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A disabled submarine (DISSUB) lacking power and/or environmental control will become cold, and the ambient air may become hypercapnic and hypoxic. This study examined if the combination of hypoxia, hypercapnia, and cold exposure would adversely affect thermoregulatory responses to acute cold exposure in survivors awaiting rescue. Seven mail submariners 33 ±6 yrs) completed a series of cold-air tests (CAT) that consisted of 20-min at Tair + 22°C, followed by a linear decline(1°C.min-1) in Tair to 12°C, which was then held constant for an additional 150-min. CAT were performed under normoxic,normocapnic conditions (D0), acute hypoxia (D1, 16.75% O2), after 4 days of chronic hypoxia, hypercapnia and cold (D5, 16.75%O2, 2.5% CO2, 4°CC), and hypoxia-only again (D8, 16.75% O2). The ?Tsk during AT was larger ($P<0.05$) on D0 (-5.2°C), vs.D1 (-4.8°C), D5 (-4.5°C), and D8 (-4.4°C). The change (relative to 0-min) in metabolic heat production (?M) at 20-min of CAT was lower ($P<0.05$) on D1, D5, and D8, vs. DO, with no differences between D1, D5 and D8. ?M was not different among trials at any time point after 20-min. The mean body temperature threshold for the onset of shivering was lower on D1 (35.08°C), D5 (34.85°C), and D8 (34.69°C), compared to D0 (36.01°C). Changes in heat storage did not differ among trials and rectal temperature was not different in D0 vs. D1, D5, and D8. Thus, mild hypoxia (16.75% F1O2) impairs vasconstrictor and initial shivering responses, but the addition of elevated F1CO2 and cold had no further effect. These thermoregulatory effector changes do not increase the risk for hypothermia in DISSUB survivors who are adequately clothed.)

14. SUBJECT TERMS
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Physiological responses to cold exposure in men: A disabled submarine study

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Castellani JW, O'Brien C, Stulz DA, Blanchard LA, DeGroot DW, Bovill ME, Francis TJ, Young AJ – Physiological responses to cold exposure in men: A disabled submarine study. Undersea Hyperb Med 2002, 29 (3): 189-203 - A disabled submarine (DISSUB) lacking power and/or environmental control will become cold, and the ambient air may become hypercapnic and hypoxic. This study examined if the combination of hypoxia, hypercapnia, and cold exposure would adversely affect thermoregulatory responses to acute cold exposure in survivors awaiting rescue. Seven male submariners (33 ± 6 yrs) completed a series of cold-air tests (CAT) that consisted of 20-min at T_{air} = 22°C, followed by a linear decline (1°C·min^{-1}) in T_{air} to 12°C, which was then held constant for an additional 150-min. CAT were performed under normoxic, normocapnic conditions (D0), acute hypoxia (D1, 16.75% O_2), after 4 days of chronic hypoxia, hypercapnia and cold (D5, 16.75% O_2, 2.5% CO_2, 4°C), and hypoxia-only again (D8, 16.75% O_2). The ΔT_{sk} during CAT was larger ($P<0.05$) on D0 (-5.2°C), vs. D1 (-4.8°C), D5 (-4.5°C), and D8 (-4.4°C). The change (relative to 0-min) in metabolic heat production (ΔM) at 20-min of CAT was lower ($P<0.05$) on D1, D5, and D8, vs. DO, with no differences between D1, D5 and D8. ΔM was not different among trials at any time point after 20-min. The mean body temperature threshold for the onset of shivering was lower on D1 (35.08°C), D5 (34.85°C), and D8 (34.69°C), compared to D0 (36.01°C). Changes in heat storage did not differ among trials and rectal temperature was not different in D0 vs. D1, D5, and D8. Thus, mild hypoxia (16.75% F_IO2) impairs vasoconstrictor and initial shivering responses, but the addition of elevated F_ICO_2 and cold had no further effect. These thermoregulatory effector changes do not increase the risk for hypothermia in DISSUB survivors who are adequately clothed.

hypercapnia, hypothermia, hypoxia, shivering, vasoconstriction

INTRODUCTION

Atmospheric conditions on submarines are maintained mildly hypoxic (18-19% F_IO_2) for fire suppression purposes. This stress is thought to have mild but well tolerated effects on the crew. However, a disabled submarine (DISSUB) unable to surface under its own power may become a hostile environment of cold (~4°C), high relative humidity (>80%), hypoxic (<17% F_IO_2), and hypercapnic (>2% F_ICO_2) conditions. Similar conditions can be found in confined spaces with poor ventilation and temperature control. These combined environmental stressors may exacerbate heat loss challenging the thermoregulatory system's defense of body temperature

since low O_2, high CO_2, and daily cold exposure all affect thermoregulatory responses during cold exposure experiments.

Acute hypoxia (F_IO_2 of <15%) typically blunts shivering and vasoconstrictor responses during whole-body cold exposure (1, 2), but the effects of mild hypoxia (F_IO2 of 15-17%) are less studied (3, 4) and these findings are equivocal. Interestingly, during localized cold exposure of the hand or finger while the rest of the body is kept warm (5, 6), vasoconstrictor responses are more pronounced the lower the F_IO_2, unlike the pattern observed during whole-body exposure. Acute hypercapnia (4% CO_2) has been shown to affect shivering onset during mild cold stress (7), and Lun et al. (8) demonstrated that shivering was transiently suppressed by hypercapnia, but rapidly returned as the acute respiratory acidosis by hypercapnic breathing was buffered in the blood. Other studies, however, found no effect on shivering responses during cold exposure after breathing 4% CO_2 for one hour (9, 10). Furthermore, Fothergill et al. (11) found that 5 minutes of breathing high CO_2 levels (6%) transiently lowered forearm blood flow during cold water immersion, compared to values observed when subjects were immersed breathing normocapnic air, suggesting that peripheral heat loss could be lower with hypercapnic breathing during less severe cold exposure, although Wagner et al. (10) observed higher thigh temperatures when breathing 4% CO_2. Brief cold air exposures (< 60-min) repeated over several weeks blunt shivering but do not affect body temperature (12) whereas longer (2-h) cold-air exposures (13) have been shown to cause habituation of the skin temperature response during whole-body exposure.

The purpose of this study was to determine whether autonomic thermoregulatory responses to whole-body and localized cold exposure are affected by long-term cold air (4°C) exposure and chronic breathing of hypercapnic, hypoxic gas mixtures characteristic of atmospheric conditions expected to develop aboard a DISSUB awaiting rescue. It was hypothesized that: 1) acutely breathing mildly hypoxic air during cold exposure would suppress shivering and whole-body vasoconstrictor responses compared to normoxic responses, whereas local cold-induced vasodilation (CIVD) of the finger would be decreased and 2) following 4 additional days of continuous exposure to mild hypoxia, combined with both elevated F_ICO_2 and 24 hour daily cold (4°C) exposure, shivering would be blunted further due to prolonged cold exposure, whole-body vasoconstriction would not change due to interactive effects of cold plus hypercapnia, and finger temperatures during CIVD experiments would be lower, compared to acute hypoxia.

METHODS

Subjects: Seven male active duty Navy submariners participated in this study, which was approved by the appropriate Institutional Review Boards. The subjects volunteered after being fully informed of the requirements and risks associated with the research. Each subject completed a physical examination. Subject characteristics were: 33 ± 2 yr of age, 175 ± 2 cm height, 83.3 ± 3.1 kg body weight; 1.98 ± 0.04 m^2 body surface area, and 19.2 ± 2.5% fat.

Preliminary testing: Body composition was measured using dual energy x-ray absorbtiometry (DEXA, Model DPX-L, Lunar Corp., Madison, WI). DEXA uses low-dose radiation to measure bone density, fat, and fat-free mass (14). Body surface area was computed from the equation of DuBois and DuBois (15).

DISSUB conditions: On day 0 (D0), ambient atmospheric conditions in the subject living space were 20.93 % F_IO_2 and 0.04 % F_ICO_2. Laboratory temperatures (mean ± S.D.) were

22.2 ± 1.1°C and RH was 50 ± 5%. From 0200 to 0530-h on Day 1 (D1), the conditions were progressively changed at a linear rate to achieve an F_IO_2 = 16.77 ± 0.03 %, F_ICO_2 = 0.44 ± 0.14 %, RH = 51 ±5 % and T_{amb} = 19.5 ± 0.76°C (when not in cold testing). These conditions are similar to those usually maintained aboard the submarine under normal conditions (i.e. before becoming disabled). At 1500-h on D1, conditions inside the chamber were gradually modified again at a linear rate to replicate the development of steady-state hypercapnic, hypoxic conditions environmental conditions inside a DISSUB, such that beginning at 1500 on D2 and ending at 1900 on D7, F_IO_2 = 16.73 ± 0.06%, F_ICO_2 = 2.49 ± 0.04%, RH = 80 ± 5%, and T_{amb} = 4.5 ± 0.6°C. On D8, conditions were returned to F_IO_2 = 16.76 ± 0.02 %, F_ICO_2 = 0.18 ± 0.08 %, RH = 51 ± 3 %, and T_{amb} = 21.2 ± 0.8°C (similar to D1). Conditions were normobaric throughout the experiment. For detailed information on chamber conditions, and the environmental control and monitoring system used to achieve the desired ambient atmospheric conditions, see DeGroot and Blanchard (16).

Food intake was *ad libitum* on D0, but strictly regimented from D1-D8 with unrestricted access to water and caffeinated beverages throughout the study period. The menu was derived based on normal inventories carried aboard submarines but nutrient composition and energy content of the subject's diet was individually calculated using the Harris Benedict Formula. An additional 10 % was added to account for the thermic effect of food. Except during experimental cold tests, subjects wore clothing that would normally be available to sailors on a 688-class submarine. It was estimated the subjects had ~ 5 clo of insulation from clothing and bedding. Subject activity was kept to a minimum throughout the eight-day period to simulate the restriction of activities that would be mandated aboard a DISSUB.

Experimental cold exposure trials: Volunteers completed 4 experimental trials for each cold-induced vasodilation (CIVD) and whole-body cold air test (CAT). Trials were completed at the same time of day (4 volunteers tested from 0700-1100 and 3 from 1200-1600 hours). Experimental trials were completed on 4 days (D0, D1, D5, and D8). The CIVD and CAT tests were conducted in a chamber connected to the living quarters chamber. The CIVD tests were conducted immediately before each CAT. Smoking or chewing tobacco was not permitted within the chamber or within 12 hours of any test. Subjects did not consume food, shower or engage in vigorous physical activities for four hours preceding any cold exposure test. Subjects abstained from alcohol throughout the study. F_IO_2 and F_ICO_2 for D0, D1, D5, and D8 were the same as described above under *DISSUB conditions*.

CIVD: Volunteers were dressed in a sweatshirt, shorts, sweatpants, and socks. They remained seated and movement and talking were minimized during the experiments. CIVD tests were conducted at 22°C and 50% RH. After a 15 min stabilization period spent sitting quietly, the volunteers immersed their middle finger to the middle phalanx in warm (42°C) water, and data collection began simultaneously. The temperature (42°C) was designed to abolish vasoconstriction and ensure a standardized finger temperature for all volunteers on all tests before cold-water finger immersion. After 15 min in warm water, the volunteer immediately transferred the finger to a cold (4°C) water bath (model RTE-111, Neslab Instruments, Newington, NH) for 30 min. A plastic cover supported the hand over the water bath. At the end of the immersion period, the volunteer withdrew his finger from the water. Rectal temperature (T_{re}) and mean skin temperature ($\overline{T}_{sk}$) were recorded every 6 seconds during the CIVD experiments.

CAT: Following completion of the CIVD test, subjects removed their sweat suit and were dressed in only shorts, socks and woolen glove liners for the CAT. Baseline values for

temperature, metabolic heat production, plasma norepinephrine, and thermal sensation were collected during a 20-minute period with T_{amb} conditions maintained at 22°C and 50% RH. Following this, T_{amb} was reduced by 1°C·min^{-1} over a ten-minute period, after which T_{amb} was maintained constant at 12°C for an additional 150 minutes. Oxygen uptake, carbon dioxide output, and minute ventilation were measured by open-circuit spirometry at min 20, 50, 80, 110 and 140. T_{re} and T_{sk} were measured every 6 seconds. Subjects were asked to subjectively rate their thermal sensation (17) at 30 min intervals beginning at min-20. While exposed to the cold, the subjects were not allowed to employ behavioral thermoregulation (no unnecessary physical activity or "huddling").

Core body temperature during DISSUB: Core body temperatures (T_{pill}) were recorded each minute throughout the 8-day experiment by an FDA-approved temperature sensing "pill" (CorTemp™, Human Technologies, INC., Palmetto, FL) which transmitted a 260kHz signal to a body core temperature monitor and data logger (BCTM 3, Personal Electronic Devices, Inc., Wellesley, MA). To ensure volunteer safety, real-time temperatures were documented manually using the digital display on the BCTM every two hours, except during the CIVD and CAT experiments when T_{re} was being recorded.

Measurements and calculations: T_{re} was measured using a thermistor inserted 10 cm past the anal sphincter. Skin temperature (T_{sk}) was measured using thermistor disk sensors (Concept Engineering, Old Saybrook, CT) attached on the skin surface (right side of body) at 10 sites (foot (ventral), calf, medial thigh, lateral thigh, chest (pectoralis), tricep, forearm (ventral), subscapular, hand (dorsal), and forehead). In addition, during the CIVD test, a thermocouple was attached to the right middle finger tip of the dominant hand along the nail bed by using ~1 cm^2 of thin tape. $\overline{T}_{sk}$ was calculated as follows: $\overline{T}_{sk} = 0.05T_{foot} + 0.15T_{calf} + 0.125T_{medial\ thigh} + 0.125T_{lateral\ thigh} + 0.125T_{chest} + 0.07T_{tricep} + 0.035T_{forearm} + 0.125T_{subscapular} + 0.035T_{hand} + 0.16T_{forehead}$. Mean body temperature ($\overline{T}_b$) during cold exposure was calculated as follows (18): $\overline{T}_b = 0.67 \cdot T_{re} + 0.33 \cdot \overline{T}_{sk}$. Percent oxygen (Model S-3A, Applied Electrochemistry) carbon dioxide (model LB-2, Beckman) and volume (Tissot spirometer, Collins) were measured from a two-minute collection of the subjects' air expired into a 150L Douglas Bag. Metabolic heat production (W·m^{-2}) was estimated from VO_2 and respiratory exchange ratio (R) using the following equation (18): $M = (0.23[R] + 0.77) \cdot (5.873)(VO_2) \cdot (60/A_D)$ where A_D is body surface area (m^2). Body heat storage (S, W·m^{-2}) was calculated as follows (18): $S = M - W - L - E - K - (R+C)$, where M is the metabolic rate, W is work rate (0 in this experiment), L is the respiratory heat losses by convection and evaporation (0.08•M), E is evaporative heat loss (presumed to be negligible in this experiment and set at 0), K represents conductive heat loss (0 in this experiment) and R+C ($0.83 \cdot [\overline{T}_{sk} - T_a]$) represents dry heat loss (18, 19).

Whole blood samples were drawn before cold exposure (min 0) and during cold air exposure at minutes 10 and 150 from an indwelling venous catheter (18 gauge) placed in a superficial forearm vein. Aliquots were centrifuged at 4°C to separate the plasma. Plasma samples were frozen at -40°C before analysis. Plasma norepinephrine (NE) concentration was determined in duplicate via high performance liquid chromatography with electrochemical detection.

Statistical Analyses: Data were analyzed using a two-factor (experimental day X measurement time) repeated-measures ANOVA. When significant F ratios were calculated, paired comparisons were made post-hoc using a Newman-Keuls test. The slope and intercept (to determine shivering sensitivity and threshold, respectively) of each individual's ΔM vs. $\overline{T}_b$ relationship during whole-body cold exposure were determined by least squares linear regression

on the temperature and metabolic data from minutes 20 to 140. Comparisons among trial days for slope and intercept data were analyzed using one-factor (experimental day) repeated-measures ANOVA. A low-pass filter (SigmaPlot 3.03, Jandel Scientific, San Rafael, CA) was used on finger temperature (T_f) results to reduce data noise. A rise or fall in T_f of at least 0.5°C was chosen to define a viable CIVD. Data were examined to identify the time (t_{min}) and temperature (T_{min}) at the first nadir, and the time (t_{max}) and temperature (T_{max}) of the first apex. For descriptive purposes, subsequent nadir and apex temperatures were also determined. The means of these data were used to construct an "average" CIVD for each of four conditions. Unless otherwise specified, the level of significance for differences reported is $P < 0.05$. Result values are reported as mean ± SE.

RESULTS

Food Intake & Pill Temperature: Energy intake was 2850 ± 405 kilocalories on D0 and was 1976 ± 173 kilocalories on Days 1 through 7. Figure 1A depicts the T_{pill} every 4 hours throughout the 8-day experiment. T_{pill} was highest between 1600-2000 h each day with the nadir at ~ 0400 h. There were no differences among experimental days in T_{pill}.

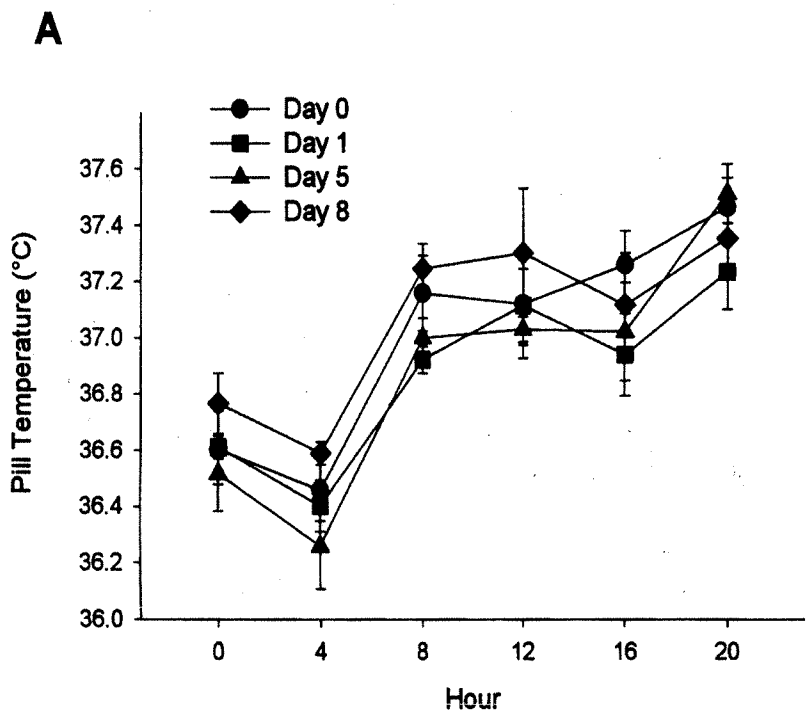

Figure 1. A. Body core temperature vs. hour of the day for the four trial days. Core temperature was measured using ingestible temperature pills.

Cold Air Test: Rectal temperatures during the cold air test are shown in Figure 1B. T_{re} was higher at minute 0 on D0 compared to D1 and D5 and higher at minute 20 on D0 vs. D1. By

the end of cold exposure, T_{re} was similar among treatments, with the exception that D5 was higher than D1.

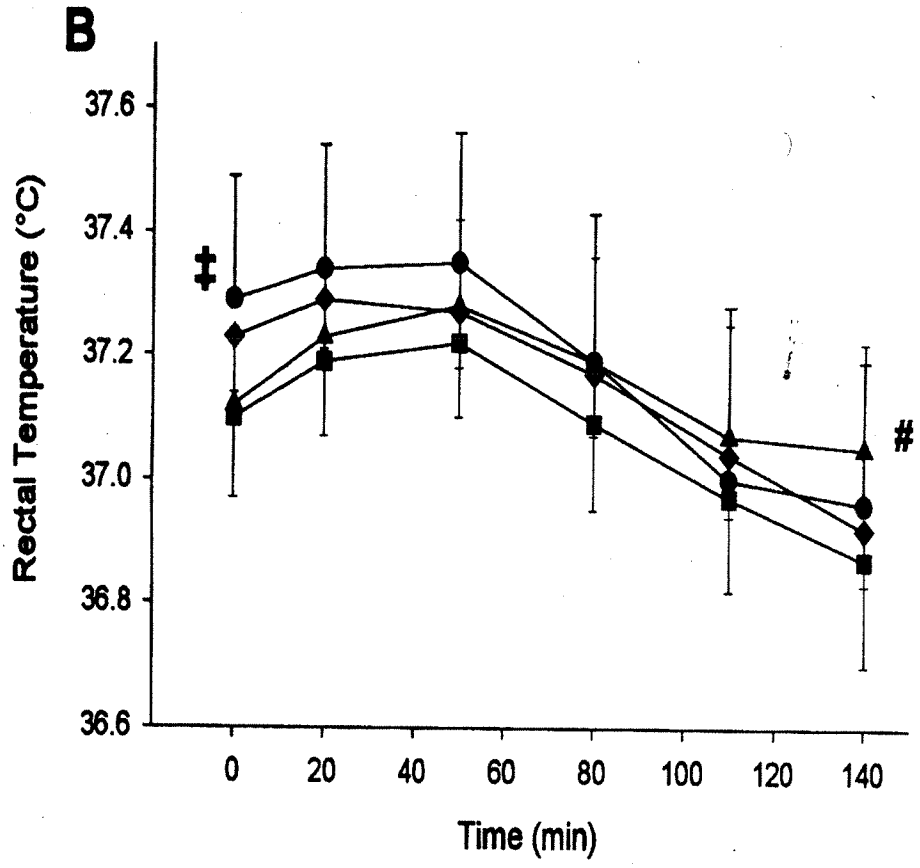

Fig. 1 B Rectal temperature vs. time during cold air test. ‡ denotes Day 0 greater than Day 1 and Day 5; # denotes Day 5 greater than Day 1. Values are mean ± S.E.

Figure 2 shows the vasoconstrictor response to cold exposure. Mean skin temperatures (°C) at baseline (minute 0, 22°C ambient temperature) were 32.39 ± 0.17, 32.59 ± 0.17, 31.95 ± 0.15, and 31.97 ± 0.24°C, for D0, D1, D5, and D8, respectively. Figure 2A (ramp time vs. $\overline{T}_{sk}$) depicts the initial cutaneous vasoconstrictor responses to acute cold exposure during each of the trials. The change in $\overline{T}_{sk}$ was greater at the end of the temperature ramp on D0 vs. D1, D5, and D8, indicating a stronger initial cutaneous vasoconstrictor response. The change in $\overline{T}_{sk}$ (Fig. 2B) over the entire cold exposure period (indicative of underlying muscle vasoconstrictor tone) was also greater on D0 compared to the other trial days.

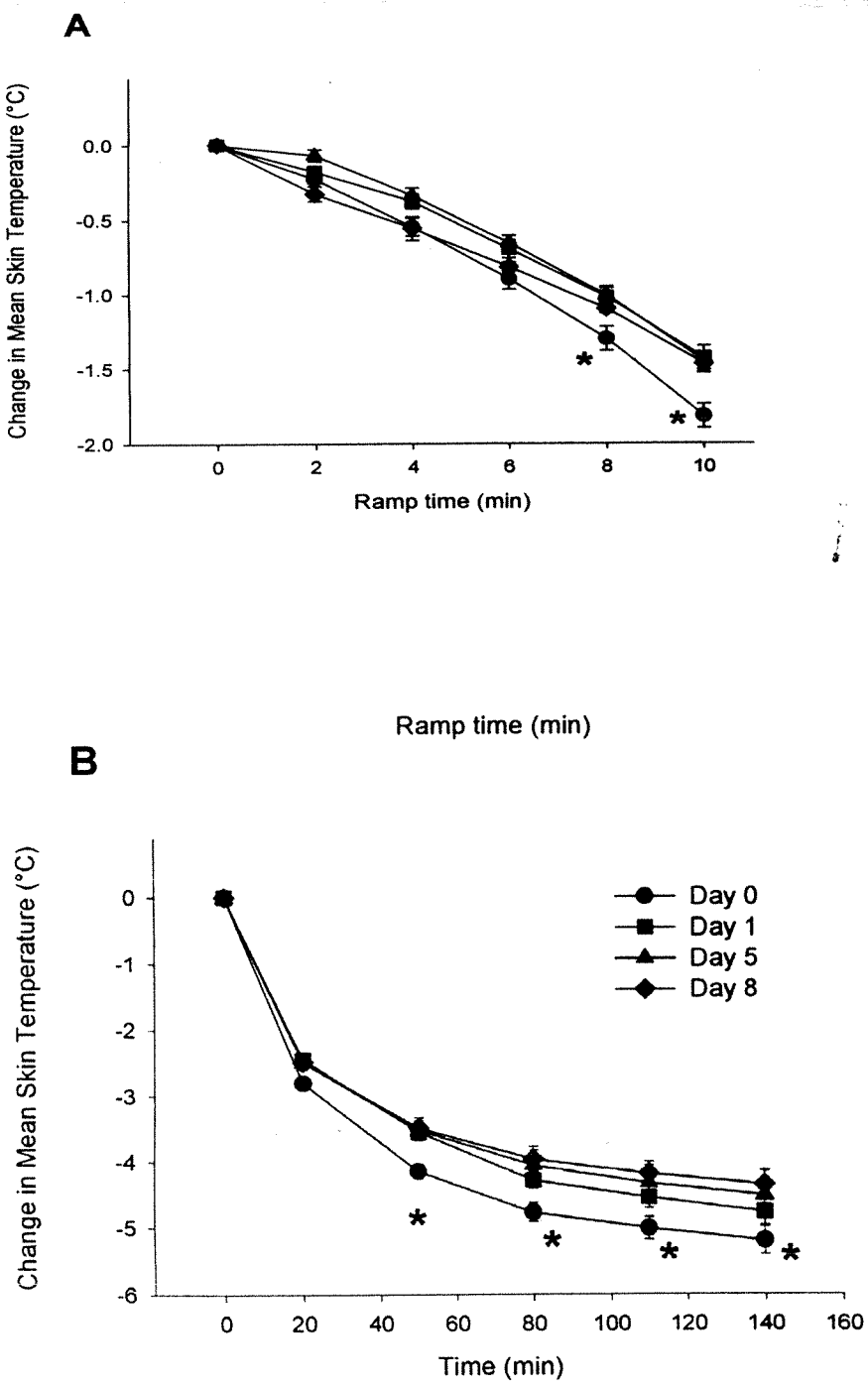

Figure 2. Ramp time (10 minutes – from 22°C to 12°C) vs. mean skin temperature (**A**) and change in mean skin temperature vs. time (**B**) for the four trial days. Change in mean skin temperature vs. ramp time was modeled using a polynomial regression and yielded the following equations (D0, $y = -0.093 \cdot time - 0.009 \cdot time^2 - 0.022$, adjusted $R^2 = 0.92$; D1, y = -0.61•time - -

$0.008 \cdot time^2 - 0.029$, $R^2 = 0.91$; D5, $y = -0.061 \cdot time - 0.009 \cdot time^2 - 0.049$, $R^2 = 0.93$; D8, $y = -0.070 \cdot time - 0.006 \cdot time^2 - 0.184$, $R^2 = 0.89$).
*, denotes D0 significantly different ($P < 0.05$) from D1, D5, and D8. Values are mean ± S.E.

Figure 3 depicts the shivering response during cold exposure. The change in metabolic heat production (Fig. 3A) was significantly higher at min-20 on D0 vs. D1, D5, and D8. There were no differences in M among trials for the remainder of the cold exposure. The shivering threshold (intercept of ΔM vs. $\bar{T}_b$ relationship) is shown in Fig. 3B and demonstrates that the onset of shivering occurred at a higher mean body temperature on D0 (n = 4) vs. D1, D5, and D8 (n = 5). The slope ($W \cdot m^{-2} \cdot °C^{-1}$) of the ΔM-$\bar{T}_b$ relationship was significantly lower on D0 (-9.1 ± 1.7; n =4) vs. D1 (-25.7 ± 5.1; n=5), D5 (-34.9 ± 6.1; n=5), and D8 (-27.7 ± 3.9; n=5). There were no differences in heat storage (kilojoules) among D0 (-1247 ± 134), D1 (-1270 ± 43), D5 (-1166 ± 47), and D8 (-1316 ± 52).

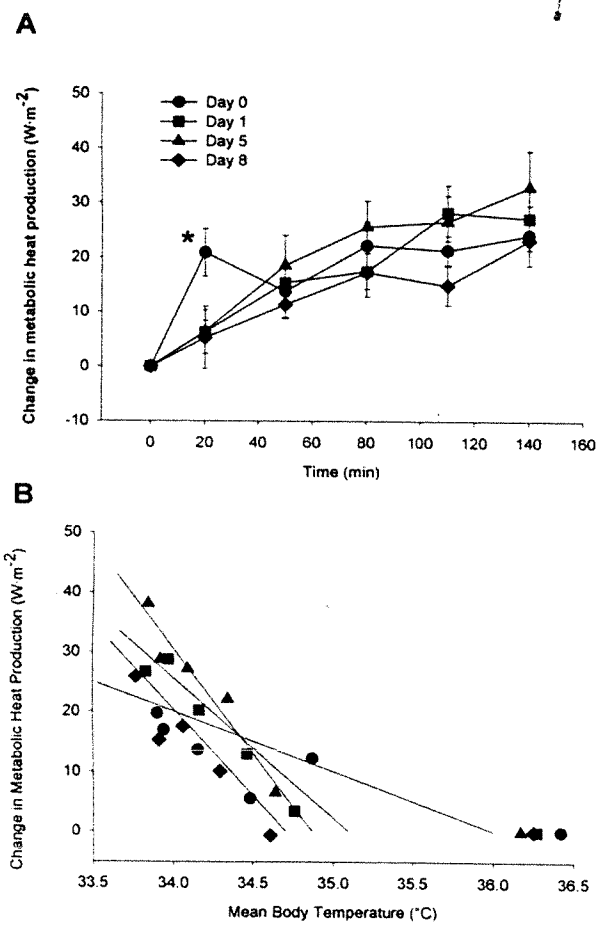

Figure 3. **A**. Change in metabolic heat production vs. time during whole-body cold exposure for the four trial days. **B**. Mean body temperature vs. change in metabolic heat production for the four trial days. Shivering threshold and sensitivity were determined using linear regression

equations from the $\bar{T}_b$-ΔM relationship from minutes 20-140. *, denotes D0 significantly different ($P < 0.05$) from D1, D5, and D8. Values are mean ± S.E.

Plasma norepinephrine concentrations are presented in Figure 4. NE was significantly higher (main effect) on D5 vs. the other trials (Fig. 4A). Figure 4B depicts the change in NE from Pre levels. NE did not increase as much upon initial cold exposure (ramp) on D5 compared to D0. By the end of cold exposure the % change in plasma NE was less on D5 compared to D0 and D1 (Fig 4B). Minute ventilation was significantly higher on D5 during the last hour of cold exposure (23.4 ± 2.1 $L \cdot min^{-1}$) vs. the other trials (17.5 ± 1.8 $L \cdot min^{-1}$) and oxygen saturation during cold exposure was lower on D1, D5, and D8 (96.9 ± 0.6 %), compared to D0 (98.3 ± 0.4 %). Thermal sensations were similar among experimental days.

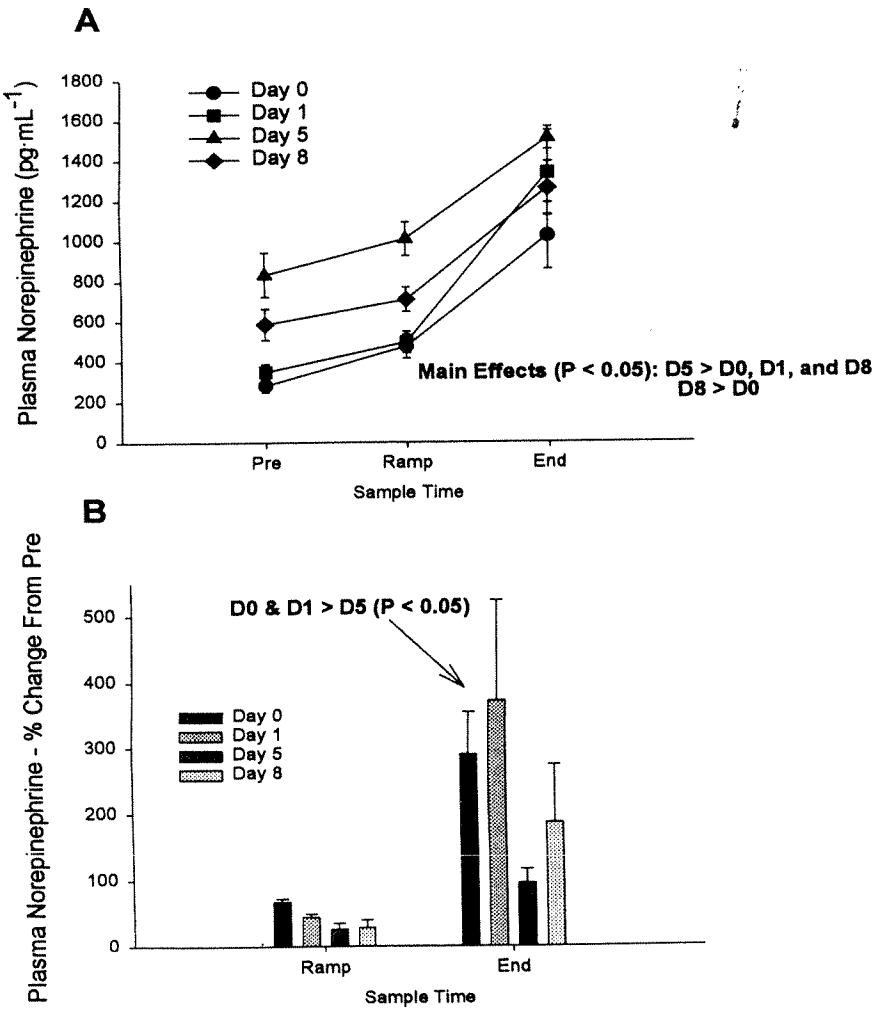

Figure 4. A. Plasma norepinephrine vs. sample time for the four trial days. Pre-samples were taken immediately before cold exposure, Ramp were taken after 10 minutes of exposure (after the ambient temperature dropped from 22°C to 12°C), End sample was obtained during the last 5 minutes of exposure at 12°C. **B.** % Change in plasma norepinephrine from Pre values for Ramp

and End sample times. Significant differences on graph are at $P < 0.05$ level. Values are mean ± S.E.

CIVD. CIVD responses are shown in Table 1. $\overline{T}_{sk}$ over the whole body was significantly lower on D5 compared to D0, D1, and D8. Concomitantly, there was a lower mean T_f and a longer time to the first nadir on D5. Figure 5 shows the forearm and hand temperatures during CAT to further demonstrate the effects of moderate hypoxia on acral and non-acral skin sites.

TABLE 1

Table 1. Temperature responses (n = 7, mean ± S.E.) during cold-induced vasodilation experiments.

Day	T_{re}	$\overline{T}_{sk}$	T_f	T_{min}	t_{min}	T_{max}	t_{max}
D0	37.3 ± 0.2	33.0 ± 0.2	8.1 ± 0.5	5.1 ± 0.2	5.1 ± 0.3	8.8 ± 0.6	13.4 ± 1.7
D1	37.2 ± 0.1	33.1 ± 0.2	7.8 ± 0.4	4.9 ± 0.1	5.2 ± 0.4	8.6 ± 0.5	12.4 ± 1.1
D5	37.3 ± 0.1	32.1 ± 0.2*	6.7 ± 0.4*	4.7 ± 0.1	6.9 ± 0.8*	7.5 ± 0.8#	12.4 ± 1.3#
D8	37.3 ± 0.1	32.6 ± 0.3	7.3 ± 0.2	5.0 ± 0.1	5.2 ± 0.3	8.5 ± 0.6	10.8 ± 1.0

Table 1 T_{re}, rectal temperature (°C); $\overline{T}_{sk}$, mean skin temperature (°C); T_f, mean finger temperature (°C); T_{min}, minimum finger temperature at first nadir (°C); t_{min}, time to first temperature nadir (min); T_{max}, maximum temperature at first apex (°C); t_{max}, time to first temperature apex (min)
# denotes n =5
*, denotes significant difference ($P<0.05$) on D5 compared to D0, D1, and D8.

DISCUSSION

A disabled submarine (DISSUB) could attain ambient conditions that are cold, hypoxic, and hypercapnic. Currently, the estimation of DISSUB survival time is based on the accumulation of CO_2 in the atmosphere, but how chronic breathing of hypoxic, hypercapnic gas while exposed to cold ambient temperatures might affect thermoregulation in the cold or susceptibility to hypothermia has not been evaluated as a potential factor influencing survival time. Recently, House et al. (20) examined responses in a simulated DISSUB for 7 days that was cold (4.4°C) but was not combined with changes in F_IO_2 and F_ICO_2. In this experiment, we exposed subjects to conditions of a DISSUB (4.5°C, 16.75% F_IO_2, 2.5% F_ICO_2) for 7 days in order to examine thermoregulatory responses to whole-body and local cold exposure. To our knowledge, this is the first study to examine the interaction of all of these ambient conditions on human thermoregulation.

The primary finding from this study was that acute moderate hypoxia (16.75% O_2) blunted vasoconstriction and initial shivering responses during whole body cold exposure, and that the addition of both high F_ICO_2 (2.5%) and living in cold T_{amb} (4.5°C) to simulate DISSUB conditions, caused no further thermoregulatory effector changes. Mild hypoxia, however, did not cause subsequent effects on core temperature during non-cold test periods (T_{pill}) or during the cold air test (T_{re}). That severe hypoxia (~12% F_IO_2) affects vasoconstriction (1, 2, 21) and shivering (1, 2) in humans has been shown before. However, the unique finding in this DISSUB study is that even very mild hypoxic conditions (16.75% F_IO_2) blunt thermoregulatory effector responses.

Cipriano and Goldman (3) observed blunted skin temperatures during cold exposure (15.5°C ambient temperature) at an altitude of 2500 meters (F_IO_2 of ~15.45%). Our data indicate that the hypoxic threshold for vasoconstriction is even higher, at or below an F_IO_2 of 16.75%. Mild hypoxia blunted the initial skin temperature response (32-32.6°C to 29-30°C) to the ambient temperature ramp (22°C to 12°C) and this reflects a change in cutaneous vasoconstrictor tone. Changes in skin temperature following maximal cutaneous vasoconstriction (T_{sk} ~ 29°C) during the remainder of the 2.5-hour exposure to 12°C air reflect reduced peripheral blood flow through muscle thus decreasing convective heat loss from the body core (22) and conductive heat loss through the overlying tissue (muscle, fat, skin). Mild hypoxia blunted this response as well with no effect caused by prolonged hypercapnia and cold exposure.

Unlike the vasoconstrictor response during whole-body cold exposure, a combination of hypoxia, hypercapnia and living in the cold for several days prior to D5 caused a lower mean finger temperature during the local CIVD experiments. This local response contrasts with skin temperature responses in the whole-body experiments where skin temperatures were higher, rather than lower, on this day. Thus the question is: why are the local and whole-body vasoconstrictor responses dissociated? Examination of the data indicates that although the rectal temperatures were similar among all 4 CIVD experiments, mean skin temperature (over the whole body) on D5 was significantly lower during this trial. Thus the combination of hypoxia/hypercapnia on D5 probably was not responsible for the blunted CIVD response, but the lower skin temperature, most likely a persistent effect caused by living in a cold environment for 4 days that triggered this response. The magnitude of changes in CIVD in the DISSUB is similar

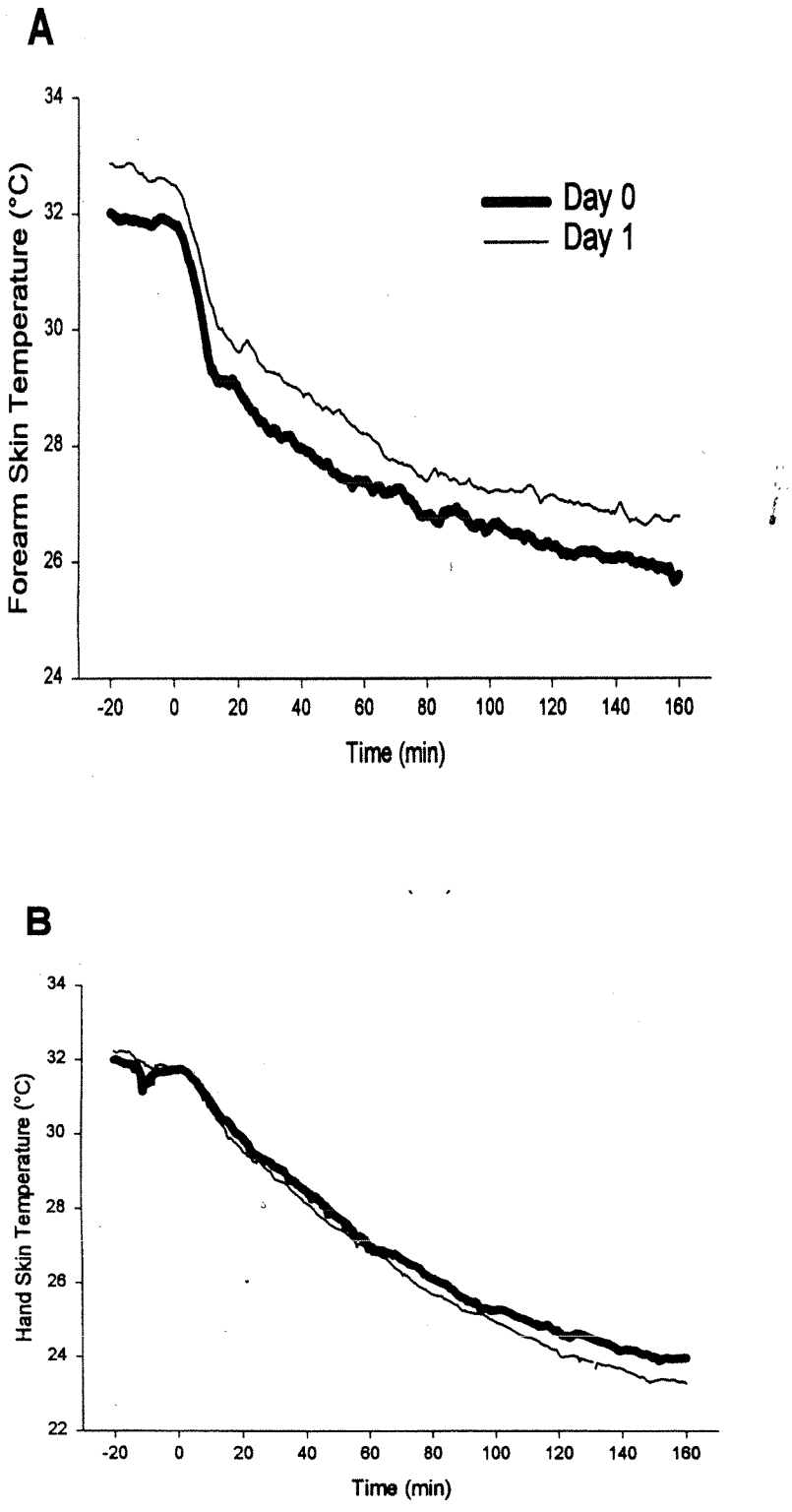

Figure 5. Mean forearm (**A**, non-acral skin site) and hand (**B**, acral skin site) skin temperature during whole-body cold air exposure

to what would be expected by the lower $\bar{T}_{sk}$, which has been observed by our laboratory following cold acclimation (23) and by others (24-26)

In the CIVD experiments in which similar core and skin temperatures were observed (D0 vs. D1), there were no differences in the CIVD response suggesting that mild hypoxia has no effect on local control of vasoconstriction in acral skin. Examination of hand and forearm skin temperatures during whole-body cold exposures (Fig. 5) also suggest that mild hypoxia itself has no reflex effect on hand vasoconstriction but does cause a blunted reflex vasoconstriction of non-acral skin sites during cold exposure. Why is there a discrepancy between vasoconstriction in acral vs. non-acral skin sites? The differential response may be due to the distribution of adrenergic receptors in the hand/finger and forearm. The primary adrenergic receptors of the finger are α-receptors, whereas the forearm is regulated through α_1, α_2, and β-adrenergic receptors. Stimulation of β-adrenergic receptors is thought to cause hypoxic-induced vasodilation (27). Since fingers do not have β-receptors and non-acral skin sites do and since hypoxia exerts its effects via β-receptors, this may be the reason why there are different findings between the CIVD and whole-body vasoconstrictor response to cold.

Shivering thermogenesis was initially blunted during acute cold exposure in mild hypoxia, with and without the addition of high F_ICO_2 and cold living conditions, but as mean skin temperature continued to decrease, shivering increased to levels observed in non-hypoxic conditions, and therefore did not cause an attenuated metabolic response over the duration of the cold exposure. Others also report that hypoxia blunts shivering during cold exposure (1, 28), but at lower F_IO_2. In contrast, Reading et al. (4) found steady-state shivering responses during cold exposure in moderate hypoxia (F_IO_2 = 15%) were not different compared to normoxia, although they did not examine the onset of shivering. Our results suggest that mild hypoxia lowers the mean body temperature threshold for the initiation of shivering, similar to that seen with more severe hypoxia, i.e., a lower F_IO_2 (2). In addition, the initial blunting of shivering was still present even when breathing 2.5% CO_2 and living in cold ambient conditions for 4 continuous days suggesting that mild hypoxia alone was the mechanism for the observed shivering response. Thus, our data do not support our initial hypothesis that breathing in a cold, hypercapnic atmosphere for four days would affect shivering thermogenesis, perhaps because the subjects remained well insulated from the ambient conditions (~5 clo insulation), the blood buffering systems have compensated for respiratory acidosis (8), or perhaps the addition of high CO_2 levels counteracted either the hypoxia (29) or prolonged cold exposure. One consideration is that human use constraints precluded studies of prolonged exposure to more severe, but more realistic DISSUB CO_2 levels (> 4%). How a combination of hypoxia with chronic CO_2 levels greater than 2.5 % for many days would affect thermoregulation is unknown.

In summary, mild hypoxia (16.75% O_2) blunted the vasoconstrictor and initial shivering responses during whole-body cold exposure. These responses were not altered by the addition of high ambient CO_2 (2.5%) levels and cold ambient temperatures. For the submariner who may be aboard a DISSUB, these thermoregulatory effector responses do not appear to increase the risk of hypothermia during acute cold exposure (< 3 hours) as rectal temperature and body heat storage were not affected by DISSUB conditions. Also, there was no effect on core temperatures (T_{pill}) during free-living periods outside of the cold air test. However, hypoxic-induced blunting of vasoconstriction could increase peripheral heat loss if adequate clothing is not available, thus potentially increasing core cooling rates and accelerating the risk of hypothermia during cold exposure lasting for days.

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