Image Cover Sheet

CLASSIFICATION	SYSTEM NUMBER
UNCLASSIFIED	518482

TITLE

Shivering Endurance and Fatique During Cold Water Immersion in Humans

System Number:

Patron Number:

Requester:

Notes:

DSIS Use only:

Deliver to: CL

THIS PAGE IS LEFT BLANK

THIS PAGE IS LEFT BLANK

Eur J Appl Physiol (2002) 87 50–58
DOI 10 1007/s00421-002-0589-1

ORIGINAL ARTICLE

P. Tikuisis · D.A. Eyolfson · X. Xu · G.G. Giesbrecht

Shivering endurance and fatigue during cold water immersion in humans

Accepted. 14 January 2002 / Published online 15 March 2002

Abstract An important component of survival time during cold exposure is shivering endurance. Nine male and three female healthy and fit subjects [mean (SD) age 24 8 (6.3) years, body mass 71.7 (13.2) kg, height 1.75 (0.10) m, body fat 22.7 (7.4)%] were immersed to the upper chest level in cold water for periods ranging from 105 to 388 min on two occasions to test a prediction of shivering endurance The water was cooled from 20 to 8°C during the first 15 min of immersion and subsequently rewarmed (<20°C) to elicit a near constant submaximal shivering response. The data were divided according to moderate (M) and high (H) levels of shivering intensity Respective mean total immersion times were 250 (75) and 199 (80) min ($P=0.086$) at different average shivering intensities of 61 (10) and 69 (8)% relative to maximal shivering ($P<0$ 001). Blood plasma glucose concentration increased during the immersion [from 3 44 (0 54) pre- to 3.94 (0.60) mmol·l^{-1} post-immersion ($P=0.037$)] and levels were higher during M ($P=0.012$). When compared to a model prediction of shivering endurance, shivering activity continued well beyond the predicted endurance times in 18 out of the 24 trials The average rates of oxygen consumption over the entire immersion period were lower ($P=0.002$) during M [0.93 (0.20) l·min^{-1}] compared to H [1.05 (0.21) l·min^{-1}], and while these rates did not change during the last 90 min of immersion, there was an increase in fat oxidation There were no trial differences in the average esophageal (T_{es}) and mean skin temperatures during the entire immersion period (36 0 and 18.0°C, respectively), yet T_{es} decreased ($P=0$ 003) approximately 0.4°C during the last 90 min of immersion. When the shivering intensity was normalized to account for this decrease, a significant downward trend of approximately 17%·h^{-1} in the normalized shivering intensity was found after the predicted end of shivering endurance. These results suggest that shivering drive, and not shivering intensity per se, decreased during the latter stages of the immersion. Underlying mechanisms such as fatigue and habituation for this diminishing cold sensitivity are discussed.

Keywords Thermogenesis · Hypothermia · Thermal stress · Prediction · Model

P Tikuisis (✉)
Defence Research and Development,
Human Protection and Performance,
1133 Sheppard Avenue West, Toronto,
PO Box 2000, Ontario, Canada M3M 3B9
E-mail peter.tikuisis@drdc-rddc gc.ca
Tel. +1-416-6352099
Fax +1-416-6352132

D A. Eyolfson X Xu G.G. Giesbrecht
Laboratory for Exercise and Environmental Medicine,
Max Bell Centre, Winnipeg, Manitoba, Canada R3T 2N2

Introduction

Survival time during cold exposure depends upon the severity of the cold stress (Tikuisis 1995, 1997). Under conditions where heat loss overwhelms the individual's capacity to generate heat, survival time is largely determined by the rate of heat debt in the body. This condition occurs, for example, during unprotected immersion in ice-cold water. If the cold is sufficiently less stressful so that individuals are able to balance their heat losses with heat production from shivering, then survival time is largely dependent on how long this level of heat production can be sustained.

A recent study by Castellani et al. (1998) examined whether serial 2 h cold water (20°C) immersions separated by 2 h over a 10 h period would lead to shivering fatigue. They observed that the metabolic rate increased 2.5 to threefold in each of the three immersions. When compared to control trials (single immersion of 2 h at the same time of day corresponding to the serial trials), the metabolic rates were lower during the two repeated immersions following the first immersion of the day. The authors suggested that this "blunting" of the metabolic response might indicate a fatiguing mechanism. It might

also indicate a habituation to a repeated cold stress (Young 1996). However, there was no clear indication that shivering intensity itself began to decrease during the 2 h in any of the immersions. Furthermore, there has been no report of shivering fatigue during continuous exposure to cold except where exercise was involved (Pugh 1967; Thompson and Hayward 1996; Young et al. 1998).

Beckman and Reeves (1966) suggested that the incidence of severe muscle cramping, as they observed in several subjects following 3–4 h of immersion in 24°C water, might indicate the limit of thermal balance and the onset of a critical drop in deep body temperature. This result, among others, inspired the development of a model to predict shivering fatigue during sedentary cold exposure (Wissler 1985). The model was based on muscle glycogen depletion and it proposed that the time to shivering fatigue (t_{end}) decreased exponentially as the relative intensity of shivering increased. This untested hypothesis evolved from the analogy of a rapidly diminishing endurance time with a relative increase in physical exertion (Gleser and Vogel 1973). In the absence of any other mathematical construct of predicting shivering fatigue, the glycogen depletion-based model of Wissler (1985) was adopted for the prediction of cold exposure survival time (Tikuisis 1995, 1997). Certain studies (Tipton et al. 1997, Young et al 1989), however, place doubt on the validity of this model while others have reported a significant depletion of muscle glycogen content during cold exposure (Martineau and Jacobs 1988, Tikuisis et al. 2000).

Irrespective of the mechanism of shivering fatigue, we define its onset as the inability of the thermoregulatory system to maintain a constant shivering sensitivity (i.e. the relationship between the integrated thermal input and shivering intensity). The aims of the present study were to identify the onset of shivering fatigue and investigate the prediction of t_{end} during continuous exposure to cold.

Methods

Subjects

A group of 12 fit, non-smoking male ($n=9$) and female ($n=3$) subjects completed all phases of the experiment These subjects were part of an original group of 15 subjects whose peak shivering intensities were determined (Eyolfson et al 2001) for the present phase of the experiment. Subjects were fully informed about the procedures and risks as approved by the Institute Human Experimentation Ethics Committees, and they subsequently signed volunteer consent forms. Details of the measurements of the subject anthropometric characteristics displayed in Table 1 are given in Eyolfson et al (2001). Also shown in Table 1 are the subjects' rates of oxygen consumption during rest ($\dot{V}O_{2rest}$) and at peak shivering intensity Note that the latter is nearly five times the former which concurs with the finding by Iampietro et al. (1960). Hereafter, it will be assumed that these peak values represent maximal shivering intensities ($\dot{V}O_{2shivmax}$). Body fatness was the only subject characteristic that differed between the men and women [mean (SD)] [19 7 (5.9) and 31 5 (2 6)%, respectively, $P=0.008$].

Protocol

Each subject participated in two cold water immersion trials separated by a minimum of 1 week and designed to elicit constant but different submaximal levels of shivering intensity No dietary or activity restrictions were placed on the subjects except on the day of the trial when they fasted for 8 h prior to their arrival at the laboratory in a well-rested state Following instrumentation, the subjects, wearing only bathing suits, were immersed to the level of the mid-upper chest, in a seated position, with arms out in a stirred water bath initially set at a temperature of 20°C The water temperature was subsequently lowered to approximately 8°C over 15°min by adding ice. After the subject's deep body temperature (defined below) had reached either 36.0 or 35 5°C depending on the trial (randomized among the subjects), the water temperature was raised to a pre-determined value to avoid further body cooling and to evoke a moderate (M) or high (H) percentage of $\dot{V}O_{2shivmax}$ The amount of the rise in water temperature was based on a prediction equation (Eq 5, Tikuisis and Giesbrecht 1999) that takes body temperatures and body fatness into account Subjects remained immersed at this water temperature until one of the following termination criteria was attained

1 by subject request,
2 by the decision of the medical supervisor or principal investigator to terminate the experiment,
3 if the subject's deep body temperature reached 34°C, or
4 if 8 h of immersion had elapsed

The subjects were then rewarmed in a separate water bath in which warm water was circulating (40°C) and released when their deep body temperature exceeded 36 5°C

Measurements

All body temperatures and metabolic rates were measured continuously during the immersion. Deep body temperature was represented by the esophageal temperature (T_{es}) measured using a thermocouple positioned at the level of the heart (Mekjavic and Rempel 1990) Obvious spurious values were removed from the analysis. Skin temperatures were measured using heat flux transducers (Concept Engineering, Old Saybrook, Conn.) positioned at 12 sites on the body to obtain a mean-weighted value ($\overline{T}_{sk}$) according to Layton et al (1983) All temperatures were measured with a precision of 0.01°C

Subjects were equipped with a facemask to monitor respiratory gas continuously. Rates of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production were measured using open circuitry (Sensor Medics Vmax Series 229, Yorba Linda, Calif.) from inspired and expired gas concentrations, and from the measured expired minute ventilation ($\pm 0.001\ l\,min^{-1}$). These data were averaged every minute for later analysis A single channel electrocardiogram (Hewlett-Packard 43100A Monitor-Defibrillator) was used to monitor heart rate and rhythm as a cautionary measure.

Blood samples were drawn from a venous catheter in the antecubetal vein of the non-dominant arm prior to immersion (pre), 1 h after the start of the immersion, and at the end of the immersion (post) to quantify fuel availability and stress. These samples were subsequently assayed for concentrations of blood lactate and plasma glucose, nonesterified fatty acid (NEFA), glycerol, β-hydroxybutyrate (β-OH), glucagon, insulin, and cortisol

Endurance prediction

According to Wissler (1985), the end-point of shivering endurance (in hours) can be predicted from

$$t_{end} = \left(\frac{18}{L_r}\right) \exp^{-4 L_r} \quad (1)$$

where 18 is the endurance constant and L_r is the relative shivering intensity given by

Table 1. Subject characteristics *BM* body mass, *HT* height, *SA* body surface area (Gehan and George 1970), *SKF* the sum of three skinfolds (biceps, triceps, subscapular), *BF* body fatness (Durnin and Womersley 1974), $\dot{V}O_{2rest}$, $\dot{V}O_{2shivmax}$ rates of oxygen consumption at rest and at peak shivering intensity, respectively (Eyolfson et al. 2001)

Subject	Sex	Age (years)	BM (kg)	HT (m)	SA (m^2)	SKF (mm)	BF (%)	$\dot{V}O_{2rest}$ ($l\,min^{-1}$)	$\dot{V}O_{2shivmax}$ ($l\,min^{-1}$)
1	m	34 0	70 0	1 80	1.88	50 5	26 7	0 341	1 515
2	m	25.0	102 0	1 93	2 34	46.2	24 2	0 363	1 973
3	m	40 0	83.3	1.83	2 07	35 6	23 4	0 302	1 303
4	m	20 0	74.5	1 82	1.95	34 8	20.4	0.436	1 694
5	m	24 0	61 0	1 66	1 69	20 8	13.6	0.318	1 478
6	m	20.0	65 0	1 73	1 78	17.0	10 9	0 357	1 712
7	m	26.0	79 5	1.84	2 02	26 3	16 7	0 387	1 843
8	m	23 0	63.0	1 65	1 71	23 1	14 9	0.326	1 484
9	m	21 0	78 5	1 72	1 95	54 7	26 6	0 287	1 295
10	f	26.0	52.2	1 61	1.54	42.0	28.6	0.225	1 141
11	f	20 0	61.0	1 67	1 69	58 0	33.6	0 274	1 443
12	f	19 0	70 5	1 72	1 85	53 6	32.4	0 341	1 514
Mean		24 8	71 7	1 75	1 87	38.6	22 7	0 330	1 533
SD		6 3	13 2	0 10	0 21	14 4	7 4	0 055	0 238

$$L_r = \frac{\dot{V}O_2 - \dot{V}O_{2test}}{\dot{V}O_{2shiv\,max} - \dot{V}O_{2rest}} \quad (2)$$

For example, if $\dot{V}O_{2shivmax} = 5\times\dot{V}O_{2rest}$, and $\dot{V}O_2$ = either 60% or 80% of $\dot{V}O_{2shivmax}$, then $L_r = 0\,5$ or 0.75, and $t_{end} = 4\,87$ or 1 19 h, respectively This example illustrates the high non-linearity in the prediction of t_{end} It also demonstrates that the prediction of t_{end} depends very strongly on the value of L_r which in turn depends on the measured metabolic rates, both actual and maximal. For example a 10% change in L_r around $L_r = 0\,5$ would predict about a 30% change in t_{end} around $t_{end} = 4.87$ Thus, the combination of high non-linearity and high sensitivity of t_{end} to the measured metabolic rates indicates a markedly narrow tolerance in the validation of Eq. 1.

According to the above equations, t_{end} is solely dependent on the relative shivering intensity Although the attainment of a constant L_r during an immersion trial was sought, it was inevitable that natural fluctuations in $\dot{V}O_2$ would occur thereby leading to variations in L_r. To accommodate these variations, Eq 1 was re-configured to isolate the endurance constant in accordance to Wissler (1985) as

$$18 = \int_0^{t_{end}} L_r \exp^{4\,L_r} \cdot dt \quad (3)$$

Equation 3 indicates that at the end of shivering endurance (implicit solution of t_{end}), the integrated value of $L_r \exp^{4L_r}$has a value of 18. Since the rate of $\dot{V}O_2$ was measured over fixed periods of time, Δt, the above integration can be rewritten as a sum

$$\text{SUM} = \sum L_r \cdot \exp^{4\,L_r}\ \Delta t \quad (4)$$

where the end of shivering endurance (i.e when $\Sigma\Delta t = t_{end}$) is now predicted when SUM = 18 To simplify the presentation of the results, SUM was normalized by dividing its value by 18 and the resultant variable is denoted as NSUM. The NSUM provides a convenient measure for comparisons: that is, shivering activity that exceeds the predicted endurance endpoint is indicated by the extent to which NSUM exceeds unity Additionally, it is to be noted that the above expressions do not allow recovery during inactive periods, although this should not be a serious concern since shivering is rarely interrupted for extended periods of time

Data treatment

Only data collected during the cold water immersion were analyzed These included, in addition to body temperatures and metabolic rates, the time when the end of shivering endurance was predicted (t_{end} or when NSUM = 1) and the value of NSUM at the end of the entire immersion period

Since shivering thermogenesis is considered to be driven by decreases in body temperature (Benzinger 1969), changes in the metabolic rate could have been expected to result from changes in T_{es} and $\bar{T}_{sk}$ during the immersion. It was important to separate these changes from any that may have been due to shivering fatigue. Thus, to account for the non-fatiguing changes, the measured metabolic rate due to shivering alone ($M_{shivmeas}$ = total minus resting metabolic rates) was normalized by dividing the measured rate by the predicted $M_{shivmeas}$ (in watts per metre squared) according to (Tikuisis and Giesbrecht 1999)

$$M_{shiv\,pred} = \frac{155\,5(37 - T_{es}) + 47\,0(33 - \bar{T}_{sk}) - 1\,57(33 - \bar{T}_{sk})^2}{\sqrt{\%BF}} \quad (5)$$

where %BF is percentage body fatness. The conversion of the $\dot{V}O_2$ to $M_{shivmeas}$ and the constraints with regard to the set-points (bracketed terms are 0 whenever the set-point temperatures of 33 and 37°C, respectively pertaining to $\bar{T}_{sk}$ and T_{es}, are exceeded) are detailed in Tikuisis and Giesbrecht (1999) If Eq 5 predicted perfectly, then the normalized value of $M_{shivmeas}$ would always be unity In this study, the normalized shivering intensity ($M_{shivmeas}/M_{shivpred}$, where $M_{shivpred}$ is the predicted shivering intensity) is represented by NSHIV.

A dependent paired Student's *t*-test was applied to check for differences between trials in the total immersion time (t_{imm}), T_{es}, $\bar{T}_{sk}$, NSHIV, t_{end}, NSUM, and average values of the absolute and relative $\dot{V}O_2$ during the immersions with acceptance at $P < 0\,05$ (Statistica, www statsoft com) A two-factor (trial×time) analysis of variance for repeated measures was also applied in the analysis of the blood samples taken during the immersion (i.e pre, 1 h, and post), and T_{es}, $\bar{T}_{sk}$, $\dot{V}O_2$, NSHIV, and the nonprotein respiratory exchange ratio (*R*) during the latter phase of the immersion with acceptance at $P < 0.05$ In addition, the slope of NSHIV after t_{end} was attained was determined by linear regression All values are provided as mean (SD)

Results

Despite the efforts to achieve constant moderate and high relative intensities of shivering during the two cold water immersion trials, the subjects' responses were highly variable in both intensity and duration. The results of one subject (no. 8 in Table 1) in the moderate intensity trial are shown in Fig. 1. In this case, the subject was immersed in cold water for 304 min, had a $\dot{V}O_2$ that averaged 0.904 $l{\cdot}min^{-1}$, a predicted shivering endurance time of 88 min, and a final NSUM = 1.823, while the values for this subject's other trial (not shown)

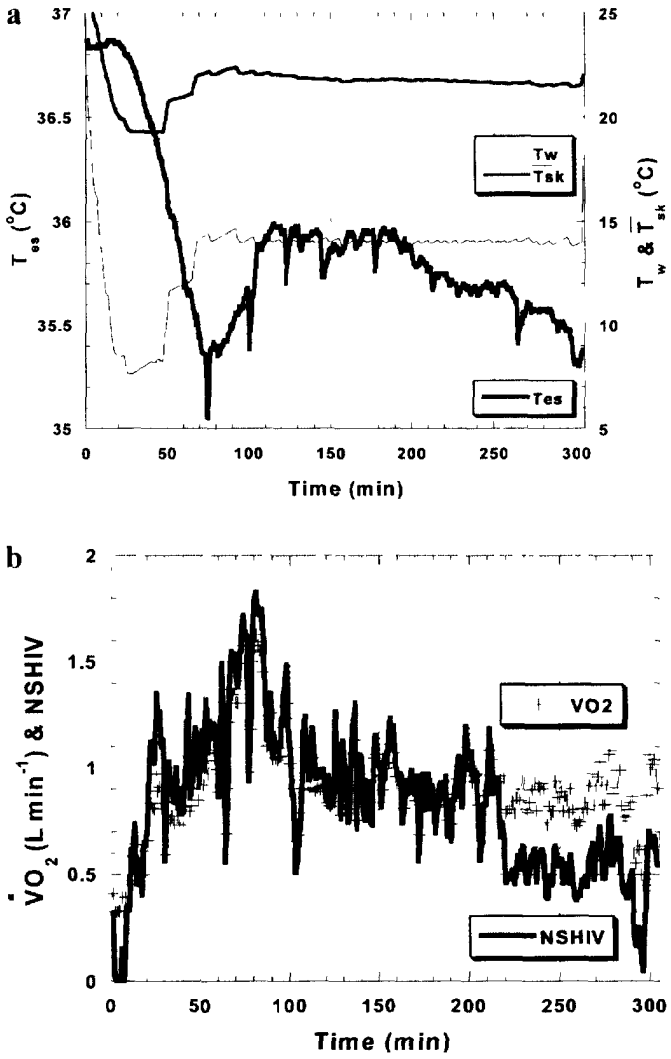

Fig. 1. **a** Water (T_w), mean skin ($\overline{T}_{sk}$), and esophageal temperatures (T_{es}), and **b** rate of oxygen consumption ($\dot{V}O_2$) and the normalized shivering heat production (*NSHIV*) plotted against time during the moderate shivering intensity trial of subject no 8

were 167 min, 1.151 l·min^{-1}, 80 min, and 3.335, respectively The NSHIV is also shown (Fig. 1b) and demonstrates how the normalization scheme led to a divergence from the $\dot{V}O_2$ values towards the end of immersion due to a continual decrease in T_{es} That is, had $\dot{V}O_2$ increased in response to the decrease in T_{es}, as expected under non-fatiguing conditions, then NSHIV would have remained approximately constant. Also note that the decreases in T_{es} (e.g. from 35 35 to 35 02°C at 74 min in Fig. 1a) were considered artefacts and were ignored in the data analysis

Table 2 provides a summary of the subjects' responses. No subject reached the termination core temperature of 34°C or completed 8 h of immersion (early withdrawal was due to discomfort). Although the total immersion time tended to be longer during M, it was not different from H and together they averaged approximately 3.7 h. Neither T_{es} nor $\overline{T}_{sk}$ were different between trials with average values of 35.9 and 18 0°C, respectively. However, the integrated shivering activity (refer to NSUM in Table 2) exceeded unity by 42% and 107% for M and H, respectively ($P = 0.010$) The t_{end} were exceeded in 8 and 10 cases out of 12 for M and H, respectively, note that these correspond to NSUM > 1. For the 7 subjects that attained t_{end} in both trials (nos. 2, 3, 6, 8 – 11) hereafter referred to as G7, t_{end} was marginally longer during M ($P = 0.047$). The average $\dot{V}O_2$ of all the subjects and its value relative to the subjects' $\dot{V}O_{2shivmax}$ were higher during H ($P = 0$ 002 and 0.001, respectively). The average NSHIV was also higher during H ($P = 0.040$). Similar differences in these variables (except for NSHIV) between trials were also found for the G7 subjects (Table 2).

Since the subjects were immersed for different periods (from 105 to 388 min), the analyses of variance of T_{es}, $\overline{T}_{sk}$, $\dot{V}O_2$, R, and NSHIV were conducted for the last 90 min of immersion. This purposely excluded the initial period of immersion to avoid any confounding effects of rapid decreases in skin temperature. The means of most of these variables for the two trials during this period are shown in Fig. 2. There were no trial differences in T_{es}, $\overline{T}_{sk}$, R, and NSHIV whereas mean $\dot{V}O_2$ was lower ($P = 0.014$) during M [0.96 (0.04) l·min^{-1}] compared to H [1.11 (0.05) l·min^{-1}] The T_{es} decreased with time ($P = 0.003$) from 36 02 (0.71) to 35.57 (0.70)°C during M and from 35 85 (0.83) to 35 52 (0.83)°C during H. Conversely, $\overline{T}_{sk}$ increased ($P < 0.001$) from 17.67 (3.49) to 19.57 (3 28)°C during M and from 17.15 (2.60) to 18.25 (3.04)°C during H. Although not significant, T_{es} tended to be lower at the beginning of this time segment during H as a consequence of cooling the body further to elicit a higher shivering intensity. There was no change in $\dot{V}O_2$ during the last 90 min of immersion in contrast to a decrease in mean R ($P < 0.007$) from 0.87 (0.04) to 0.84 (0 04) during M and from 0.86 (0.05) to 0 084 (0.03) during H, indicating an increasing dependence on fat oxidation with lengthening immersion time. Also, there was a significant decrease in NSHIV ($P < 0.001$) from 1.33 (0.65) to 0.96 (0.47) during M and from 1.42 (0.66) to 1.23 (0.41) during H. Finally, there was no trial×time interaction in any of the above variables during the last 90 min of immersion.

Complete blood samples were obtained and analyzed for 9 subjects (missing were samples from 3 men, subjects nos. 2, 4, and 7) Mean glucose concentration was the only component that was different between trials [3.93 (0.43) and 3.66 (0.41) mmol·l^{-1} for M and H, respectively; $P = 0.012$] All blood metabolites increased during the immersion; following are their respective mean pre and post concentrations. lactate [0.77 (0.21) and 1.39 (0.45) mmol·l^{-1}; $P = 0$ 003], glucose [3.46 (0.47) and 3.91 (0.41) mmol·l^{-1}; $P = 0.004$], NEFA [0.32 (0.22) and 0 89 (0 29) mmol·l^{-1}; $P < 0.001$], glycerol [0 06 (0.03) and 0 16 (0.03) mmol·l^{-1}; $P < 0.001$], and β-OH [0.13 (0.12) and 0.47 (0.25) mmol·l^{-1}; $P < 0.001$]. Concentrations of cortisol, the only stress indicator measured, increased during the immersion [17.8 (6.4) and 27.22 (9.0) μg·dl^{-1} for pre and post immersion,

Table 2. Summary of the subjects' responses. t_{imm} total immersion time, T_{es}, *overline*T_{sk} average esophageal and mean skin temperatures, *NSUM* normalized measure of shivering endurance, t_{end} time when the end of shivering endurance is predicted according to Eq 4 (blank values indicate that t_{end} was not reached), $\dot{V}O_{2avg}$ average rate of oxygen consumption during the immersion, *NSHIV* average ratio of the measured to predicted shivering metabolic rate over the entire cold water immersion period

Subject	Trial	t_{imm} (min)	T_{es} (°C)	$\overline{T}_{sk}$ (°C)	NSUM (min)	t_{end}	$\dot{V}O_{2avg}$ (l min^{-1})	$\dot{V}O_{2avg}$/ $\dot{V}O_{2shivmax}$ (%)	NSHIV
1	M	221	36 94	16.31	0 643		0.817	54 0	1 30
	H	170	36 86	14 96	1 609	102	1 013	66 8	1 90
2	M	281	35 94	14 96	1 706	173	1 112	56 4	1 19
	H	388	35 84	14 91	2 059	181	1 154	58.5	1 08
3	M	332	35 85	21 50	1 634	144	0 791	60 7	0 77
	H	203	35.19	18 67	2 348	104	0.910	69 9	0 76
4	M	195	36 40	20 12	0.508		0 906	53 5	0 90
	H	180	36 66	18 48	1 486	117	1 101	65 0	1 34
5	M	299	34.94	22.62	1 694	99	0 875	59.2	0 65
	H	107	34 94	19 91	0 900		0 940	63 6	0 68
6	M	108	35.58	18 20	2 739	48	1 492	87 1	1 42
	H	125	35 34	21.78	3 375	42	1.511	88 2	1 31
7	M	312	35 60	18 45	0 845		0 967	52 5	0.76
	H	200	35 28	15.84	2.739	94	1.283	69 6	1 15
8	M	304	35 88	21 62	1.823	88	0 904	60 9	0 84
	H	167	35 29	19 75	3 335	80	1 151	77 6	1 09
9	M	325	35 96	15 87	1 228	283	0 721	55 6	0 78
	H	260	36 41	17 47	1 262	205	0 776	59 9	1.00
10	M	197	35.36	17 30	2 422	100	0.818	71.6	1 22
	H	268	36 19	20 81	3 516	76	0 848	74 3	1 65
11	M	250	36 63	14 55	1 408	189	0.929	64 3	2 07
	H	220	36 39	14 17	1.542	145	0 964	66 8	2 01
12	M	139	36 70	17 52	0 408		0 861	56 8	1 45
	H	105	36.32	15.18	0 640		0 927	61 2	1 40
Mean (SD)	M (all)	249.9 (74 8)	35 98 (0.59)	18.25 (2 70)	1 422* (0.735)		0.933* (0 202)	61 1* (9.8)	1.11* ± 0.41
Mean (SD)	H (all)	199 4 (79 6)	35 89 (0 66)	17 66 (2 60)	2 068 (0 992)		1 048 (0 205)	68.5 (8 4)	1 28 (0 41)
Mean (SD)	M (G7)	256 7 (80.5)	35.89 (0 39)	17 71 (2 92)	1.851* (0 543)	146.4* (77 9)	0 967* (0 263)	65 2* (11 1)	1.18 (0 46)
Mean (SD)	H (G7)	233 0 (84.7)	35 81 (0 54)	18 22 (2.88)	2 491 (0 928)	119 0 (59 8)	1 045 (0 250)	70 7 (10 4)	1 27 (0 43)

*indicates a significant difference between the trials

respectively; $P < 0.001$] while those of the hormones glucagon [86.9 (21 7) and 96.8 (18.5) pg·ml^{-1} for M and H, respectively; $P = 0.445$] and insulin [9.23 (3.56) and 7.96 (1.77) μU·ml^{-1}; $P = 0.372$] did not. The measured changes are consistent with those reported from other cold exposure studies (Haight and Keatinge 1973; Tikuisis et al. 1999).

The following results pertain to the regression of NSHIV for G7 after t_{end} was attained As noted above, NSHIV was not different between trials but decreased during the last 90 min of immersion for all subjects. There was no difference in NSHIV for G7 during the 30 min preceding t_{end} when compared to the same period following t_{end}, yet NSHIV was lower during the last 30 min of immersion compared to the same period immediately before or after t_{end} ($P < 0.016$). During the period of immersion following t_{end} [110 (67) and 114 (60) min for M and H, respectively], NSHIV decreased at rates of 0.0039 (0.0019) and 0 0018 (0.0028) min^{-1} for M and H, respectively. These slopes, which were not different between trials ($P = 0.226$), are to be interpreted as the fractional change in NSHIV per minute. Multiplication by 6,000 yields the percentage change per hour of immersion. For example, the average fractional decrease of both trials in NSHIV of about –0.0028 min^{-1} during the last hour of immersion converted to a decrease of about 17%·h^{-1}

Discussion

Although rewarming of the water bath began once the subjects had reached the target T_{es} of 36.0 and 35.5°C for M and H, respectively, a characteristic afterdrop (Giesbrecht and Bristow 1992) resulted in lower values of T_{es}. Minimal values were 35.23 (0.99) and 35 12 (0.86)°C, respectively, although these were not significantly different. An example of the after-drop is shown in Fig. 1a, where the subject's T_{es} reached a nadir of 35 35°C. How the normalization of the metabolic rate due to shivering compensated the shivering response for changes in body temperatures is demonstrated in Fig. 1b. In this example, $\dot{V}O_2$ values appear to be uniformly distributed during the latter half of the immersion whereas NSHIV indicates a downward trend. This suppression was caused by a continual decrease in T_{es} (Fig. 1a), which normally would be expected to increase the shivering drive/metabolism (Benzinger 1969). It failed to do so even though the subject's $\dot{V}O_2$ (average approximately 0.9 l·min^{-1}) was well below his maximal shivering capacity (1.48 l·min^{-1}).

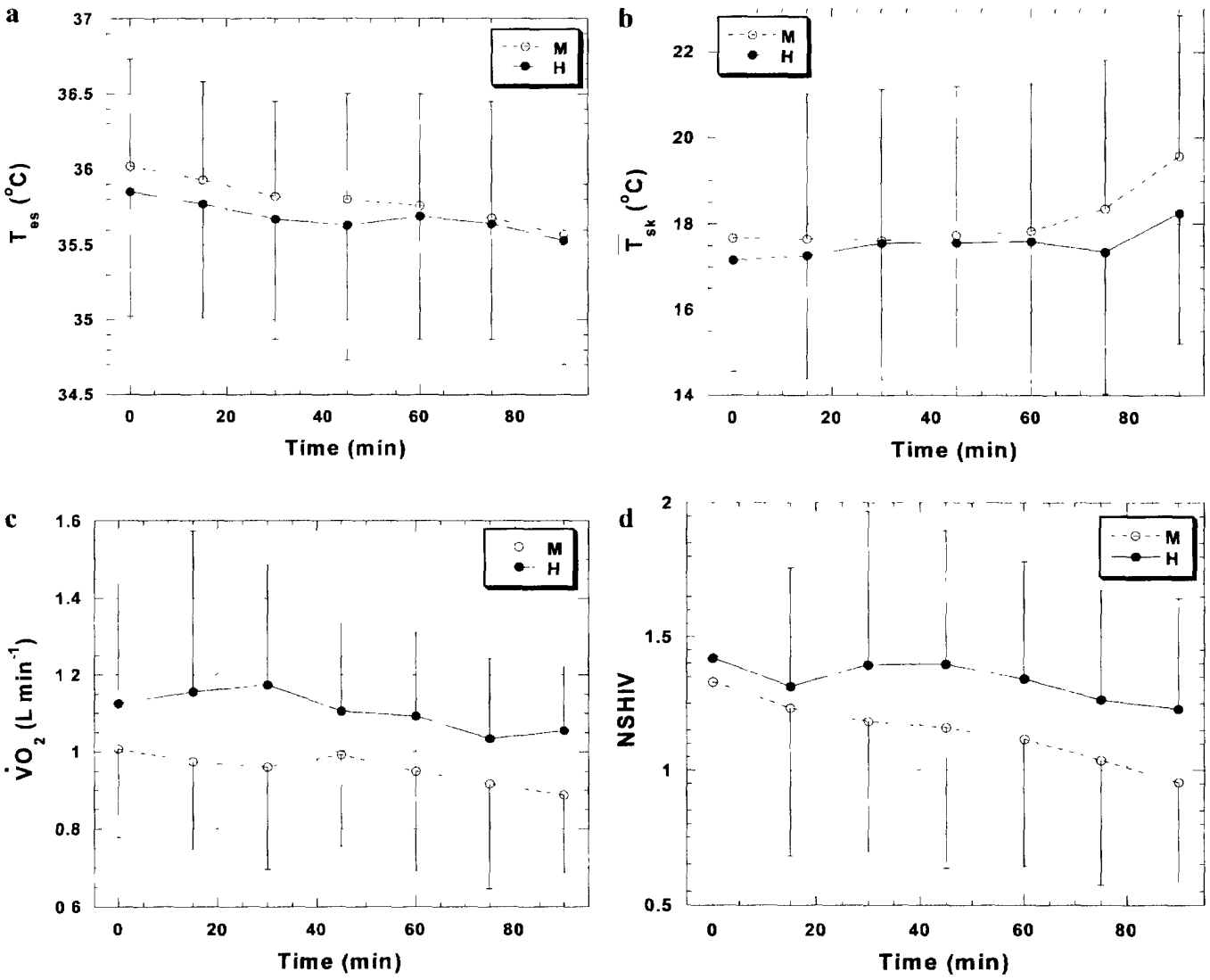

Fig. 2. Comparison of the mean (SD) values of the subjects' **a** esophageal temperature (T_{es}) **b** mean skin temperature ($\overline{T}_{sk}$), **c** rate of oxygen consumption ($\dot{V}O_2$), and **d** normalized shivering intensity (*NSHIV*) during the last 90 min of immersion in the moderate (*M*) and high (*H*) shivering intensity trials

Despite attempts to adjust the water bath temperatures to levels that would elicit a larger difference in shivering intensities between trials, subjects shivered at intensities that were much closer than expected, specifically at 61% (M) and 69% (H) of their maximal shivering capacity (Table 2). While these values and their $\dot{M}_{shivmeas}$ of 115 (40) and 138 (38) W·m^{-2}, respectively, were different between the trials ($P=0.004$), the subjects' total energy expenditures were not different [826 (231) and 833 (366) W h) owing to the tendency for longer total immersion times for M.

That the average NSHIV exceeded unity in the M and H trials by 11% and 28%, respectively (Table 2), was an indication that the prediction of $\dot{M}_{shiv}$ (Eq 5) generally underestimated the observed values. However, this underestimation was primarily caused by the response of the women. The NSHIV was the only variable in Table 2 that was different between the men and women within each trial [0.96 (0.27) compared to 1.58 (0.44) ($P=0.0140$) during M, and 1.15 (0.36) compared to 1.69 (0 31) ($P=0.0422$) during H, respectively]. These results validate the use of Eq. 5 for men where NSHIV was not different from unity, but not necessarily for women. Furthermore, Eq. 5 was regressed from data exclusively involving the male response to cold (Tikuisis and Giesbrecht 1999). The underestimation for women might be attributed to inappropriate weighting coefficients and/or too great an attenuation of the shivering response due to body fatness. However, this should not adversely affect the analysis of shivering fatigue since relative changes in the shivering response were examined. Further, no sex differences were found in the rates of change of NSHIV during the last 90 min of immersion.

While sex differences can account for the general overestimation of NSHIV, the trial difference in NSHIV (1.11 compared to 1.28 for M and H, respectively) can

be attributed to the lower average metabolic rate for M (115 $W \cdot m^{-2}$) compared to H (138 $W \cdot m^{-2}$). This is because NSHIV was calculated as the ratio of $\dot{M}_{shivmeas}/\dot{M}_{shivpred}$ and $\dot{M}_{shivpred}$ was not different between M and H. Thus, the trial difference in NSHIV was due not to the predicted shivering metabolic rate, but to the measured values. Indeed, the strategy to achieve a lower body temperature during H successfully caused a higher sustained shivering intensity even though the average T_{es} [35.89 (0.66)°C] and $\overline{T}_{sk}$ [17.66 (2.60)°C] were not statistically lower compared to M [35.98 (0.59) and 18.25 (2.70)°C, respectively].

The mean total immersion times of 257 and 233 min of G7 during M and H exceeded the mean predicted times to t_{end} of 146 and 119 min, respectively, by 76% and 96%. The observation that these subjects continued to shiver well beyond their predicted t_{end} suggests that the "glycogen depletion" model originally proposed by Wissler (1985) underestimated shivering endurance. Certainly, it can be concluded from these results that shivering does not cease abruptly once t_{end} is attained. The model developed by Wissler (1985) was originally based on the incidence of severe and persistent muscle cramping in 13 out of 24 male subjects immersed up to the neck level in 24°C water, as reported by Beckman and Reeves (1966). Wissler (private communication) interpreted the onset of muscle cramping as an indication of shivering fatigue.

That shivering did not cease abruptly in the present study concurs with the suggestion of Tipton et al. (1997) that shivering and exercise should not be regarded as analogous processes. While all the subjects' average $\dot{V}O_2$ during the entire immersion period were 61.1% (M) and 68.5% (H) of their maximal shivering intensities, they represent only 25.4% and 28.4%, respectively, of the subjects' maximal oxygen uptake ($\dot{V}O_{2max}$) (Eyolfson et al. 2001). By comparison, aerobic metabolic activity at these levels for up to 4 h would normally not be fatiguing (Bink 1962), yet the regression analysis of NSHIV following t_{end} indicated that the shivering drive decreased, although not suddenly. Thus, t_{end} might signal not the abrupt end of steady-state shivering, but the start of a diminishing cold sensitivity. Indeed, this concurs with the original intent of Wissler (1985) who acknowledged that shivering fatigue might not occur as rapidly as exercise fatigue at similar relative intensities of effort, and that the endurance prediction might more accurately pertain to the end of a sustained shivering drive.

It is also noteworthy that while the mean $\overline{T}_{sk}$ of all subjects increased modestly but significantly (17.4 to 18.9°C) during the last 90 min of immersion, NSHIV decreased by an average of about 21%·h^{-1}. Since the increase in $\overline{T}_{sk}$ has a negligible influence on $\dot{M}_{shivpred}$ (< 0.2% according to Eq. 5 when $\overline{T}_{sk}$ was approximately 18°C), the magnitude of the decrease in NSHIV cannot be attributed to the change in $\overline{T}_{sk}$. Nor can the decrease in NSHIV be attributed to T_{es}, which actually decreased during this period and should have driven shivering activity even higher (Benzinger 1969). Thus, the decrease in NSHIV could again be interpreted as an indication of a diminishing cold sensitivity. The decrease in NSHIV for G7 (average of about 17%·h^{-1}) during the period of immersion following t_{end} further supports the proposal of a desensitizing mechanism. While no attempt was made to identify the mechanism of this diminishing cold sensitivity, such a mechanism would clearly be distinct from exercise fatigue which would not be expected to occur at levels of intensity below 30% of $\dot{V}O_{2max}$ within 4 h of continuous exercise (Bink 1962, Gleser and Vogel 1973).

Extenuating circumstances have caused shivering suppression in certain previous investigations. For example, Haight and Keatinge (1973) reported that hypoglycemia (mean plasma glucose concentrations of 2.2 $mmol \cdot l^{-1}$) induced by exercise and ethanol ingestion effectively blocked a metabolic response to decreasing deep body temperature. Gale et al. (1981) also reported suppression of shivering when plasma glucose concentration fell below 2.5 $mmol \cdot l^{-1}$. However, such low levels of plasma glucose concentration were not attained by any of the subjects in the present study, and thus hypoglycemia would not have been a factor in any suppression of shivering. Mekjavic et al. (1995) reported another cause of shivering suppression due to cognitive impairment induced by nitrogen narcosis during diving. However, there was no evidence of a similar impairment in cognition in the present study.

One interpretation of a diminishing cold sensitivity is shivering fatigue concomitant with a depletion of glycogen. Yet certain previous studies place doubt on whether glycogen depletion was a factor in the present study. Young et al. (1989) reported no significant depletion of muscle glycogen content in male subjects immersed to the neck level in 18°C water for 2 h. In contrast, Martineau and Jacobs (1988) found a significant depletion (approximately 23%) of muscle glycogen content in male subjects also immersed to the neck level in 18°C water but for a shorter time (1.5 h). More recently, Tikuisis et al. (2000) found a similar and significant decrease of muscle glycogen content in women using the same experiment protocol as Martineau and Jacobs (1988).

There are two reasons why the above reported results of no or only a small decrease in muscle glycogen content do not necessarily refute the possibility that glycogen depletion might have been responsible for the decrease in NSHIV in the present study. First, the water immersion times of the above-cited studies were not sufficiently long to exceed t_{end} at the reported levels of shivering intensity, and thus appreciable depletion of glycogen should have not been expected. Second, the site of muscle glycogen sampling was from the thigh (specifically the vastus lateralis muscle) and this region of the body has been shown to contribute only about 20% of the total shivering heat production in men (as represented by the rectus femoris muscle; Bell et al. 1992). Hence, the absence or only a small glycogen depletion in

the thigh does not necessarily disprove the possibility of glycogen depletion in a more active shivering muscle such as found in the torso (Bell et al. 1992).

While a correspondence between glycogen depletion (however small) and shivering endurance is uncertain, the mathematical form of Eq. 1 appears to be satisfactory for the prediction of survival time in the cold (Tikuisis 1995, 1997). Indeed, the finding of a decrease in shivering drive after t_{end} was attained supports the use of Eq. 1, especially considering the high non-linearity and sensitivity of t_{end} with respect to the value of the relative shivering intensity, even though the underlying mechanism of glycogen depletion and its correlation to shivering drive has not been identified.

Another interpretation of a diminishing cold sensitivity is a relaxation of the shivering drive due to habituation to the cold stress. Bruck (1984) proposed that short-term adaptation, of the order of minutes, involving shivering threshold changes might be attributed to alterations in the central integrative nervous structure of the thermoregulatory system. That the measured metabolic rate remained unchanged during the last 90 min of immersion suggests a steady-state level of shivering that is unresponsive to further slow decreases in deep body temperature. A similar response is also evident in the results of Thompson and Hayward (1996). The advantage of such an adaptive shift in cold tolerance would be preservation of metabolic stores That is, any consequential lowering of body temperature due to an imbalance between heat production and heat loss would lessen the temperature gradient for further heat loss. This, in turn, would reduce the metabolic requirement for the restoration and maintenance of heat balance. Such a thermoregulatory modification has also been termed "metabolic adaptation" observed after a lengthy series of cold exposure trials (Bittel 1987). The blunting of the metabolic response after repeated cold exposures within the same day has also been described as a process of habituation (Young 1996) The possibility of such a modification during the course of a single lengthy exposure to cold as implied by the present observations concurs with the supposition of Bruck (1984).

While the present results do not support the prediction of a decrease in shivering intensity per se, they do suggest that shivering drive decreases once t_{end} is surpassed. The consequence of the latter response can ultimately be just as catastrophic. Without an increase in total heat production as body temperatures fall, continued heat debt and progressive hypothermia are inevitable. Hence, survival time during cold exposure may not necessarily depend on when shivering finally ceases, but rather on when the shivering drive decreases to a point of no return when heat balance can no longer be restored.

Acknowledgements The authors gratefully acknowledge the technical assistance of G Weseen during the course of this work, and the expert opinion offered by Dr. E.H Wissler during the preparation of this manuscript This study was supported by the Canadian Department of National Defence New Search and Rescue Initiatives programme (contract no 2668ND18BN04099 FL707) and the Natural Science and Engineering Research Council of Canada

References

Beckman EL, Reeves E (1966) Physiological implications as to survival during immersion in water at 75°F Aerosp Med 37 1136–1142

Bell DG, Tikuisis P, Jacobs I (1992) Relative intensity of muscular contraction during shivering J Appl Physiol 72 2336–2342

Benzinger TH (1969) Heat regulation homeostasis of central temperature in man Physiol Rev 49:671–759

Bink B (1962) The physical working capacity in relation to working time and age Ergonomics 5 25–28

Bittel JHM (1987) Heat debt as an index for cold adaptation in men J Appl Physiol 62 1627–1634

Bruck K (1984) Basic mechansims in thermal long-term and short-term adaptation J Therm Biol 11 73–77

Castellani JW, Young AJ, Sawka MN, Pandolf KB (1998) Human thermoregulatory responses during serial cold-water immersions. J Appl Physiol 85 204–209

Durnin JVGA, Womersley J (1974) Body density assessed from total body density and its estimation from skinfold thickness measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 32 77–97

Eyolfson DA, Tikuisis P, Xiaogiang X, Weseen G, Giesbrecht GG (2001) Measurement and prediction of maximal shivering intensity in humans. Eur J Appl Physiol 84 100–106

Gale EAM, Bennett T, Hilary Green J, Macdonald IA (1981) Hypoglycaemia, hypothermia and shivering in man Clin Sci 61 463–469

Gehan EA, George SL (1970) Estimation of human body surface area from height and weight I. Can Chemother Rep 54 225–235

Giesbrecht GG, Bristow GK (1992) A second postcooling afterdrop more evidence for a convective mechanism J Appl Physiol 73 1253–1258

Gleser MA, Vogel JA (1973) Endurance capacity for prolonged exercise on the bicycle ergometer J Appl Physiol 34 438–442

Haight JSJ, Keatinge WR (1973) Failure of the thermoregulation in the cold during hypoglycaemia induced by exercise and ethanol J Physiol (Lond) 229 87–97

Iampietro PF, Vaughan JA, Goldman RF, Kreider MB, Masucci F, Bass DE (1960) Heat production from shivering. J Appl Physiol 15 632–634

Layton RP, Mints WHJ, Annis JF, Rack MJ, Webb P (1983) Calorimetry with heat flux transducers comparison with a suit calorimeter J Appl Physiol 54 1361–1367

Martineau L, Jacobs (1988) Muscle glycogen utilization during shivering thermogenesis in humans J Appl Physiol 65 2046–2050

Mekjavic IB, Rempel ME (1990) Determination of esophageal probe insertion length based on standing and sitting height J Appl Physiol 69 376–379

Mekjavic IB, Savic SA, Eiken O (1995) Nitrogen narcosis attenuates shivering thermogenesis J Appl Physiol 78.2241–2244

Pugh LGC (1967) Cold stress and muscular exercise, with special reference to accidental hypothermia BMJ II 333–337

Thompson RL, Hayward JS (1996) Wet-cold exposure and hypothermia· thermal and metabolic responses to prolonged exercise in rain J Appl Physiol 81 1128–1137

Tikuisis P (1995) Predicting survival time for cold exposure Int J Biometeorol 39 94–102

Tikuisis P (1997) Prediction of survival time at sea based on observed body cooling rates Aviat Space Environ Med 68 441–448

Tikuisis P, Giesbrecht (1999) Prediction of shivering heat production from core and mean skin temperatures Eur J Appl Physiol 79 221–229

Tikuisis P, Ducharme MB, Moroz D, Jacobs I (1999) Physiological responses of exercised-fatigued individuals exposed to wet-cold conditions J Appl Physiol 86 1319–1328

Tikuisis P, Jacobs I, Moroz D, Vallerand AL, Martineau L (2000) Comparison of thermoregulatory responses between males and females immersed in cold water. J Appl Physiol 89 1403–1411

Tipton MJ, Franks GM, Meneilly GS, Mekjavic IB (1997) Substrate utilization during exercise and shivering Eur J Appl Physiol 76 103–108

Wissler EH (1985) Mathematical simulation of human thermal behavior using whole-body models In Shitzer A, Eberhart RC (eds) Heat transfer in medicine and biology. vol 1. Plenum Press, New York, pp 347–355

Young AJ (1996) Homeostatic responses to prolonged cold exposure human cold acclimatization In Fregly MJ, Blatteis CM (eds) Handbook of physiology Environmental physiology, section 4, vol 1 Oxford University Press, New York, pp 419–438

Young AJ, Sawka MN, Neufer PD, Muza SR, Askew EW, Pandolf KB (1989) Thermoregulation during cold water immersion is unimpaired by low muscle glycogen levels J Appl Physiol 66 1809–1816

Young AJ, Castellani JW, O'Brien C, Shippee RL, Tikuisis P, Meyer LG, Blanchard LA, Kain JE, Cadarette BS, Sawka MN (1998) Exertional fatigue, sleep loss, and negative energy balance increase susceptibility to hypothermia J Appl Physiol 85 1210–1217

#518482