ranges in  $\times$  RMR for shivering intensities reported in the literature. N/A is for studies where fuel oxidation values were available but not the data needed to calculate  $\times$  RMR.

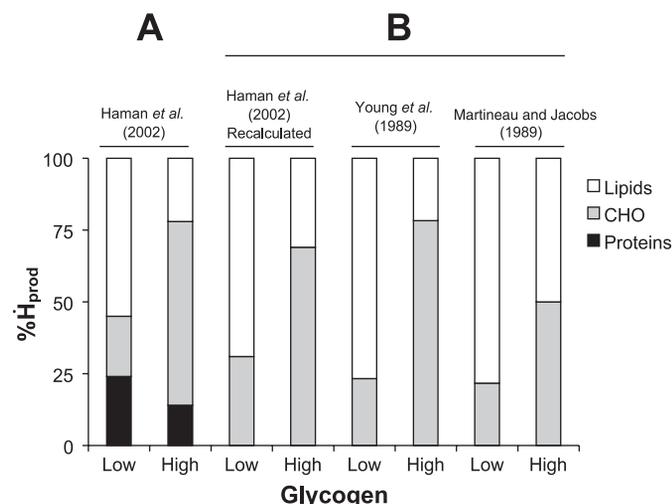


Fig. 2. A: relative contributions of lipids, CHO, and proteins to total  $\dot{H}_{\text{prod}}$  measured between 60 and 90 min in men with low (Low) and high glycogen (High) reserves exposed to 10°C using a liquid-conditioned suit (2). B: comparison of the relative contributions of lipids and CHO to total  $\dot{H}_{\text{prod}}$  calculated from nonprotein respiratory exchange ratio measured between 60 and 90 min in men with low and high glycogen reserves exposed to either 10°C using a liquid-conditioned suit (10) or immersed in 18°C water (21, 44).

selection in MECHANISMS OF FUEL SELECTION IN THE COLD). Relative contributions of oxidative fuels to total heat generation measured in glycogen-depleted and glycogen-loaded men during low- (10) and moderate-intensity shivering (21, 44) are presented in Fig. 2. Because oxidation rates reported for moderate-intensity shivering were not corrected to account for protein oxidation rate, nonprotein respiratory exchange ratios measured during low-intensity shivering (Fig. 2A) were used to recalculate the relative contributions of CHO and lipids to total  $\dot{H}_{\text{prod}}$  for comparison (Fig. 2B). At both shivering intensities, modifying the size of glycogen reserves caused a large shift in fuel use from CHO dominance (up to ~80%  $\dot{H}_{\text{prod}}$ ) to lipid dominance (up to ~80%  $\dot{H}_{\text{prod}}$ ). These changes in the respective contributions of CHO and lipid to total  $\dot{H}_{\text{prod}}$  are similar in all studies when glycogen reserves are low. However, when glycogen reserves are high, a greater dependence on CHO was observed by Young et al. (44) and Haman et al. (10) (~70%  $\dot{H}_{\text{prod}}$ ) than by Martineau et al. (21) (50%  $\dot{H}_{\text{prod}}$ ). This divergence is most likely due to differences in glycogen-loading protocols (10). The reciprocal regulation of CHO and lipid oxidation under conditions of low- and high-CHO availability may include factors such as modifications in circulating hormones, transmembrane transporters, and intracellular metabolites (8). While the relative importance of these factors in controlling fuel use is better understood during exercise (16, 30), no information is currently available of their role during shivering.

Most importantly, Haman et al. (10) indicated that protein oxidation plays a more substantial role (~25%  $\dot{H}_{\text{prod}}$ ) than previously anticipated in compensating for the decrease in CHO oxidation when glycogen reserves are low. In fact, failing to account for the oxidation of proteins in the total energy budget may result in a significant overestimation of CHO and lipid oxidation rates. It is generally accepted that absolute rates of protein oxidation remain unaffected by cold exposure, and in effect, the cold-induced increases in metabolic rate is gen-

erally accompanied by a proportional decrease in the relative use of this fuel (10, 12). Consequently, when protein oxidation rate is high before cold exposure, the relative importance of this fuel to total heat production remains elevated during shivering. In contrast, when it is low, its contribution tends to become minimal. For example, during low-intensity shivering (Fig. 2A), proteins provide only 10%  $\dot{H}_{\text{prod}}$  (25%  $\dot{H}_{\text{prod}}$  before cold exposure) when glycogen reserves are high but as much as 25%  $\dot{H}_{\text{prod}}$  (40%  $\dot{H}_{\text{prod}}$  before cold exposure) when glycogen reserves are low. Together these observations indicate that future shivering studies should not only normalize subjects as much as possible for differences in nutritional status (i.e., size of glycogen reserves) but also provide estimates of protein oxidation rates to allow interstudy comparisons.

*Interindividual differences in shivering pattern.* During shivering, two electromyographic (EMG) patterns associated with the recruitment of specific fibers have been identified (15, 23). Continuous, low-intensity shivering is related to low-threshold fibers (type I, specialized for lipid use), whereas high-intensity bursts are associated with high-threshold fibers (type II, specialized for CHO use). EMG analysis reveals that muscle shivering activity varies greatly between individuals (1, 9). Even when subjects are normalized as much as possible for morphology, percent body fat, diet, and level of cold acclimation (9), large interindividual differences in the relative contributions of muscles to total shivering intensity and shivering EMG pattern are observed (Fig. 3). Until recently, little was known on the effects of these variations in muscle recruitment on substrate metabolism. During moderate-intensity shivering,

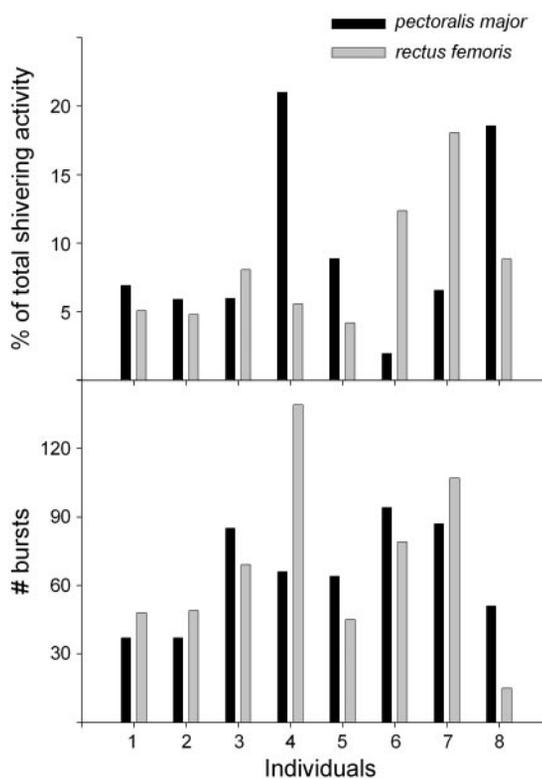


Fig. 3. Relative contributions to total shivering activity (A) and number of bursts measured in pectoralis major (black bars) and rectus femoris (gray bars) in the last 15 min of moderate-intensity shivering (B) [ $\sim 3.3 \times \text{RMR}$ ; data obtained from Haman et al. (9)].

large variations in the relative use of CHO and lipid have been found among subjects (9). As for differences in fuel use observed between shivering studies (Fig. 1), values range from 33 to 78%  $\dot{H}_{\text{prod}}$  for CHO and from 14 to 60%  $\dot{H}_{\text{prod}}$  for lipids depending on the individual. Again, this variability in fuel selection was not explained by differences in metabolic rate. Instead, analysis of EMG activity shows that variations in CHO oxidation rates are closely correlated with burst shivering rate (or with the recruitment of CHO-specific type II fibers). This finding is consistent with the second mechanism of fuel selection, whereby different fuel mixes are obtained by the selective recruitment of specific subpopulations of fibers within the same muscle. This evidence indicates that modulating the relative importance of bursts of high-intensity shivering and continuous, low-intensity shivering plays a key role in orchestrating fuel selection. Consequently, when comparing fuel selection measurements between studies, it may also be essential to normalize subjects for differences in EMG shivering pattern.

#### FROM MECHANISMS TO SURVIVAL

From a practical perspective, how does the choice in fuel selection mechanism influence human survival in the cold? Survival depends on the capacity to counterbalance the rate of

heat loss by increasing thermogenic rate. In extreme cold environmental conditions, when the rate of heat loss is too great to be compensated, survival is determined by the time it takes to reach a critical/fatal core temperature. For example, in cold water, core temperature may decrease continuously by  $\sim 1^{\circ}\text{C}$  every 10 min (28), and, under these conditions, any heat generated by shivering only delays the onset of critical hypothermia. In contrast, during milder cold exposures, thermogenic rates can offset rates of heat dissipation and prevent any decreases in core temperature. Under such conditions, survival time depends on shivering endurance or on the amount of time a specific thermogenic rate can be maintained (31). Over the years, shivering studies have focused on muscle glycogen depletion as a possible limiting factor for heat production because 1) CHO represent such a small fraction of total energy stores, 2) muscle glycogen contributes as much as 30–40%  $\dot{H}_{\text{prod}}$  of the total energy budget during shivering (12), and 3) this fuel is well known to be limiting during endurance exercise. Consequently, finding the right fuel mix and/or muscle fiber recruitment to optimize heat production and spare glycogen reserves may be critical for long-term survival in cold environments.

*Finding the optimal fuel mix.* Several shivering studies have shown that humans are able to sustain rates of heat production

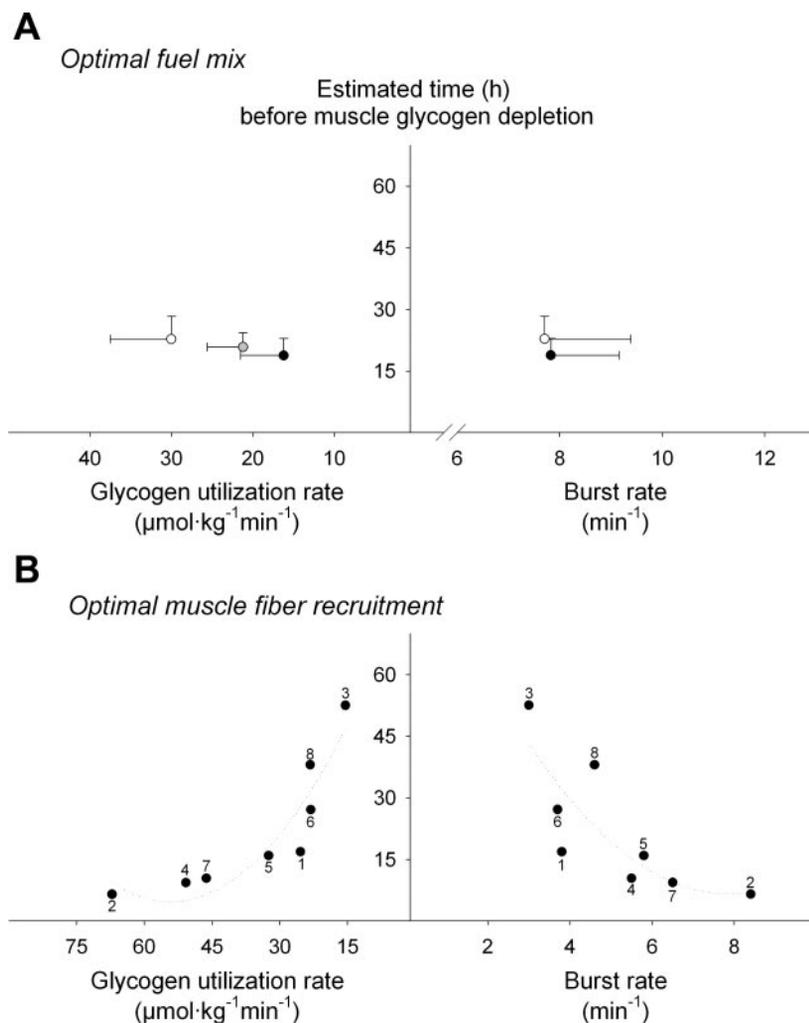


Fig. 4. Theoretical estimates of time before muscle glycogen depletion as a function of utilization rate and burst shivering rate in glycogen-depleted (black circles), normal (gray circles), and loaded men (white circles) during low-intensity shivering (A) and in men with normal glycogen reserves during moderate-intensity shivering (B). For A, values are presented as means  $\pm$  SE, and burst shivering rate was not determined in subjects with normal glycogen reserves. For B, each subject is identified numerically above or below data points, and dotted lines indicate the trend of the relationship. Data obtained from Haman et al. (8–11).

for up to 2 h using a variety of fuel mixtures (10, 20, 21, 44). During low-intensity shivering, these large differences in oxidative fuel selection occur without altering muscle and fiber recruitment (8). Unfortunately, none of these studies have been conducted in excess of 2 h, and consequently little is still known on whether a specific fuel mixture can maintain heat production for longer and improve chances for survival. Assuming that muscle glycogen is essential for shivering, any increase in lipid utilization rate would theoretically constitute an important strategy to spare CHO reserves and prolong survival time (11). What could be the optimal fuel mix for sustaining shivering? In an attempt to answer this question, estimates of the time before muscle glycogen depletion were calculated using three different fuel mixtures measured in 1) glycogen-depleted (L; 53% lipids, 28% CHO and 19%  $\dot{H}_{\text{prod}}$  proteins) (10), 2) glycogen-normal (N; 50% lipids, 40% CHO and 10%  $\dot{H}_{\text{prod}}$  proteins) (11), and 3) glycogen-loaded men (H; 23% lipids, 65% CHO and 12%  $\dot{H}_{\text{prod}}$  proteins) (10). It was assumed that 1) individuals shivered at 200 W; 2) the relative use of the different fuels remained the same until glycogen depletion; 3) 80% of total muscle glycogen was available for oxidation; 4) active muscle mass during shivering was 70% of 36 kg; 5) mean muscle glycogen concentrations were 62, 102, and 137 mmol glucosyl units/kg wet mass as observed in Young et al. (44); and 6) muscle glycogen oxidation rate was 16, 21, and 30  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  as observed in Haman et al. (10, 11) for L, N and H, respectively. Results are plotted in Fig. 4A as a function of muscle glycogen oxidation rate and burst shivering rate. These calculations suggest that humans are able to maintain a thermogenic rate of 200 W for the same amount of time ( $\sim 20$  h) independently of differences in the composition of fuels being used. Although this could be true during low-intensity shivering, it is still unclear whether this would also be the case at higher shivering intensities. Important increases in the use of muscle glycogen reserves have been found as shivering intensifies (12). Clearly, additional research is needed to determine whether the selection of a specific fuel mixture affects survival time at higher shivering intensities.

It is important to note that shivering endurance may depend not only on the status of glycogen reserves but also on the relative use of plasma glucose. Hypoglycemia has been shown to inhibit shivering thermogenesis (3, 7, 24). For example, a 20% decrease in  $\dot{H}_{\text{prod}}$  was reported when glycemia was artificially decreased to 2.8 mM (24), and a complete inhibition of shivering was found below 2.5 mM (3). This inhibitory effect does not seem to be related to the lack of metabolic substrate but rather to the inhibition of cold-sensitive neurons in the hypothalamic region of the brain (3). To date, no evidence indicates that shivering alone can elicit hypoglycemia. In humans, plasma glucose oxidation rates always remains minor during shivering (10–15%  $\dot{H}_{\text{prod}}$ ) (12). In addition, glycemia has even been shown to increase by  $\sim 10\%$  during intense cold exposure (average of 3–4 h at 60–70% peak shivering) (31). Further work is needed to determine whether hypoglycemia can occur after longer and more severe cold exposures.

**Finding the optimal muscle fiber recruitment.** During moderate shivering intensity, Haman et al. (9) reported that humans have the ability to sustain the same thermogenic rate by recruiting different combinations of fuel-specific fibers that

oxidize widely different fuel mixtures. The relationships between burst shivering activity, and rates of heat production, plasma glucose oxidation, and muscle glycogen oxidation are presented in Fig. 5 (data from Refs. 9, 12). Results show that, whereas heat production rate (Fig. 5, *top*) and plasma glucose oxidation (Fig. 5, *middle*) are not associated with rates of burst shivering, burst activity is closely and positively correlated with rates of muscle glycogen oxidation (Fig. 5, *bottom*). Consequently, maintaining a low burst shivering rate may provide an important selective advantage for cold survival by protecting limited glycogen reserves. What could be the “best” burst shivering rate to optimize cold endurance? Again, estimates of maximal cold endurance were calculated and plotted as a function of muscle glycogen oxidation rate and burst shivering rate [assuming that 1) the relative use of the different fuels remains the same as after 90 min of shivering, 2) 80% of total muscle glycogen is available for oxidation, 3) active muscle mass during shivering is 70% of 36 kg, 4) mean muscle glycogen concentrations are 100 mmol glucosyl units/kg wet mass as observed in Martineau et al. (21), and 5) muscle glycogen oxidation rates range between 15 and 51  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (12)]. According to these estimates, individuals with high ( $\sim 8$  bursts/min) and low burst shivering rates ( $\sim 3$  bursts/min) would shiver respectively at 300 W for  $\sim 5$  h

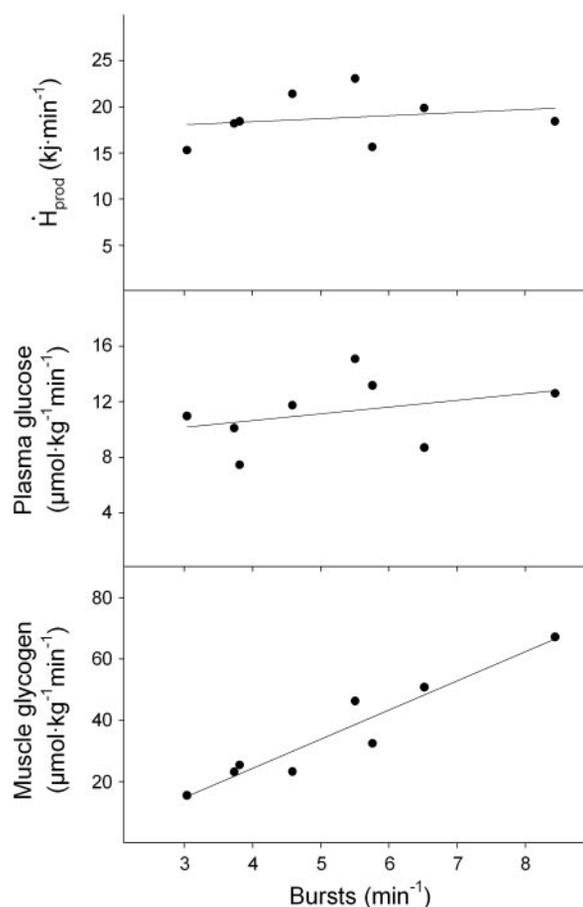


Fig. 5. Relationship between burst shivering rate and  $\dot{H}_{\text{prod}}$  (*top*;  $r^2 = 0.05$ ,  $P = 0.60$ ), plasma glucose utilization rate (*middle*;  $r^2 = 0.12$ ,  $P = 0.40$ ), and muscle glycogen utilization rate (*bottom*;  $r^2 = 0.91$ ,  $P < 0.001$ ) found in nonacclimated men ( $n = 8$ ) during moderate-intensity shivering [ $\sim 3 \times \text{RMR}$ ; Data obtained from Haman et al. (9, 12)].

and ~50 h before depleting muscle glycogen reserves (Fig. 4B). These estimates confirm that reducing burst shivering activity rate may be a key strategy to improve survival time in the cold. Animal studies suggest that high-intensity shivering bursts originate from the spinal cord (6, 13, 17, 29) and may be modulated by variations in skin temperature (19) and/or by differences in the fiber composition of shivering muscles (14). Much work is still needed to fully understand the physiological significance of variations of shivering pattern on thermogenic rate and oxidative fuel selection.

Conclusions drawn above based on estimates of shivering endurance depend to a large extent on the assumption that muscle glycogen is essential for shivering. If it is, these calculations show that 1) modifying the fuel mix used for shivering does not provide a survival advantage and 2) cold endurance varies greatly among individuals shivering at the same relative intensity because of large differences in fiber recruitment pattern. If muscle glycogen is not essential, lipids and proteins are able to compensate for varying contributions from CHO, and the above estimates of cold endurance can be increased substantially. These estimates also assume that no significant shift in fuel selection occurs after 120 min of mild shivering (see *Finding the optimal fuel mix*) or 90 min of moderate shivering (see *Finding the optimal muscle fiber recruitment*). In the only study reporting fuel selection measurements for up to 4 h in the cold, the relative contribution of lipids to total heat production increased gradually as shivering progressed (from 43%  $\dot{H}_{\text{prod}}$  before to 53%  $\dot{H}_{\text{prod}}$  by the end of cold exposure) (31). Whether this upward trend in lipid use continues in excess of 4 h remains to be established, but if it does, failing to account for this change could lead to significant underestimations in the actual time before glycogen depletion. More elaborate models for predicting survival time are currently in development (31, 43) but clearly, much research is still needed to establish what limits shivering endurance during cold exposure.

## CONCLUSIONS

Results from these studies show that muscles can sustain shivering over several hours using a variety of fuel mixtures achieved by modifying diet (changing the size of CHO reserves) or by changing muscle fiber recruitment (increasing or decreasing the recruitment of type II fibers). To allow inter-study comparisons, future research in this area should be particularly careful to normalize subjects for differences in nutritional status and protein oxidation rates as well as for variations in EMG shivering activity (burst vs continuous shivering). From the standpoint of survival, further research is still needed to determine whether shivering fatigue actually occurs and if it does, what factors contribute to its onset? Based on a glycogen-depletion model, estimates of shivering endurance show that the oxidation of widely different fuel mixtures does not improve survival time. However, the selective recruitment of fuel-specific muscle fibers seems to provide a substantial advantage for cold endurance. By combining fundamental research on fuel metabolism and applied strategies to improve shivering endurance, future work in this area promises to yield important new information on what limits human survival in the cold.

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