

## Human temperature regulation at sub-anesthetic levels of nitrous oxide-induced narcosis

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## INTRODUCTION

Nitrous oxide ( $N_2O$ ) is an inert gas that is often used as a general anesthetic and as a behavioural analog to hyperbaric  $N_2$ . Mekjavic and Sundberg (1992), using 30%  $N_2O$ , found a shift in the threshold for shivering onset to lower core temperatures and a consequent widening of the thermoregulatory "null-zone," which they defined as the range of core body temperature between the cessation of sweating and the onset of shivering in subjects immersed in 28 °C water. Passias *et al.* (1992) also found that breathing 30%  $N_2O$  significantly attenuated the shivering response in 15 °C water, resulting in an increased core cooling rate. Assuming that  $N_2$  at high pressures produces similar impairment of the body's thermoregulatory ability as those induced by  $N_2O$ , inert gas narcosis may be a significant contributor to the hypothermia commonly experienced by divers in a hyperbaric environment. Supporting evidence was provided by Mekjavic *et al.* (1993), who reported a substantial depression of the shivering response in subjects at 6 ATA ( $P_{N_2} = 4.8$  ATA) in 15 °C water similar to that observed by Passias *et al.* (1992). The question of whether inhibition of shivering by  $N_2O$  or hyperbaric  $N_2$  occurs in a similar manner remains unclear, as few studies have attempted to investigate thermoregulatory response at different levels of narcosis.

While a behavioural qualitative equivalency between  $N_2O$  and hyperbaric  $N_2$  has been proposed (Fowler *et al.* 1985), it is uncertain whether a similar equivalency exists with regards to autonomic mechanisms such as thermoregulation. In addition, the majority of studies investigating the effects of  $N_2O$  on behaviour have utilized concentrations of 30%  $N_2O$  or greater, a level of narcosis equated to breathing air at 6-8 atmospheres absolute (ATA) by Biersner *et al.* (1977). This is at or exceeds the legal limit of 6 ATA for compressed air exposure, and it is unknown whether lower levels of narcosis would impair thermoregulatory abilities in a similar manner. Iwamoto *et al.* (1988) immersed subjects at 1 and 2 ATA, and observed no difference in the critical water temperature ( $T_{CW}$ ), the water temperature at which subjects could remain immersed for two hours without the initiation of shivering. The primary aim of the present study was to investigate the existence and nature of a dose-dependent response between the percentage of inspired  $N_2O$  and the attenuation of shivering thermogenesis. The effect on shivering thermogenesis from inspiring either air or a normoxic mixture containing 10, 15, 20, or 25%  $N_2O$  during immersion in 20 °C water was compared. It was hypothesized that, with increasing levels of narcosis, central thermoregulation would be progressively impaired, producing a dose-dependent attenuation of shivering and a corresponding increase in the amount and rate of core cooling.

## METHOD

The experimental protocol and instrumentation in the present study were approved by the Ethics Review Committee of Simon Fraser University. Seven male volunteers, ranging in age from 23-30 yr, took part in the study. Some of the subjects had previous experience with hypothermia studies and/or  $N_2O$  exposure. Each subject was immersed to the neck in a 20 °C water bath while wearing only a bathing suit on five separate occasions, with the inspired  $N_2O$  concentration as the controlled variable. The inspired gas was either air (AIR) or a normoxic mixture containing either 10, 15, 20, or 25%  $N_2O$  balanced with  $N_2$ . The order of the treatments was randomized among the subjects in a Latin Square design to eliminate order effects.

Once the subject was instrumented, he was seated in a bosun's chair harness, mechanically raised above the immersion tank by a pneumatic winch, and began breathing through a respiratory valve for ten minutes while resting values were recorded. Thereafter, the subject was lowered into the stirred water bath and immersed to the neck, with transfer time requiring < 15 s in all cases. The subject was instructed to avoid voluntary movements and tensing of the body, and remained immersed while breathing the gas mixture. The immersion was terminated after 60 min or if the subject's esophageal temperature decreased 2.0 °C from the pre-immersion value or to 35.0 °C. The breathing mixture to the subject was humidified by passing it through a water bath maintained at room temperature, expanded in a Douglas bag, and inspired via a low-resistance Hans-Rudolph respiratory valve.

## RESULTS

Esophageal temperature ( $T_{es}$ ) remained stable for the first 10 min. of immersion, and thereafter decreased in a linear manner for all conditions. By the end of the 60 min. immersion period, the relative decrease in  $T_{es}$  from resting pre-immersion levels ( $\Delta T_{es}$ ) for the experimental conditions were  $-0.86 \pm 0.52$  °C (AIR),  $-1.13 \pm 0.57$  °C (10%  $N_2O$ ),  $-1.12 \pm 0.56$  °C (15%  $N_2O$ ),  $-1.08 \pm 0.47$  °C (20%  $N_2O$ ), and  $-1.09 \pm 0.58$  °C (25%  $N_2O$ ). Analyzed using repeated measures ANOVA, the  $\Delta T_{es}$  observed during the AIR condition was significantly less than observed during each of the four  $N_2O$  conditions, with no difference in  $\Delta T_{es}$  among the  $N_2O$  conditions. No significant difference in heat flux ( $Q$ ) was observed among any of the experimental conditions throughout the course of the immersion. The results indicate that, despite similar rates of heat loss ( $Q$ ), all concentrations of  $N_2O$  yielded a significantly greater  $\Delta T_{es}$  than that observed during the AIR trial, with no significant differences in  $T_{es}$  among the  $N_2O$  conditions.

For all subjects in each condition, the rate of cooling of  $T_{es}$  ( $\dot{T}_{es}$ , °C·hr<sup>-1</sup>) was calculated by performing a regression over the linear portion of the temporal response of  $T_{es}$ .  $\dot{T}_{es}$  while breathing 10%  $N_2O$  tended to be greater than during AIR immersion, though the difference was not significant. However, a significant increase in  $\dot{T}_{es}$  was observed during the 15, 20, and 25%  $N_2O$  immersions when compared to AIR, again with no significant difference in  $\dot{T}_{es}$  among the four  $N_2O$  concentrations.

## CONCLUSIONS

The principal aim of the present study was to investigate whether inhalation of  $N_2O$  concentrations from 10 to 25% during immersion in 20 °C water induced dose-dependent responses of shivering and core temperature cooling ( $\Delta T_{es}$ , °C). Thus the present study confirms the depressant action of  $N_2O$  on the thermoregulatory response observed during cold water immersion as reported by Mekjavic and Sundberg (1992) and Passias *et al.* (1992). and demonstrates that  $N_2O$  concentrations at subanesthetic levels do not impair human thermoregulatory responses in a dose-dependent manner.

Extrapolating from the similar thermoregulatory reaction observed with 30%  $N_2O$  and 6 ATA (Passias *et al.* 1991, Mekjavic *et al.* 1993), the increased cooling rate while breathing 10, 15, 20, or 25%  $N_2O$  in the present study suggests that a depressed thermoregulatory response may be present in hyperbaric situations with even minor increases in  $PN_2$  from surface pressure. Furthermore, as indicated by the lack of a dose-dependent response of  $\Delta T_{es}$  to  $N_2O$  concentration, divers at even shallow depths would be equally susceptible to increased risks of hypothermia as at greater depths. It would be of interest to study shivering thermogenesis at a range of pressures from 1-6 ATA, to further test the equivalency of  $N_2O$  and  $N_2$  on thermoregulatory responses and to correlate the common range of  $PN_2$  employed in hyperbaric applications to the range of  $N_2O$  presented in this study.

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