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DOSE-DEPENDENT EFFECTS OF SUB-ANESTHETIC LEVELS OF NITROUS OXIDE ON THERMAL BALANCE IN HUMANS

by

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Abstract

The decrease of body core temperature is a common occurrence in surgical subjects exposed to general anesthesia. Divers and caisson workers breathing air in hyperbaric conditions are also at an increased risk of hypothermia. The narcotic effects of exposure to anesthetics in the former and increased PN_2 in the latter may be responsible for the impairment of the thermoregulatory system, resulting in increased heat loss or decreased heat production. It was previously demonstrated that mild narcosis induced by inhaling a gas mixture containing 30% nitrous oxide (N_2O) depressed thermoregulatory responses and increased the rate of core cooling. The aim of the present study was to investigate whether a dose-dependent relation existed between the observed attenuation of shivering thermogenesis and N_2O concentration. Seven male subjects were immersed to the neck for 60 minutes in 20 °C water on five separate occasions, while breathing either air (AIR) or a normoxic mixture of 10, 15, 20, or 25% N_2O balanced with N_2. All N_2O concentrations investigated caused a significant ($p \leq 0.02$) depression in shivering thermogenesis, as evidenced by the decreased ranking of electromyographic intensity while breathing any of the N_2O concentrations compared to AIR. Despite similar heat flux from the skin ($\dot{Q}$), the relative change in esophageal temperature (ΔT_{es}) while breathing 10, 15, 20, or 25% N_2O were all significantly ($p \leq 0.05$) greater than during AIR exposure, with no significant difference among the N_2O conditions. T_{es} decreased in a linear manner and the rate of core cooling ($\dot{T}_{es}$) was significantly greater for the 15, 20, and 25% N_2O trials than AIR. Inspired ventilation was significantly higher while breathing AIR than any of the N_2O condtions, but no difference was observed in the slope of the $\dot{V}O_2$ vs. ΔT_{es} relationship among AIR or the N_2O conditions, indicating a similar thermosensitivity of the shivering response. A dose-dependent response of thermal comfort (TCV) to N_2O was evident, with each increase in N_2O concentration resulting in warmer median

TCV. The results indicate that no practical dose-dependent response of shivering thermogenesis to N_2O exist, with thermoregulation in hypothermic conditions being significantly impaired even with minor levels of inert gas narcosis.

Dedication

My parents, Daisy and Tom Cheung, for their unwavering love and support, giving me the courage to go after my dreams and for teaching me to live life fully and passionately.

Ken Cheung for looking out for me all these years as only a big brother can.

My friends near and far.
You are never far from my heart.

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BACKGROUND

Underwater diving is an activity that exposes humans to cold environmental temperatures. In many cases, the body may lose an excessive amount of thermal energy to the environment, leading to a decrease in body core temperature and a dangerous state of hypothermia (Keatinge *et al.* 1980, Bridgman 1990). Non-thermal factors, including inert gas narcosis, may increase the risk of hypothermia due to their effects on the thermogenic and thermolytic ability of the body. Exposure to an inert gas such as nitrous oxide (N_2O) delayed and attenuated shivering thermogenesis, thereby promoting body cooling to a greater degree than cold ambient temperatures alone (Passias *et al.* 1992, Mekjavic and Sundberg 1992). Similarly, the increased partial pressure of nitrogen present in compressed air has a narcotic effect on the body, and may also increase the risk of hypothermia by impairing human thermoregulatory ability.

The following sections will briefly review temperature regulation in mammals in response to cold, and the thermoregulatory problems encountered in diving. The effects of inert gas narcosis on the body will then be discussed, particularly the effects on the central nervous system and the regulation of heat production and retention.

1. Temperature regulation in humans

a) Heat loss / retention

Humans are homeothermic creatures, and their body temperature is maintained throughout their lives within a stable and narrow range, despite exposure to a wide range of environmental temperatures. Thermostasis is achieved by balancing heat production, heat retention, and heat loss to the environment (Hissa 1990). In a cold environment, a thermal gradient from the body to the environment is established, and heat transfer may

occur by conduction, convection, radiation, and evaporation (Webb 1982). The first three mechanisms dominate between tissues and at the skin, while evaporation in the respiratory tract may be significant, due to the necessity of warming and humidifying the inhaled air. The magnitude of heat loss, and the relative contribution of each mechanism, is dependent on the size of the thermal gradient, and also upon the thermal conductivity of the surrounding environment. When heat loss exceeds heat production, body temperature decreases, eventually producing a state of hypothermia.

The onset of hypothermia in humans is considered to occur when the central body temperature falls below 35 °C (Webb 1982); clinical symptoms include mental confusion, lethargy, poor speech articulation, hallucination, decreased sensation and impaired motor function. If core temperature continues to fall to 32 °C or lower, the victim may experience cardiac and respiratory irregularities, and eventually lapse into a state of unconsciousness and death (reviewed in Webb 1982). A major contributing factor to the impairment of mental processes, such as logical reasoning, reaction time, and short-term memory, may be distraction and discomfort due to the cold (Stang and Weiner 1970, Davis *et al.* 1975) or alterations in arousal levels (Ellis *et al.* 1985). In addition, motor functions such as manual dexterity and muscle strength decreases in hypothermia (Bowen 1968). As a result of both impaired mental and physical functioning, hypothermic victims may become disoriented and unable to remove themselves from the cold environment (Bridgman 1990).

The body initially attempts to conserve heat by decreasing tissue heat conductance through maximizing the insulative capacity of the subcutaneous fat layer (Rennie 1987). This is accomplished by the redistribution of blood flow via the modulation of peripheral vasomotor tone. Upon cold exposure, skin temperature rapidly falls, and peripheral cold thermoreceptors increase their firing rate. Both the local effects of the cold and the increased nervous stimulation from the sympathetic nerves promote the contraction of the smooth muscles surrounding blood vessels (Rennie 1988). Vasoconstriction decreases

perfusion of the subcutaneous layer, causing it to cool to near ambient temperature. The thermal gradient between the skin and environment is decreased, thus reducing conductive/convective heat loss. Subcutaneous vasoconstriction is not a uniform process, occuring mainly in the limbs, and somewhat in the trunk (Keatinge 1969, Tikuisis *et al.* 1991). Blood flow to the brain, heart, lungs, and other essential organs is maintained, while no vasoconstriction occurs in the head even under severe cold stress making it a site of considerable heat loss (Froese and Burton 1957, Shvartz 1970).

b) Heat production

When heat retention measures such as peripheral vasoconstriction are insufficient to prevent heat loss and central core temperature begins to drop, endogenous heat production, through shivering or non-shivering thermogenesis, is increased in an attempt to maintain thermostasis. Shivering is defined as "an increase in reflex, nonlocomotor muscular tone attributable to exposure to cold, with and without visible tremor" (Kleinebeckel and Klussmann 1990). By converting chemical energy into rhythmic, alternating contractions of flexor and extensor muscles that produce little gross body movement (Bawa *et al.* 1987), shivering is a mode of muscular activity which, while mechanically inefficient, is capable of greatly increasing the metabolic heat production in an organism above basal levels, to a predicted maximum of 400-425 kcal/h in 4.4 °C air with a 16 km/h wind (Iampietro *et al.* 1960). As such, shivering is a very effective mechanism for maintaining the body temperature constant in a cold environment (Sowood 1984).

Non-shivering thermogenesis is an increase in metabolic heat production due to processes other than motor activity, and has been primarily attributed to an increase in metabolism in brown adipose tissue (BAT). BAT and non-shivering thermogenesis are commonly found in many mammals (Leblanc 1988), including possibly neonate humans

(Foster and Frydman 1979). In young (>1 yr.) and adult humans, however, brown adipose tissue is present in only very minor quantities, and shivering is the primary source of active heat production (Glickman *et al.* 1967, Astrup 1986).

Shivering can occur in nearly every muscle in the body, but is concentrated initially in the masticatory muscles, progressing to the trunk and the extremities (Stuart *et al.* 1963, Hensel *et al.* 1973, Jansky 1979). The large muscles of the trunk are the dominant sites of shivering activity, likely to maintain central core temperature (Bell *et al.* 1992). Also, excessive shivering in the extremities would result in increased perfusion, and increased heat loss via conduction/convection (Stuart *et al.* 1963, Mekjavic *et al.* 1987). Oxygen uptake by the body increases with shivering, in order to fuel the increased muscle activity, and has been used in many thermoregulatory studies as a measure of shivering. Gopfert and Stufler (1952, referenced in Kleinebeckel and Klussman 1990), employed electromyography (EMG) to measure and categorize cold-induced shivering. The initial phase of shivering began with the first appearance of increased regular and repetitive EMG activity. Visible tremor is absent in the intial phase, as the muscle action potentials have yet to become synchronous. This was followed by the adaptation phase, wherein muscle activity decreased. In the final shivering phase, muscle action potentials become rhythmically synchronized, producing grouped EMG discharges and visible cold tremor. Power spectral analysis revealed a dominant centroid frequency ranging from 65 Hz in the pectoralis major to 110 Hz in the rectus femoris, indicating a possible difference in the fibre type of muscle predominantly recruited for shivering in different muscles (Bell *et al.* 1992). The authors hypothesized that type I and IIa fibres were preferentially recruited for shivering, due to their resistance to fatigue allowing prolonged shivering. During the shivering phase, the EMG pattern typically features alternating periods of strong activity (phasic shivering) and weaker activity (tonic shivering), occuring at a frequency of 8 - 10 Hz (Pozos *et al.*, 1987). Furthermore, the amplitude of the phasic component waxes and wanes at a frequency of 6 - 8 cycles per minute; this phenomenon was termed "slow

amplitude modulation by Israel and Pozos (1989). Another feature of shivering activity was the synchronization of both the grouped discharges and the slow amplitude modulation over the entire body, producing a characteristic rhythmic pattern of shivering (Pozos *et al.*, 1987; Sessler *et al.*, 1988a; Israel and Pozos, 1989).

Shivering is initiated when both the peripheral and core temperatures fall below a critical threshold, and the integrated cold stimulus becomes sufficiently strong (Mekjavic et al, 1991). In addition, the dynamic characteristics of thermoreceptor activity, indicated by the rate of body cooling, may be an important determinant of shivering thermogenesis (Mekjavic and Morrison 1984, Mittleman and Mekjavic 1991). Within a range of central temperature between the cessation of sweating and the onset of shivering, termed the null-zone (Mekjavic *et al.* 1991), modulation of vasomotor tone is sufficient to maintain thermoneutrality (Mekjavic and Bligh 1989). While a localized vasomotor response to thermal stimulus may be elicited, the overall control of thermoregulatory response appears to be located in the central nervous system (Bligh 1984). Satinoff (1983) proposed a hierarchic system of thermoregulatory centres located throughout the CNS, progressing in its complexity of control through the course of evolution. In mammals, this progression culminates at the hypothalamus.

Large concentrations of neurons whose spontaneous rates of firing responded to local temperature changes between 35 and 41 ^{o}C in a temperature-dependent manner are located within the preoptic and anterior region of the hypothalamus (Hori 1991). Clusters of thermosensitive (TS) neurons have also been found in other regions of the CNS, including the medulla oblongata and the spinal cord (Hammel 1988, Boulant and Dean 1986). These TS neurons appear to play a significant role in maintaining thermal balance. Localized cooling of the hypothalamus, medulla oblongata, or spinal cord resulted in shivering and nonshivering thermogenesis as well as behavioural modifications in animal studies (Hori 1991, Jessen 1990, Hammel 1988, Sharp and Hammel 1972, Satinoff 1964). TS neurons also receive afferent input from peripheral and core thermoreceptors, with

spontaneous firing rates responding in an integrative manner to combinations of hypothalamic and extra-hypothalamic temperatures (Nakayama 1985). Bligh (1984) proposed that integrated thermoregulatory responses were produced within the CNS through a system of cross-inhibition between warm and cold sensors. In this model, activation of cold sensors in the CNS stimulate heat production responses while at the same time inhibiting heat loss responses. Conversely, stimulation of warm sensors promote heat loss responses and inhibits heat production. In this way, body temperature may be maintained without the requirement of a central or fixed reference temperature, and numerous thermoregulatory sites may be located throughout the CNS working in parallel to produce a net response to thermal stress (Satinoff 1983).

c) Thermal problems during cold water immersion

i) Normobaria

Several characteristics of the water environment combine to increase the risk of excessive body heat loss and hypothermia in humans. Open water is generally cold, whether in oceans, lakes, or rivers, and is warmed by the atmosphere according to latitude and climate. Ignoring the effects of currents and upwelling events, surface water temperatures are approximately 30 °C at the Equator, decreasing with increasing latitude to near 0 °C at the poles (Webb 1982). This range of temperatures is much lower than the typical core temperature of 37 °C found in humans. Therefore, in cold water, a strong heat transfer gradient is established between the warm body and the cooler water.

In a cold water environment, heat loss is a function of the size of the thermal gradient and the thermal conductivity of the surrounding environment, with conduction and convection across the skin surface the dominant modes of heat loss. The cold water

strongly inhibits the secretion of sweat across the skin, while radiation is non-existent in water (Webb 1982). Conduction refers to the flow of heat down a thermal gradient when two regions of differing heat content are in contact. Heat transfer occurs via direct molecular communication, with no appreciable displacement of the fluids. Relative to air, water has a much higher specific heat and thermal conductivity, potentiating conductive heat loss in a water environment (Webb 1982). Convection involves the conductive heat transfer between two fluids in motion. The thin immediate layer surrounding the region of higher heat content is warmed by conduction. This layer is then carried away by fluid movement and replaced with colder fluid. The rate of fluid flow determines the magnitude of convective heat loss, such that a subject swimming will have a much higher convective heat loss than a subject motionless in water.

The range of water temperature which may be tolerated for a prolonged period - two hours or more without significant shivering activity - is 33-36 ^{o}C for unprotected humans, and has been termed the critical water temperature (T_{cw}) (Rennie *et al.* 1962, Rennie *et al.* 1987). Above this temperature range, heat loss is reduced by peripheral vasoconstriction and is matched by basal metabolic heat production, while below T_{cw}, heat loss becomes significant. Vasoconstriction is strong and rapid due to peripheral cold thermoreceptor stimulus, but is insufficient to prevent significant heat loss at temperatures lower than T_{cw}. The central body temperature begins to fall, and heat production via shivering is initiated.

Individual susceptibility to hypothermia during cold water immersion varies within a wide range, with the thickness of the subcutaneous fat layer a major determining factor (Keatinge 1960, Hayward and Eckerson 1984). An individual with a thicker subcutaneous fat layer has a greater tissue insulative capacity upon peripheral vasoconstriction, and would be able to decrease conductive/convective heat loss and delay central cooling compared to an individual with minimal subcutaneous fat (Rennie *et al.* 1987, Tikuisis *et al.* 1991). Individual variations in both the threshold and the magnitude of thermogenic

response to cold stimulus is another important factor affecting body cooling rate (Mekjavic *et al.* 1986, Mekjavic *et al.* 1987, McDonald *et al.* 1989, Mittleman and Mekjavic 1991). Variations in thermogenic responses were observed during both the initial phase of immersion, when skin temperature rapidly decreased with a stable core temperature, as well as during prolonged immersion, when skin temperature stabilized and core temperature decreased (Mekjavic *et al.* 1986). Despite similar rates of core cooling, subjects exhibited significant differences in shivering intensity throughout cold immersion (Mekjavic *et al.* 1986, Mittleman and Mekjavic 1991). The sensitivity and magnitude of the thermogenic response have also been observed to decrease with age, and are correlated with an increased rate of body cooling in a cold environment in the elderly (Goldberg and Roe 1966, Roe *et al.* 1966, Vaughan *et al.* 1981, Stjernstrom *et al.* 1985, McDonald *et al.* 1989, Anderson 1993). Differences in peripheral and central thermosensitivity to cold stimulus may therefore play an important role in determining the initiation and intensity of shivering, and hence the rate of body core cooling and tolerance time in a cold environment.

ii)Hyperbaria

Divers exposed to a water environment with elevated ambient pressures face additional thermal stress when compared to normobaric immersion. With increasing depth, water temperature generally decreases, further increasing the thermal gradient from the diver to the environment and the magnitude of conductive/convective heat loss via the skin (Webb 1982). At normobaria, heat loss through the respiratory tract constitutes approximately 10% of total heat loss (Webb 1982), but may increase significantly in relative importance at depth (Flynn *et al.* 1974). Adequate thermal protection of divers at pressure therefore requires both proper insulation of the skin and reduction of respiratory

heat loss due to breathing cold gas (Brubakk *et al.* 1982). The magnitude of respiratory heat loss is dependent on the thermal gradient between inspired and expired air, the rate of respiration, and the density and specific heat capacity of the gas being breathed.

Before reaching the distal regions of the lungs, inspired air at normobaria is warmed and humidified to 37 °C and 47 mmHg vapour pressure, respectively, in the first 10-15 cm of the respiratory tract (Webb 1982). Air supplied to the diver is typically cold and dry, and may experience further cooling by the surrounding water prior to inhalation. Since inspired air is typically colder than the body environment, heat must be supplied to warm it; inhaled air is almost always devoid of water vapour, and more heat is required for the evaporation of water from the respiratory tract to saturate incoming air. Some heat may be recovered upon expiration, but evaporative heat loss remains a major avenue of respiratory heat loss at depth (Webb 1982). Gas temperature also affects airflow and the work of breathing, and cold gas may penetrate further into the respiratory tract before being warmed and humidified, leading to bronchial constriction and other unusual physiological responses (Webb 1982).

Gas density and thermal conductivity increases proportionately with increasing ambient hydrostatic pressure. Higher gas density slows gas flow and increases the work of breathing, resulting in higher energy expenditures required for respiration, while higher thermal conductivity increases conductive/convective heat loss from the respiratory tract. Different gas mixtures feature characteristic densities and thermal conductivities. Helium is often substituted for nitrogen in deep diving applications. While less dense than nitrogen, helium has a much higher thermal conductivity (Flynn *et al.* 1974). Piantodosi *et al.* (1981) observed core cooling in subjects breathing 14 °C heliox in a warm environment throughout a range of ambient pressures, with the drop in rectal temperatures increasing in proportion to pressure and gas density. Raymond *et al.* (1968) and Webb (1970) observed a slight increase in resting metabolism and body temperature, akin to mild hyperthyroidism, during prolonged heliox exposures, which may have reflected an increase

in resting heat production to compensate for the increased heat drain due to the heliox environment. Hoke *et al.* (1975) exercised subjects breathing 4 °C heliox at 26 atmospheres absolute (ATA). Despite the warm (30 °C) ambient temperature and the significant endogenous heat production from exercise, the subjects shivered violently due to respiratory heat loss and core cooling. Increased respiration rate further increases the relative importance of respiratory heat loss, due to the necessity for warming and humidifying a larger gas volume (Webb 1982). Therefore, divers increasing their level of O_2 consumption by increased exercise or shivering would hasten body cooling and the onset of hypothermia due to increased respiratory heat loss.

One non-thermal factor present in diving that has been hypothesized to promote the onset of hypothermia, due to a depressive effect on thermoregulatory abilities, is inert gas narcosis from the increased nitrogen partial pressure present at depth. The following section will review the theories of the mechanism of inert gas narcosis and the known effects of narcosis on the central nervous system (CNS) and on human thermoregulation.

2. Inert gas narcosis

The existence of impaired performance in humans exposed to a compressed air environment for prolonged periods, such as divers and tunnel workers, has been generally recognized since the initial documentation by Junod in 1835 (referenced in Bennett 1982a). At compressed air pressures exceeding 4 ATA, symptoms of intoxication, euphoria, and narcosis were observed. As pressure further increased to 7-10 ATA, mental processes and decision making ability slowed, loss of memory and neuromuscular coordination occurred (Abraini and Joulia 1992), and the subject eventually suffered loss of consciousness (reviewed in Bennett 1982a).

Many causes for this impairment at depth have been proposed, including the effects of pressure itself, latent suppressed claustrophobia, altered circulation leading to blood stagnation, and impurities in the breathing mixture (for review, see Bennett 1982a). Behnke *et al.* (1935) was the first to deduce the cause of impairment as being due to the increased nitrogen pressure in the compressed air acting as an anesthetic agent. This compressed air intoxication has been termed inert gas narcosis, and has been compared to the symptoms during the early stages of anesthesia.

The chemical structure of an inert gas is unaltered in the body, and no covalent or hydrogen bonds are formed with the body tissues under biological conditions (Featherstone and Muehlbaecher, 1963). Inert gases include the clinical anesthetics nitrous oxide (N_2O), ethylene, and cyclopropane, along with the noble gases nitrogen, xenon, argon, krypton, neon, and helium. Of the noble gases, some are narcotic at atmospheric pressures, while others - such as nitrogen - are only narcotic at supra-atmospheric pressures, and neon and helium produce no narcosis even at extreme pressures (Bennett 1982a).

Inert gases and other anesthetics produce many common effects in the body, such as the loss of sensation and consciousness, and may operate by the same mechanism (Hille

1980). Inert gases are in common usage as a general anesthetic in clinical settings, and the terms inert gas narcosis and anesthesia have often been interchanged. The mechanism of anesthesic action remains unknown, although recent theories centre on the effects of the substances on neural membranes. The following section will review the major theories of inert gas narcosis, and discuss their effects on neural membranes, the CNS, and thermoregulation.

a) Theories of inert gas narcosis

Due to the unreactivity of inert gases, biophysical, rather than biochemical, causes of inert gas narcosis have been stressed. Near the turn of the 20th century, Meyer (1899) and Overton (1901) separately observed a strong correlation between the solubility of an anesthetic agent in lipid and its narcotic potency. This correlation was also found among the noble gases, leading to the contention that the site of anesthetic action is located in the lipid portion of membranes. (referenced in Bennett 1982a).

Inert gases were found to desensitize mice to electroshock stimulation (Carpenter 1953, 1954). In those same studies, the partial pressure of the various gases differed for a given level of narcosis. However, the concentration of the narcotic within the lipid phase was found to be similar. This supported the Meyer-Overton contention that anesthesia occurs simply through their general dissolution into the lipid membrane, with no specific receptor site for anesthetic molecules.

Seeman (1972) dissolved anesthetics and inert gases into a variety of lipid model systems, and found that all exhibited expansion. Johnson and Flagler (1950) found that the application of hydrostatic pressure reversed the effects of anesthesia in tadpoles, with a higher pressure requiring a higher anesthetic dose to maintain isonarcosis. This and subsequent studies on pressure reversal of anesthesia in animals (Lever *et al.* 1971a,b) led to the synthesis of the "critical volume hypothesis" for anesthetic action (Miller 1974,

Miller *et al.* 1973). Anesthesia was proposed to occur through dissolution into the lipid membrane region, resulting in the expansion of the membrane and disruption of neural functioning. In contrast, hydrostatic pressure was felt to compress the membrane, thereby directly antagonizing the effects of narcosis. Both effects were felt to occur at a single shared and undefined molecular site. The critical volume hypothesis is a simple and elegant theory; however, direct antagonism may be an oversimplification. Halsey *et al.* (1978, 1980) presented a "multi-site receptor hypothesis." This modification of the critical volume theory suggested that several membrane sites may be affected by anesthetics through neural expansion, with pressure acting as an indirect antagonist (Wardley-Smith and Halsey 1980).

b) Neuronal effects and pressure reversal of narcosis

As stated above, it is suggested that inert gases dissolve in the lipid region of membranes, expanding the membrane and thereby disrupting the function of the cell. The expansion of neural membranes would alter its ability to conduct ions across the membrane, resulting in alterations to the propagation of an action potential (Kendig *et al.* 1975, Kendig 1980). The anesthetic action may occur through the alteration of transmitter release from the presynaptic terminal (Krnjevic 1992) or a decrease in postsynaptic electrogenesis (Thesleff 1956, Hsaio *et al.* 1992). Volatile anesthetics were found to depress excitatory synaptic transmission with negligible effects on resting membrane potential or axonal conduction (Krnjevic 1992). Hsaio *et al.* (1992) reported that N_2O inhibited postsynaptic electrogenesis in granule cells.

Since Johnson and Flagler's (1950) initial observation, the antagonistic action of pressure to the depressant effects of anesthetics on neural functioning, also known as pressure reversal, has been observed in whole animals and in tissue preparations with a variety of anesthetic agents. Most anesthetic agents seem to be affected by pressure

reversal, including alcohol (Garcia-Cabrera and Berge 1990), inert gases (Brauer *et al.* 1974), and volatile anesthetics and tranquilizers (Halsey and Wardley-Smith 1975). Pressure has therefore been used extensively as a research tool in the search for the mechanism and site of action of anesthesia. Similarly, inert gases at low pressures have been used to counteract the symptoms of HPNS (High Pressure Neurological Syndrome) observed at high ambient pressures (Brauer *et al.* 1974). The search has been particularly intense for a common site of action, where pressure and narcosis would be directly antagonistic. If inert gas narcosis and hydrostatic pressure operate at different membrane sites, countering HPNS by the use of inert gases may mask potentially dangerous complications associated with HPNS (Brauer *et al.* 1974, Bennett 1982b, Parmentier *et al.* 1985).

Axonal effects of anesthetics were felt to be minor by Larrabee and Posternak (1952), who found a greater sensitivity to anesthetics in the synapse. This was supported by Carpenter (1954), who found that very high partial pressures of inert gases were required to block axonal conduction. Richter *et al.* (1977) further found that the postsynaptic sensitivity was higher than in the presynaptic membrane. However, the sodium channel is critical in the proper propagation of the action potential, and has recently been proposed as a possible site of pressure-narcosis antagonism. Kendig *et al.* (1975) and Kendig (1980) found no evidence of pressure/anesthesia antagonism at the postsynaptic membrane, and that pressure added to, rather than opposed, the depressant effect of anesthetics on synaptic transmission. However, a partial antagonism of the depressed action potential conduction by pressure was observed. Kendig (1984a,b) found that inert gases shifted the inactivation curve of the sodium channel in a hyperpolarizing direction, whereas pressure shifted the curve in a depolarizing direction. Axonal conduction is therefore a mechanism of anesthesia that would be compatible with the concept of pressure reversibility. Contradictory observations were noted by Parmentier *et al.* (1985), who studied the effects of halothane and hydrostatic pressure on sodium

conductance in the squid giant axon. Pressure was found to affect membrane kinetics, while halothane primarily altered peak conductance, thus pressure and anesthesia may not share a common site of action. Interestingly, halothane effects were similar to that due to hyperbaric nitrogen (Kendig 1984b), lending support to the theory that anesthetics and inert gases may share common physiological mechanisms and effects.

Another possible mechanism of antagonism along the axon may be due to the phenomenon of repetitive impulse generation, or multiple responses to a single stimulus (Kendig 1980). Anesthetics and high temperature inhibits repetitive impulses, and may be due to increased membrane fluidity. In contrast, low temperatures and pressure increased the probability of repetitive impulses (Kendig *et al.* 1978).

In summary, the sensitivity of the synapse to anesthetic agents lead to the assumption that the site of anesthetic action is at the pre- or postsynaptic membrane. However, the site of the pressure reversal of narcosis may be along the axon, affecting the propagation of action potentials in an indirect fashion.

c) Narcosis and the CNS

Anesthetics may affect thermoregulatory response in humans by impairing either the sensitivity of afferent peripheral and central thermoreceptor neurons, the integration of thermal information, the functioning of the responding organs, or some combination thereof (Hammel 1988). Of these possibilities, impairment at the CNS and specifically the hypothalamus, which integrates thermal input and generates appropriate responses to thermal stress, is the favoured explanation for the disruption of thermoregulation during general anesthesia (Hammel 1988, Sessler *et al.* 1988b,c, Sessler 1991, Sessler *et al.* 1991, Poterack *et al.* 1991).

Sharp and Hammel (1972) locally heated the preoptic and anterior hypothalamus (POAH) in dogs. In unanesthetized dogs, heating or cooling of the POAH activated a

heat loss or heat production response, respectively. However, upon anesthesia by chloralose-urethane, vasodilation of the ear and core cooling were observed, and heating or cooling the POAH had no effect on either vasodilation or metabolism. The hypothalamus was therefore postulated to be an important component of thermoregulation, and sensitive to anesthesia. Poterack *et al.* (1991) measured activity in isolated thermosensitive neurons from the hypothalamus in cats. Halothane was found to produce a progressive decrease in spontaneous firing rate and thermosensitivity.

Sessler *et al.* (1988b,c) measured vasoconstriction in the extremities by comparing skin surface temperature of the forearm and fingertips. Total digital skin blood flow consists of nutritional (capillary) and thermoregulatory (arterio-venous shunt) components, with vasoconstriction affecting mainly the cutaneous arterio-venous shunts. Vasoconstriction was defined as occurring when the temperature gradient exceeded 4 ^{o}C, and the temperature at which vasoconstriction first occurs was labelled the threshold for active thermoregulation. In surgical patients undergoing elective donor nephrectomy with either halothane or nitrous oxide/fentanyl anesthesia, strong active vasoconstriction was observed, but not until core temperature had decreased by 2.5 ^{o}C. However, the intensity and sensitivity of the vasoconstrictory response, once initiated, did not differ from unanesthetized subjects. This was concluded to indicate a widening of the thermoregulatory null-zone by anesthesia.

From the above studies, Sessler (1991) argued that the hypothalamus, the final integrating centre according to the heirarchial thermoregulatory system proposed by Satinoff (1983), controlled the critical thresholds for hot or cold thermoregulation. Anesthetics have a profound effect on the hypothalamus, and would result in the disruption of fine control of the null-zone. Because the "mechanical details" such as intensity and sensitivity of thermoregulatory responses upon crossing the null zone was not affected by anesthesia, their control may be located at lower centre on the CNS unaffected by anesthesia.

d) Narcosis and thermoregulation

The occurrence of hypothermia in patients exposed to general anesthetics during surgery is a common and well-documented phenomenon (Imrie and Hall 1990). The development of hypothermia has been attributed to the large thermal stresses imposed on the patient by the irrigation of the body by cold fluids (Stjernstrom *et al.* 1985), cold ambient temperatures and the opening and exposure of the body cavities (Goldberg and Roe 1966), skin preparation lotions (Imrie and Hall 1990), and the breathing of cold and dry anesthetic gases (Shanks 1974). These environmental factors, combined with long operation times, establish a large thermal deficit from the body to the environment during surgery. General anesthesia has been observed to impair both the behaviourial and the autonomic thermoregulatory reflexes in humans (Hammel 1988). Vasomotor control is inhibited, resulting in full subcutaneous vasodilation and increased conductive/convective heat loss in the peripheries. However, the extent of the contribution to hypothermia from premedications and patient pathologies remain uncertain (Sessler *et al.* 1988b,c).

Clinical evidence supporting the inhibition of endogenous heat production via decreased muscle activity during general anesthesia, resulting in a strong imbalance between heat loss and heat production, are plentiful (Jones and McLaren 1965, Goldberg and Roe 1966, Roe *et al.* 1966, Stjernstrom *et al.* 1985, Sessler *et al.* 1988b,c). Despite hypothermic conditions and central core cooling, shivering is typically absent in patients during surgery with general anesthesia, with no significant difference in shivering attenuation among various inhaled anesthetics (Jones and McLaren 1965, Roe *et al.* 1966). Administering the inert gas N_2O at sub-anesthetic levels to non-surgical subjects also resulted in the attenuation of shivering during hypothermia (Passias *et al.* 1992, Mekjavic and Sundberg 1992). However, upon removal of anesthesia during postoperative recovery, hypothermic patients often experienced the rapid onset of violent

muscular activity and shivering, with the intensity varying directly with the magnitude of temperature drop during anesthesia (Sessler *et al.* 1991). Postoperative shivering may result in the raising of oxygen uptake and metabolic rate by 400%, putting the patient at risk of disruption of delicate surgical repairs and increasing the stress imposed on the cardiorespiratory system by hypothermia (Imrie and Hall 1990).

Not all postoperative muscular activity may be of a thermoregulatory nature. Electromyographic records of anesthetized and hypothermic surgical patients were compared to records taken from hypothermic but unanesthetized non-surgical subjects, and were found to differ in several key characteristics (Pozos *et al.* 1987, Sessler *et al.* 1988a, Israel and Pozos 1989). Thermal-induced shivering EMG typically featured a repetitive waxing and waning pattern synchronized among all muscle groups, with a frequency of 6-8 cycles/min and a peak power range between 8-12 Hz. In contrast, post-anesthetic EMG resembled clonic tremor in patients with transected spinal cords, featuring long trains of EMG activity, with a dominant power range of 5-6 Hz and lacking the synchronous waxing and waning pattern across muscle groups. To eliminate the effects of premedications and pathologies, Sessler *et al.* (1991) compared EMG in non-surgical subjects, and observed dissimilar EMG patterns between the same anesthetized and unanesthetized subjects during hypothermia. Thermal-induced EMG patterns were not observed until patients became either severely hypothermic (< 34.5 ^{o}C) or residual anesthetic volume decreased to below a threshold of < 0.4 %. Furthermore, muscular activity correlated well with end-tidal anesthetic concentration but not with rectal temperature (Sessler *et al.* 1988a). The above studies therefore concluded that, while general anesthetics depresses thermogenic activity, initial postoperative muscular activity upon anesthetic removal was not a thermogenic response to hypothermia, and should not be termed "shivering." Instead, postoperative tremors may be due to spinal reflex hyperactivity that results when descending cortical control is inhibited by residual anesthetic.

As stated previously, an important assumption of experiments on inert gas narcosis is that their mechanism of action and their physiological effects are similar to those of other general anesthetics. Passias *et al.* (1992) and Mekjavic and Sundberg (1992) immersed subjects at 1 ATA while exposed to 30% N_2O or to air. Subjects during the N_2O trials were observed to cool much more rapidly than during the air trials and had significantly decreased shivering, as measured by oxygen uptake. The null-zone between the thresholds for cessation of sweating and onset of shivering, was enlarged from 0.59 and 0.59 °C while breathing air, as determined with esophageal and rectal temperature measurements, to 0.95 and 1.32 °C while breathing N_2O (Mekjavic and Sundberg 1992). The authors concluded that N_2O attenuated heat production through generalized inhibition of synaptic activity affecting possibly all phases of thermoregulation, from conveyance of afferent stimulus, to integration of thermal stimulus at the CNS, to proper functioning of the effector mechanisms.

Extrapolating from a unitary hypothesis of anesthetic action, it has been generally assumed that the various inert gases induce qualitatively similar effects on humans (Fowler *et al.* 1985), though little work has been performed to directly compare and correlate the effects of two inert gases such as N_2 and N_2O. Argon, which is narcotic at normobaria, was found to produce similar qualitative effects as hyperbaric N_2 on mental arithmetic and subjective symptoms with trained divers (Fowler and Ackles 1972). Biersner (1977) found similar decreases in learning rate at 7.5 ATA as while breathing 30% N_2O. In addition, much of the research on the effects of inert gases have concentrated on qualitative behaviour or mental performance, and have deliberately employed high concentrations to elicit an unambiguous level of narcosis. Therefore, the degree of narcosis in such studies are typically higher than the PN_2 faced by hyperbaric workers, who are legally limited to 6-7 ATA compressed air exposure, and the effects of subanesthetic levels of inert gas narcosis on behaviour remain unclear. Assuming that a qualitative equivalency exists among the inert gases with regards to physiological effects,

the depression in metabolic heat production observed in hypothermic humans exposed to N_2O may implicate N_2 as a significant contributing factor in the hypothermia experienced by divers in an underwater environment (Passias *et al.* 1992, Mekjavic and Sundberg 1992).

An investigation on thermoregulation during diving, where the nitrogen component of compressed air is the narcotic substance, was performed by Iwamoto *et al.* (1988), which found no difference in the 2 h critical water temperature at 2 ATA compared to 1 ATA in nude subjects. Park *et al.* (1988) observed a progressive increase in T_{cw} at 2 and 2.5 ATA, but attributed the increase to the increasing pressure producing a corresponding decrease in the insulation of the wetsuits. However, 2-2.5 ATA may not be sufficient to induce significant inert gas narcosis in subjects, as the limit for the onset of behavioural inert gas narcosis was rated at between 4-7 ATA (Bennett 1982a, Fowler *et al.* 1985, Abraini and Joulia 1992). Mekjavic *et al.* (1993) found a significant decrease in shivering and esophageal temperature in nude subjects immersed in 15 ^{o}C water at 6 ATA compared to 1 ATA.

Diving research performed in either open water or in hyperbaric chambers are inherently complex and expensive. If a qualitative and quantitative equivalency can be established between the narcotic effects of hyperbaric N_2 and another inert gas, studies using other inert gases may be generalized to hyperbaric applications, increasing experimental simplicity, safety and economy.

INTRODUCTION

Human temperature regulation is a process of dynamic equilibrium between heat dissipation to the environment and heat gain from both endogenous heat production and exogenous sources. This ability to maintain thermostasis may be impaired by the presence of various non-thermal factors in the environment. Two situations that appear to have clinically similar depressant effects on thermoregulation are found in patients undergoing prolonged general anesthesia and in divers exposed to hyperbaric nitrogen; in both cases, subjects are exposed to narcotic gases in a high heat loss environment, and often experience an enhanced susceptibility to the development of hypothermia. Clinical studies have reported that, in divers and caisson workers breathing air in hyperbaric conditions, the body's thermoregulatory abilities may be impaired, promoting the development of hypothermia (Keatinge, 1980; Bennett, 1982a; Webb, 1982; Bridgman, 1990). Narcosis from anesthetic gases or hyperbaric nitrogen may inhibit central thermoregulation in both situations, limiting the ability of the body to regulate core temperature.

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, with 30% N_2O being equated to breathing air at 6-8 atmospheres absolute (ATA) (Biersner *et al.* 1977, Biersner 1972). 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 attenuated the shivering response in 15 °C water, resulting in an increased core cooling rate. Assuming that N_2 at high pressures produces similar effects on 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. Mekjavic *et al.* (1993) found a similar substantial depression of the shivering response in subjects at 6 ATA in 15 °C water as found by Passias *et al.* (1992). However, Iwamoto *et al.* (1988) observed no difference in the 2 h critical water temperature (T_{cw}) between 1 and 2 ATA. The question of whether inhibition of shivering by N_2O or hyperbaric N_2 occurs in a dose-dependent manner therefore 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. The primary aim of the present study was to investigate the existence and nature of a dose-dependent response between the attenuation of shivering thermogenesis and the depth of N_2O-induced narcosis, as a prelude to investigating the possibility of an equivalent dose-dependent response in hyperbaric conditions. 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.

METHODS

1. Subjects

Seven male volunteers participated in the study upon approval by a physician. None of the subjects smoked, were obese or on medication, or had a history of hypertension. Some of the subjects had previous experience with hypothermia studies and/or N_2O exposure. Before giving their informed consent, subjects were familiarized with the experimental procedures and the possible risks involved, and informed of their right to withdraw their participation in the experiment or the study at any time. A physician was on call throughout the course of each experiment. Subjects (Table 1) ranged in age from 23-30 yr (mean $\pm$ SD = 25.9 $\pm$ 2.7), in height from 171.6-182.9 cm (178.6 $\pm$ 3.9), and in weight from 62.5-90.0 kg (76.2 $\pm$ 10.5).

2. Protocol

The experimental protocol and instrumentation in the present study were approved by the Ethics Review Committee of Simon Fraser University. Each subject was immersed to the neck in a 20 ^{o}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 room air (AIR) or a normoxic mixture containing either 10, 15, 20, or 25% N_2O balanced with N_2. A water temperature of 20 ^{o}C was chosen to reflect the lower range of typical skin temperature conditions encountered by wet-suited divers (Bridgman 1990). The five trials were spaced at least one week apart to avoid acclimation to cold and/or inert gas narcosis, and the order of the treatments was randomized among the subjects to eliminate order effects. Any effects of circadian rhythms were minimized by performing the experiments during the same time of the

day. Each subject was asked to avoid strenuous exercise during the day preceding the experiment, and to have a light meal 2 hours prior to testing. They also agreed to maintain a similar diet as well as physical activity and sleeping schedules during the 2 days prior to each trial, thus diminishing the effect of the above factors on the physiological responses recorded.

The protocol for each immersion was identical except for the inspired gas mixture (AIR, 10, 15, 20, or 25% N_2O). The order of the conditions were randomized with a Latin Square design to eliminate order and period effects. Upon arrival at the laboratory, the subject assumed a sitting position while the transducers were positioned. Ambient room temperature was maintained throughout the experiment between 21 - 25 ^oC. Following the instrumentation procedure, maximal voluntary contractions (MVC) of the trapezius were recorded for the normalization of the electromyograph (EMG). The subject was seated in a bosun's chair harness, mechanically raised above the immersion tank by a pneumatic winch, and began breathing through the respiratory valve for ten minutes while resting values were recorded. This rest period served to ensure that the recordings at the start of the immersion were obtained from a steady state level of anesthesia (Kety *et al.*, 1947, Salanitre *et al.*, 1962).

After resting values were recorded, the subject was mechanically 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 ^oC from the pre-immersion value, or to 35.0 ^oC. 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 breathed via a low-resistance Hans-Rudolph respiratory valve. The subject wore a noseclip throughout the experiment. Passing the gas through the water bath increased patient comfort, as it ensured humidification

of the gas mixtures used in each experimental condition, and minimized respiratory evaporative heat loss to a similar degree for all conditions.

At the end of the immersion period, the subject was mechanically raised and removed from the tank. Thereafter, the subject was immediately disconnected from the recording equipment and transferred to a hot bath for complete reinstatement of body temperature.

3. Instrumentation

Subjects were immersed in a tank measuring 200 x 105 x 200 cm. The water temperature was maintained at 20 °C by a refrigeration/heating unit. A battery-powered propeller stirred the water at a constant velocity to prevent the warming and maintenance of an insulative layer of water around the body.

a) Heat flux ($\dot{Q}$, $W \cdot m^{-2}$) and skin temperature (T_{sk}, °C)

Heat flux from the skin surface was measured with heat flux transducers (Thermonetics Corporation, California, USA). Thermistors embedded in the transducer's surface placed on the skin allowed simultaneous measurement of skin temperature. Heat flux and skin temperatures were measured at six sites (chest, abdomen, back, arm, thigh, and calf) and are reported as unweighted averages. The transducers were attached to the skin with waterproof tape (Elastoplast, Smith and Nephew Inc., Quebec, Canada).

b) Core temperature (T_C, ^oC)

Esophageal (T_{es}) temperature was measured using a thermistor probe (YSI 702, Yellow Springs Instruments, Ohio, USA) inserted to the level of the right atrium. The esophageal probe insertion length was determined from sitting height as suggested by Mekjavic and Rempel (1990).

c) Heart rate (H.R., min^{-1})

An electrocardiogram was obtained from a bipolar precordial lead using an electrocardiograph (Physio-Control Systems, Washington, USA) in combination with an extended, shielded patient cable. Waterproof tape was used to protect the electrode cable connections from water and contamination of the recorded signal. Electrocardiograms were examined for arrythmias, and heart rate was determined from the average R-R interval of six consecutive beats.

d) Electromyography (EMG)

Electrical activity of the trapezius was recorded with a bipolar surface electrode (Grass Instruments, Massachussets, USA). The signal was passed through a preamplifier (P15D, Grass Instruments, Massachussets, USA) with an amplification of 1000x and a bandpass range of 10 Hz to 1 KHz and then stored on an FM tape recorder (HP 3968A, Hewlett Packard, California, USA) for subsequent analysis. Prior to each experimental trial, the amplitude of the EMG signal was normalized by the recording of a MVC from 5 rapid and brief (2 s) isometric shoulder elevations with 30 s rest in between. MVC's were produced by the subject performing a shoulder elevation with

the elbow extended and the hand gripping the edge of his seat. Waterproof tape was used to position and to insulate the electrode.

Analysis of EMG was performed on a customized program. A 60 s block of EMG signal was analyzed from the FM tape at rest (prior to immersion) and at every 0.2 °C drop in T_{es}. The signal was digitized at 1024 Hz. The amplitude of the EMG signal was determined from calculation of the root mean square (RMS). EMG during immersion was normalized as a percentage relative to the largest RMS value obtained during the 5 MVC's.

e) Ventilation and oxygen uptake ($\dot{V}_I$, $\dot{V}O_2$, $L \cdot min^{-1}$ STPD)

Inspired ventilation was measured using a turbine flowmeter (VMM1, Alpha Technologies). Oxygen uptake was determined from the analysis of mixed expired gases (O_2 and CO_2) and inspired minute ventilation. A continuous 500 $mL \cdot min^{-1}$ sample of mixed expired gas was drawn from the mixing box and analyzed for oxygen (S-3A/II, Ametek Systems, Pennsylvania, USA) and carbon dioxide (Capnograph Type 146, Godart Industries, Bilthoven, Holland) contents. A gas mixture containing N_2O may affect both the absorption of infrared by CO_2, due to the foreign gas broadening phenomenon (Mekjavic 1979, Bhavani-Shankar *et al.* 1992), and also the detection of O_2. Therefore, for the N_2O trials, the O_2 and CO_2 analyzers were calibrated with two calibration gases containing 30% N_2O in combination with O_2, CO_2, and N_2.

f) Thermal Comfort Vote (TCV)

Subjects were asked to give a subjective rating of their thermal comfort at 5 min intervals throughout the immersion period. The 21 point scale ranged from +10 (very very hot) to -10 (very very cold), with 0 as neutral.

g) Data acquisition

With the exception of EMG and heart rate, all physiological variables were recorded at 10 s intervals with a data acquisition system (HP 3497A, Hewlett Packard, California, USA) controlled by a MacIntosh® II computer. Values were subsequently averaged over minute intervals. Heart rate was constantly monitored for the safety of the subject, and manually recorded at minute intervals.

4. Statistical analysis

The study was a 2-factor design with repeated measures, with the concentration of N_2O and time as the independent variables. A 2-way analysis of variance (ANOVA) with repeated measures was performed to compare the effects of varying N_2O concentrations on T_{sk}, $\dot{Q}$, ΔT_{es}, $\dot{V}_I$, and $\dot{V}O_2$. If a significant difference was found among the mean values, a multiple comparison of means, using the Student Neulman-Keuls test, was performed to determine the source of difference. A regression analysis was performed over the linear segments of core cooling for each subject and the rates of core cooling were compared among the test conditions using a one-way repeated measures ANOVA. For each subject, the linear regressions were derived over the same time period for all conditions. The magnitude of the RMS of the EMG was ranked over the five experimental conditions for each subject individually. Rankings were based on the RMS at the final 0.2 ^{o}C interval. In cases of similar RMS, the threshold core temperature at which RMS increased above a baseline level of $> 5\%$ MVC was used as a secondary criterion, with a tie between two conditions allowed. A non-parametric comparison of the rankings of the EMG intensity during the five experimental conditions was performed using the Friedman chi-squared test.

Unless noted otherwise, the 5 % level was chosen as the level of statistical significance for all analyses.

RESULTS

All subjects reported a sensation of intoxication when exposed to N_2O, with an increase in N_2O concentrations potentiating the level of intoxication. Over the course of immersion, the magnitude of narcosis was diminished somewhat, and disappeared altogether for several of the subjects during the latter stages of immersion while breathing 10 and 15% N_2O. Subjects also reported being more relaxed both before and during immersion while breathing N_2O, particularly with the higher concentrations. Using 20 or 25% N_2O as the gas inhalate, subjects reported an increased feeling of comfort and warmth, with minimal or no shivering throughout immersion. Though all subjects remained conscious throughout immersion, several were somewhat somnolent while breathing 20 and 25% N_2O. None experienced any nausea while breathing N_2O.

All recorded variables were similar in the five experimental conditions during the 10 min rest period. Therefore, the values at minute 10 were used as the resting value for T_{sk}, $\dot{Q}$, T_{es}, $\dot{V}_I$, $\dot{V}O_2$, and TCV. Immersions had to be terminated for one subject prematurely, as his T_{es} had dropped to 35.0 °C after 55 min of immersion with 20% N_2O, and after 45 min with 25% N_2O. Of note was the fact that this subject was the lightest of the seven.

The results are reported for the 60 min of immersion as the average values for the seven subjects $\pm$ SD. For the purpose of clarity, SD bars are omitted from the graphical presentation of the results.

1. Esophageal Temperature

T_{es} remained stable for the first 10 min. of immersion and thereafter decreased in a linear manner for all conditions, as seen in Fig. 1. By the end of the immersion period, the relative decrease in T_{es} from resting pre-immersion levels (ΔT_{es}) for the

experimental conditions were -0.86 ± 0.52 °C (AIR), -1.13 ± 0.57 °C (10% N_2O), -1.12 ± 0.56 °C (15% N_2O), -1.08 ± 0.47 °C (20% N_2O), and -1.09 ± 0.58 °C (25% N_2O). The ΔT_{es} observed during the AIR condition was significantly less than observed during each of the four N_2O conditions, with no difference in ΔT_{es} among the N_2O conditions.

For all subjects in each condition, the rate of cooling of T_{es} ($\dot{T}_{es}$, °C·hr^{-1}) was calculated by performing a regression over the linear portion of the T_{es} response with time (Table 2). Although no difference was noted between the AIR and 10% N_2O trial, $\dot{T}_{es}$ during the AIR trials was significantly lower than observed during the 15, 20, and 25% N_2O conditions.

2. Skin Temperature

Upon immersion, T_{sk} decreased rapidly from resting values of 33.60 ± 1.00 °C (AIR), 32.77 ± 1.80 °C (10% N_2O), 32.76 ± 0.63 °C (15% N_2O), 32.76 ± 0.41 °C (20% N_2O) and 33.04 ± 0.64 °C (25% N_2O) to a level slightly above the water temperature of 20 °C (Fig. 2). This drop occurred during the first 5-10 min of immersion, whereupon skin temperature remained stable for the remainder of the immersion period. T_{sk} over the course of immersion was found to be lower while breathing 10 and 25% N_2O than observed during AIR, despite the water bath being maintained at 20 °C for all immersions.

3. Heat Flux

Unweighted mean heat flux from the skin (W·m^{-2}) was similar for the five experimental conditions prior to immersion (Fig. 3): 59.2 ± 9.1 W·m^{-2} (AIR), 66.0 ± 18.1 W·m^{-2} (10% N_2O), 61.7 ± 14.8 W·m^{-2} (15% N_2O), 57.4 ± 7.9 W·m^{-2} (20%

N_2O), and 64.4 ± 12.6 $W \cdot m^{-2}$ (25% N_2O). In all conditions, $\dot{Q}$ increased very rapidly upon entry into the water, peaking at values ranging from 470 to 600 $W \cdot m^{-2}$ within 1 min. Following this transient increase, $\dot{Q}$ then rapidly decreased to stable levels within approximately 10-15 min of immersion, reaching end-immersion values of 123.2 ± 40.7 $W \cdot m^{-2}$ (AIR), 101.9 ± 48.1 $W \cdot m^{-2}$ (10% N_2O), 101.1 ± 39.7 $W \cdot m^{-2}$ (15% N_2O), 102.4 ± 36.3 $W \cdot m^{-2}$ (20% N_2O), and 111.6 ± 16.1 $W \cdot m^{-2}$ (25% N_2O). No significant difference in $\dot{Q}$ was observed among any of the experimental conditions throughout the immersion.

4. Ventilation Rate and Oxygen Uptake

The pattern of changes in $\dot{V}_I$ was similar for all five experimental conditions, and is illustrated in Fig. 4. Upon immersion, ventilation increased due to the hydrostatic effect and the gasping reflex. This transient increase in $\dot{V}_I$ was followed by a return to slightly above resting values after 5 min, whereupon $\dot{V}_I$ gradually increased throughout the course of immersion, reaching 27.4 ± 7.0 $L \cdot min^{-1}$ (AIR), 24.8 ± 10.7 $L \cdot min^{-1}$ (10% N_2O), 21.9 ± 8.0 $L \cdot min^{-1}$ (15% N_2O), 18.9 ± 8.4 $L \cdot min^{-1}$ (20% N_2O), and 22.0 ±11.1 $L \cdot min^{-1}$ (25% N_2O) at the end of immersion. $\dot{V}_I$ while breathing AIR was significantly higher than breathing any of the N_2O concentrations throughout the course of immersion. In addition, $\dot{V}_I$ during 10% N_2O was higher than observed with 20% N_2O.

Oxygen uptake followed a similar pattern in all trials, exhibiting a gradual increase throughout the course of immersion (Fig. 5). $\dot{V}O_2$ transiently increased upon immersion, from pre-immersion resting values of 0.38 ± 0.14 $L \cdot min^{-1}$ (AIR), 0.53 ± 0.10 $L \cdot min^{-1}$ (10% N_2O), 0.53 ± 0.09 $L \cdot min^{-1}$ (15% N_2O), 0.47 ± 0.10 $L \cdot min^{-1}$ (20% N_2O), and 0.39 ± 0.13 $L \cdot min^{-1}$ (25% N_2O), to peak values ranging from 0.72 - 1.11 $L \cdot min^{-1}$ after the first minute. After this transient increase, $\dot{V}O_2$ decreased to

levels slightly above resting values after 5 min, then increased significantly above resting values in all conditions, concomitant with time and decreasing T_{es}. $\dot{V}O_2$ attained end-immersion values of 0.97 ± 0.36 L·min^{-1} (AIR), 1.30 ± 0.53 L·min^{-1} (10% N_2O), 1.10 ± 0.31 L·min^{-1} (15% N_2O), 0.97 ± 0.46 L·min^{-1} (20% N_2O), and 0.87 ± 0.47 L·min^{-1} (25% N_2O). Unlike ventilation rate, the highest $\dot{V}O_2$ did not occur in AIR. Rather, $\dot{V}O_2$ during the 10% N_2O trial was higher than with AIR, which in turn was higher than observed with 25% N_2O.

Despite the increased $\dot{V}O_2$ over the course of immersion while breathing 10% N_2O, no difference was observed in the slope of the $\dot{V}O_2$ versus ΔT_{es} relationship among any of the conditions. The thermosenstitivity of the shivering response were -0.34 ± 0.27 L·min^{-1}·^{o}C (AIR), -0.57 ± 0.32 L·min^{-1}·^{o}C (10% N_2O), -0.41 ± 0.27 L·min^{-1}·^{o}C (15% N_2O), -0.26 ± 0.27 L·min^{-1}·^{o}C (20% N_2O), and -0.32 ± 0.18 L·min^{-1}·^{o}C (25% N_2O). Therefore, the stronger peripheral drive due to the lower T_{sk} with 10% N_2O may be responsible for the increased $\dot{V}O_2$.

5. Thermal Comfort

All subjects reported being more relaxed and comfortable while breathing N_2O, and this was reflected in their reporting a warmer TCV. The dose-dependent response of TCV to N_2O is presented in Fig. 5, with higher median TCV values reported with higher N_2O concentrations throughout the immersion. TCV decreased rapidly upon immersion, and continued to gradually decrease throughout the immersion period. By the end of immersion, median TCV had decreased to -7 (AIR), -6.5 (10% N_2O), -6 (15% N_2O), -5 (20% N_2O), and -2 (25% N_2O).

6. Electromyography

At rest, the RMS of the EMG was very low, typically ranging from 0.5 - 3.0% MVC (Table 3). As T_{es} decreased by -0.2 to -0.4 °C, a noticeable increase in RMS was observed for most subjects while breathing AIR. However, during the N_2O conditions, peak RMS tended to be both lower and also to begin increasing at a lower ΔT_{es}. Subjects who cooled only a small amount ($\Delta T_{es} < 1.0$ °C) during the immersions typically featured an elevated RMS in AIR by the end of immersion, with minimal or slight increases in RMS during N_2O conditions. In contrast, the RMS for subjects who had $\Delta T_{es} > 1.0$ °C were elevated for all conditions, again with AIR conditions eliciting a more rapid and intense response to decreasing T_{es}. The AIR condition was ranked as having the strongest EMG for six of the seven subjects (Table 4). When the overall rankings for the intensity of shivering in the five conditions were compared non-parametrically using the Friedman chi-squared tests, the ranking for the AIR condition was found to be significantly stronger than the four N_2O conditions ($p < 0.02$).

DISCUSSION

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 induce dose-dependent responses of shivering and core temperature cooling (ΔT_{es}, °C). The results indicate that there were no significant differences in ΔT_{es} among the N_2O conditions, though all concentrations of N_2O yielded a significantly greater ΔT_{es} than that observed during the AIR trial. The lack of a dose-dependent effect was also reflected in the EMG activity of the trapezius muscle. Namely, the shivering response was attenuated significantly and to a similar degree by all N_2O concentrations. Thus the present study confirms the depressant action of N_2O on the shivering 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.

Thermal balance of the body is a dynamic function of the rate at which heat is generated from either endogenous or exogenous sources versus the rate at which heat is lost to the environment. In the present study, $\dot{T}_{es}$ was found to be significantly greater while breathing 15, 20, or 25% N_2O compared with AIR, with 10% N_2O $\dot{T}_{es}$ at an intermediate value between AIR and the higher N_2O concentrations. No differences in heat loss, as measured by heat flux from the skin ($\dot{Q}$) were observed among the AIR or N_2O conditions. Therefore, the increased $\dot{T}_{es}$ in N_2O should be due to a corresponding decrease in heat production. However, despite the slight increase in $\dot{T}_{es}$, $\dot{V}O_2$ during 10% N_2O was significantly higher than AIR. This may be due to the lower T_{sk} present during the 10% N_2O immersions increasing $\dot{V}O_2$ despite the water bath being maintained at 20 °C for all immersions. But given the significant ΔT_{es} present with 10% N_2O, this increase in $\dot{V}O_2$ may not be of a thermoregulatory nature. Direct measurement of shivering activity via EMG may be a better correlate of heat

production. The intensity of the EMG at the trapezius muscle was significantly stronger in AIR than in any of the N_2O conditions, with significant attenuation of shivering with all N_2O conditions and with no difference among concentrations. The narcotic effects of 10% N_2O may have overridden the stronger peripheral cold stimulus present due to the decreased T_{sk} during the 10% N_2O immersions, producing no increase in shivering output.

Behavioural thermoregulation is often the primary and most effective defence against hypothermia. Narcosis, however, impairs perception of thermal status (Mekjavic *et al.* 1993) and thus the ability to initiate effective countermeasures, excacerbating the progression to hypothermia. Thermal comfort in the present study responded in a dose-dependent manner to N_2O, with the cold water reported as being less thermally uncomfortable with each increasing N_2O concentration. Though an increase in thermal comfort was observed, subjects reported feeling noticeably cold during both 10% and 15% N_2O, but felt comfortable in the water with 20 and 25% N_2O. Therefore, a practical impairment of behavioural thermoregulation may not be evident until N_2O concentration increases above 20%.

Shivering of the muscles is the major source of metabolic heat production in hypothermic conditions, allowing the body to offset or reduce heat loss (Kleinbeckel and Klussman 1990, Sowood 1984). Muscle groups are recruited for shivering in a progressive manner, with shivering activity initially concentrated in the masticatory muscles, progressing to the upper trunk and eventually the lower trunk and extremities (Tikuisis *et al.* 1991, Jansky 1979). Trunk muscles were estimated to generate over 70% of the total heat produced, optimizing heat production and storage in the core while minimizing movement and convective heat loss in the peripheral muscles (Bell *et al.* 1992). The intensity of shivering EMG at the trapezius muscle reached peak values of 15-20% MVC in AIR immersion in the present study, though one subject had higher peak RMS values of 25-30% MVC. However, this subject was noticeably tense

throughout all immersions, and the involuntary tensing may have contributed to the higher RMS. Though the trapezius was not tested, similar peak EMG intensities were reported by Bell *et al.* (1992), with a maximum intensity of 5-16% MVC in central muscles and 1-4% MVC in peripheral muscles.

Theoretical Considerations

Components of the thermoregulatory system include temperature sensors situated in central and peripheral regions, afferents conveying frequency-coded thermal information from these sensors, central neural foci where thermal afferent information is integrated, and effectors which are activated to maintain thermal balance. N_2O may exert its depressant effect on thermoregulation by impairing the function of one or more of these components. The effects exerted by N_2O on cutaneous thermoreception and the peripheral conduction of thermal stimuli were reported to be negligible by Jong and Nace (1967) and Somjen (1967), so the CNS or the muscle shivering effectors may be the main site of narcotic impairment.

It is generally agreed that, in mammals, the dominant site of autonomic thermoregulation resides within the hypothalamus (Hori 1991, Sessler 1991, Jessen 1990, Hammel 1988). Located within the preoptic region of the anterior hypothalamus (PO/AH) are large concentrations of neurons whose spontaneous firing rates are altered in a temperature-dependent manner (Hori 1991, Curras *et al.* 1991, Boulant 1981). Thermosensitive (TS) neurons have also been located within the medulla oblongata and spinal cord, and additional extra-hypothalamic sites are possible (Hammel 1988, Boulant and Dean 1986). TS neurons within the CNS receive abundant thermal afferent input from other TS regions of the CNS and from the peripheries, forming a complex interconnected system of thermal integration (Hori 1991, Hammel 1988). The importance of thermosensitive neurons in thermoregulation has been amply

demonstrated in numerous studies, with localized cooling of the hypothalamus or stimulation of cold-sensitive neurons resulting in shivering and nonshivering thermogenesis as well as behavioural modifications in animals (Halvorson and Thornhill 1993, Hori 1991, Jessen 1990, Hammel 1988, Satinoff 1964). Satinoff (1983) proposed a heirarchic organization of thermoregulatory control, with progressively more effective, complex, and finer control developing over the course of evolution, culminating at the hypothalamus. Narcosis was observed to depress the threshold for initiation of thermoregulatory responses to lower core temperatures; however, upon initiation, the sensitivity and maximal intensity of response was found to be similar in air or under narcosis (Mekjavic and Sundberg 1992, Passias *et al.* 1992, Sessler *et al.* 1988b,c). Sessler (1991) proposed that the hypothalamus was mainly responsible for regulating the threshold for the initiation of thermoregulatory responses, while thermosensitivity and maximal intensity of response may be regulated at lower centres within the CNS, possibly the medulla oblongata and/or the spinal cord, which were less complex in terms of synaptic connections and therefore less susceptible to narcotic impairment.

Narcosis impairs synaptic transmission at either the pre- or post-synaptic junction, and has a minimal effect on axonal conduction (Krnjevic 1992, Hsiao *et al.* 1992, Thesleff 1956, Larrabee and Posternak 1952). Consequently, for a given inspired level of N_2O, the greater the complexity of a neural pathway in terms of number of synaptic connections, the greater the magnitude of attenuation of the neural information being conveyed along this pathway. The premise of the present study was that graded levels of narcosis induced with different concentrations of inspired N_2O would affect the shivering response in a dose-dependent manner by affecting synaptic transmission within this pathway in a dose-dependent manner. The results, however, demonstrate no significant dose-dependent effect for the range of concentrations investigated. In view of the dose-dependent effect of N_2O on perception of thermal comfort, the likelihood of a

dose-dependent effect on autonomic functions cannot be excluded. The conclusion that may be drawn from the present results is that the range of N_2O concentrations investigated did not exert a measurable difference in the shivering response. For the same range of N_2O concentration, however, a greater effect on TCV was reported with greater N_2O concentrations. The observation of a significant effect of this range of N_2O concentration on behavioural but not autononic responses may be explained on the basis of the greater complexity, in terms of synaptic connections, of the behavioural pathway. A given N_2O concentration would therefore have a greater effect on behavioural responses than on autonomic responses, and a range of N_2O concentrations producing dose-dependent effects on behavioural responses may not produce discernible dose-dependent effects on autonomic responses.

It is unclear from the present results whether the dominant site of narcotic impairment is within the CNS or at the muscle site itself. Eiken *et al.* (1987) reported that 6 ATA compressed air significantly decreased the peak EMG produced during maximal voluntary contractions of the quadriceps. Though the contribution from hydrostatic pressure cannot be discounted, the results suggests that narcosis has a depressant effect at the integrating site, the integrator-efferent pathway, or at the muscle itself. It would be of interest to investigate the effects of narcosis at the neuromuscular junction or the muscle membrane to isolate the effects of narcosis on muscle excitation-contraction coupling.

Practical Considerations

The interest in the effects of N_2O on thermoregulation in the present study and in recent studies (Mekjavic and Sundberg 1992, Passias *et al.* 1992) was spurred by the belief that experimentation carried out with N_2O is applicable to diving applications, where hyperbaric N_2 is the narcotic agent. Although confounding effects due to hydrostatic pressure are difficult to eliminate, an inherent assumption in transferring

studies with other inert gases to hyperbaric conditions is that a qualitative equivalency exists among the inert gases, with each inert gas producing similar narcotic symptoms, albeit at different partial pressures (Fowler *et al.* 1985, Fowler *et al.* 1983, Bennett 1982a, Fowler *et al.* 1980, Biersner *et al.* 1977, Biersner 1972). However, most of the quantitative studies comparing inert gases have focused on the concentrations required to achieve behavioural endpoints, such as the loss of the righting reflex (Fowler *et al.* 1985). These studies and other studies on behavioural effects of inert gases have typically been performed at higher levels of narcosis than is faced by compressed air divers, and it is unclear whether a similar equivalency exists in autonomic mechanisms such as thermoregulation at narcotic levels common in commercial diving. Mekjavic *et al.* (1993) found that, in 15 °C water, subjects at 6 ATA responded in a similar manner as subjects in 15 °C breathing 30% N_2O (Passias *et al.* 1992). In both studies, shivering thermogenesis was significantly inhibited during narcotic conditions, leading to decreased heat production to combat the strong rate of heat loss. $\dot{T}_{es}$ during air immersions were similar in both studies; while greater during narcotic conditions, $\dot{T}_{es}$ was again similar with either 6 ATA or 30% N_2O (Fig. 7). Subjects in both studies did not feel as cold in the narcotic conditions compared to AIR, so behavioural thermoregulation may also have been impaired in a similar manner with both N_2O and increased PN_2.

Extrapolating from the similar thermoregulatory reaction observed with 30% N_2O and 6 ATA, the increased cooling rate while breathing 10, 15, 20, or 25% N_2O in the present study would suggest that a depressed thermoregulatory response may be present in hyperbaric situations with even minor increases in PN_2 from surface pressure. Furthermore, divers at even shallow depths would be equally susceptible to increased risks of hypothermia, as indicated by the lack of a dose-dependent response of ΔT_{es} to N_2O concentration. The exact PN_2 at which shivering thermogenesis would begin to be significantly attenuated is unknown. Iwamoto *et al.* (1988) did not find a

difference in T_{cw} between 1 and 2 ATA. Due to the lack of direct comparative studies between N_2O and N_2, it is not known what concentration of N_2O would correspond to 2 ATA compressed air. However, in behavioural studies, mental performance was found to be significantly impaired at 4 ATA (Kiessling and Maag 1962) and 7 ATA (Abraini and Joulia 1992), thus PN_2 at 2 ATA air may not be of sufficient narcotic potency to cause significant thermoregulatory impairment. Clearly, 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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TABLES
AND
FIGURES

Subject	Age (yr)	Height (cm)	Weight (kg)
1	24	177.0	62.5
2	29	171.6	72.0
3	30	179.0	80.0
4	23	182.0	64.5
5	25	180.0	81.7
6	26	177.5	83.5
7	24	182.9	90.0
Mean	**25.9**	**178.6**	**76.2**
SD	**2.7**	**3.9**	**10.5**

Table 1: Subjects' physical characteristics.

	$\dot{T}_{es}$ ($^{o}C \cdot hr^{-1}$)				
Subject	**AIR**	**10% N_2O**	**15% N_2O**	**20% N_2O**	**25% N_2O**
1	1.68	2.30	2.75	2.40	3.70
2	0.92	1.24	1.62	2.15	1.63
3	0.53	1.11	0.73	1.46	0.81
4	2.05	1.53	1.16	1.63	1.82
5	0.89	1.04	1.06	1.05	1.24
6	0.88	0.90	1.69	1.33	1.03
7	0.37	1.40	1.61	1.45	1.26
Mean	**1.05**	**1.36^{ns}**	**1.52***	**1.64***	**1.64***
SD	**0.61**	**0.47**	**0.65**	**0.47**	**0.97**

Table 2: $\dot{T}_{es}$ in the N_2O trials were compared with that observed during the AIR trial (ns = not significant; * $p \leq 0.05$).

	Ranking of EMG Intensity				
Subject	**AIR**	**10% N_2O**	**15% N_2O**	**20% N_2O**	**25% N_2O**
1	1	2	4	3	5
2	1	2	5	4	3
3	1	3	4	2	5
4	1	2	5	4	3
5	1	2.5	4	2.5	5
6	3	5	2	4	1
7	1	3	5	4	2
Mean Ranking	**1.29***	**2.79**	**4.14**	**3.36**	**3.43**

Table 3: Non-parametric rankings of the intensity of the EMG signal, as quantified by the RMS analyzed at rest and at every 0.2 °C drop in T_{es}. (* EMG intensity was significantly ($p \leq 0.02$) stronger in AIR than in any of the four N_2O conditions).

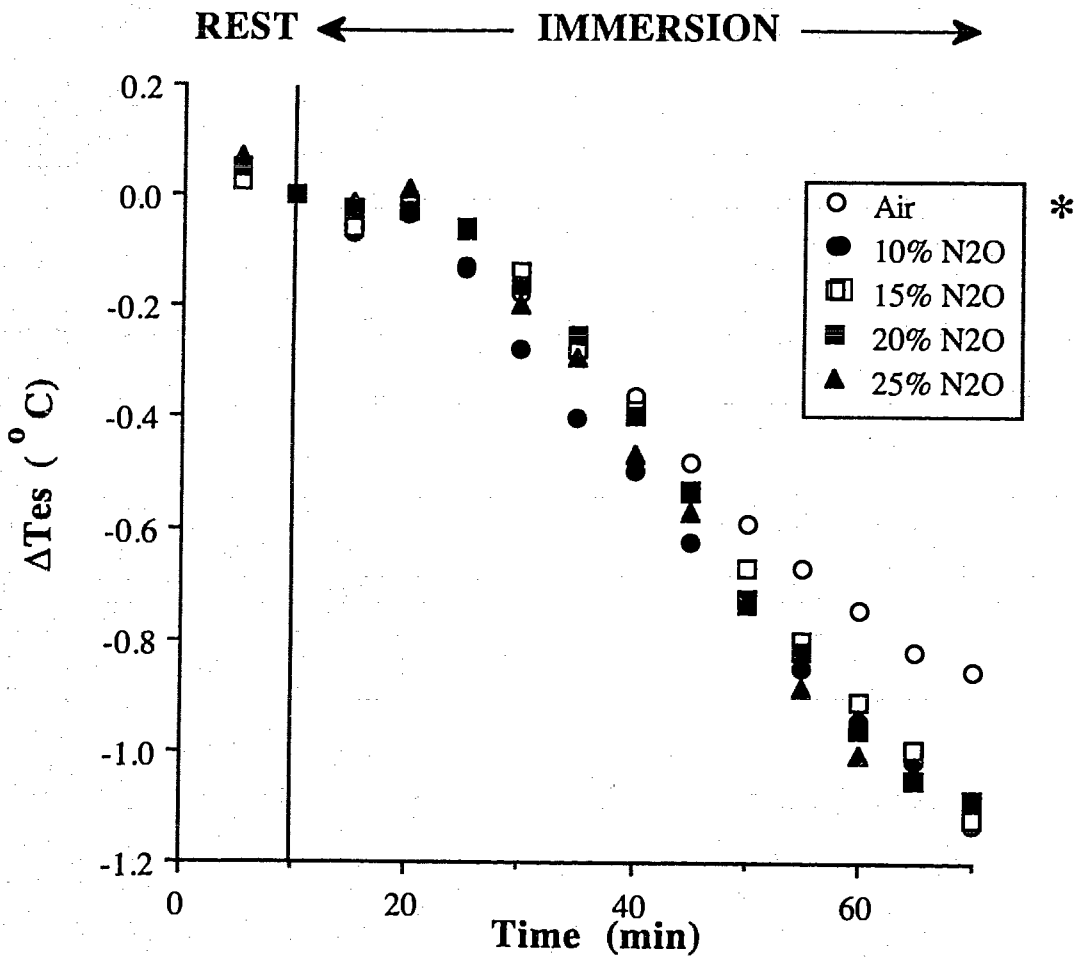

Fig. 1. Mean relative change in esophageal temperature (ΔT_{es}) during rest and immersion in AIR, 10, 15, 20, and 25% N_2O. * ΔT_{es} in AIR was significantly ($p \leq 0.05$) less than in any N_2O condition for the last 10 min of the immersion phase.

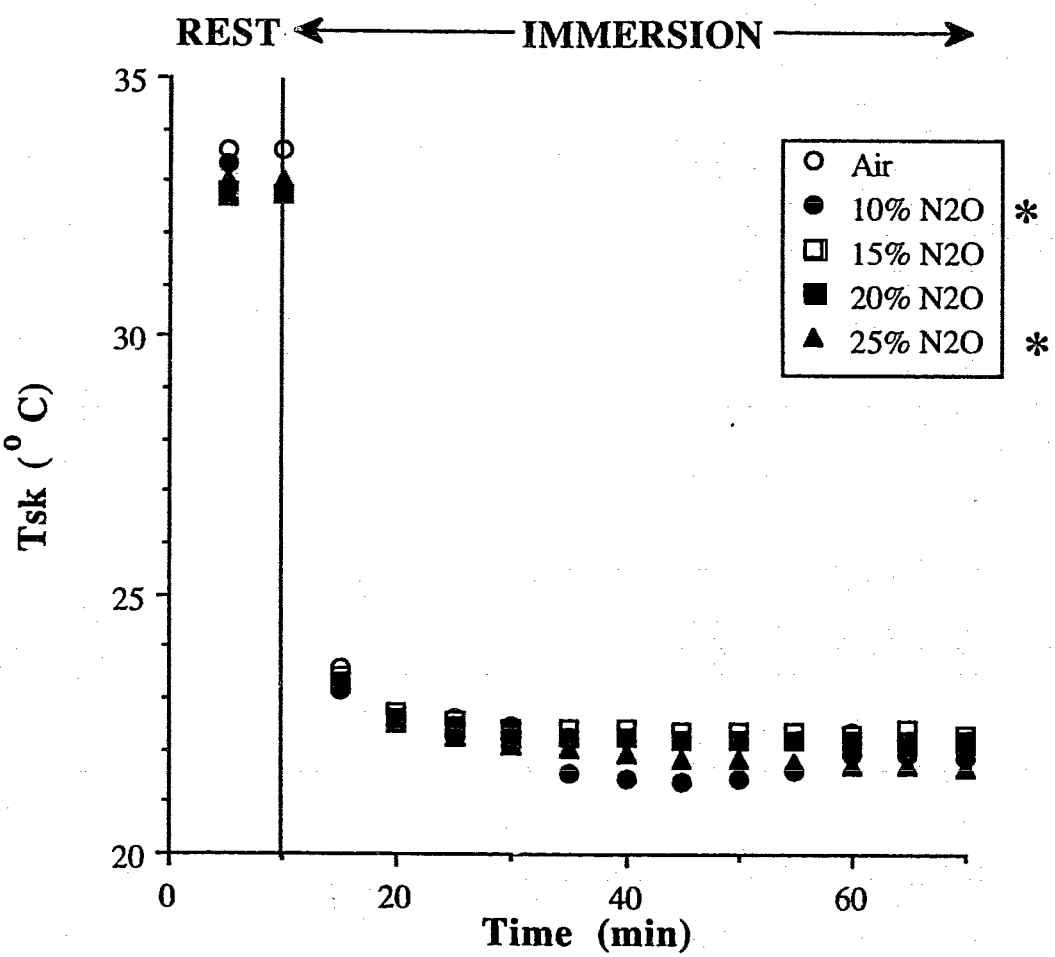

Fig. 2. Mean skin temperature (T_{sk}) during rest and immersion in AIR, 10, 15, 20, 25% N_2O. * T_{sk} was significantly ($p \leq 0.05$) less in 10 and 25% N_2O than in AIR during the immersion phase.

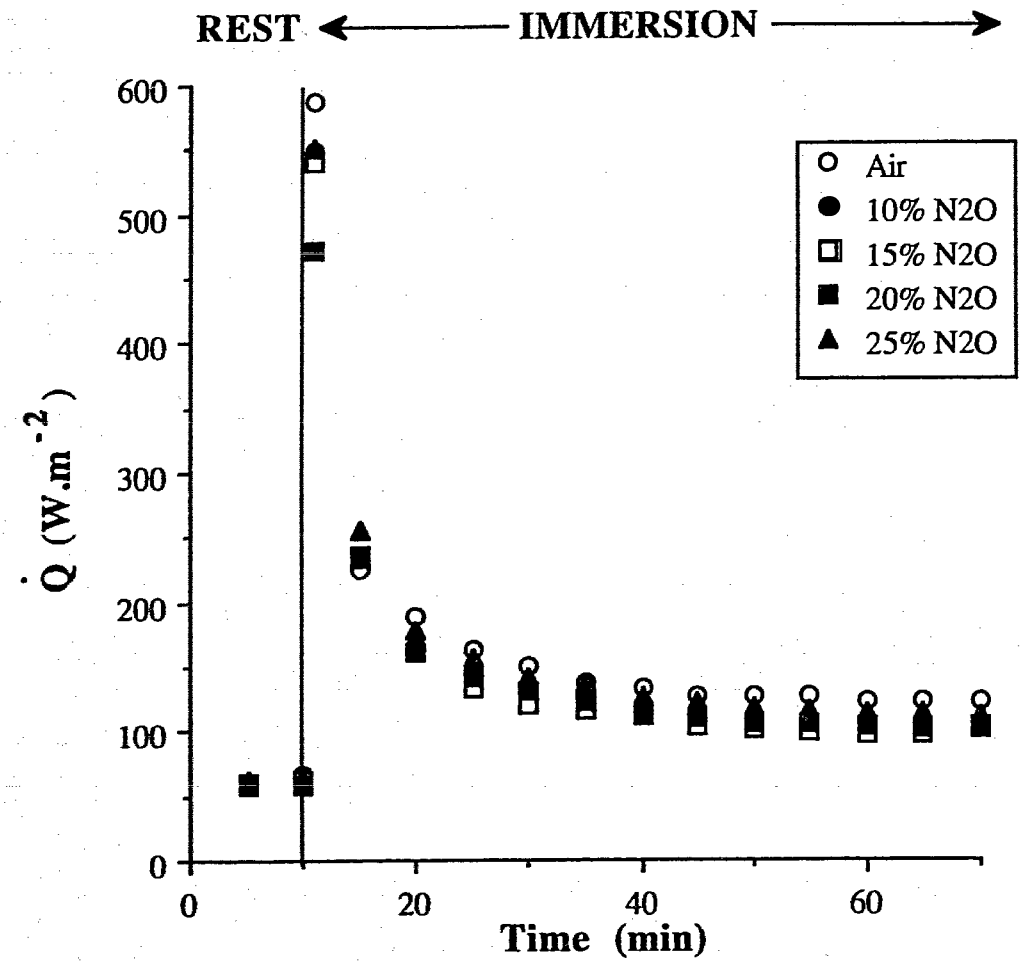

Fig. 3. Mean heat flux ($\dot{Q}$) from the skin during rest and immersion in AIR, 10, 15, 20, 25% N_2O.

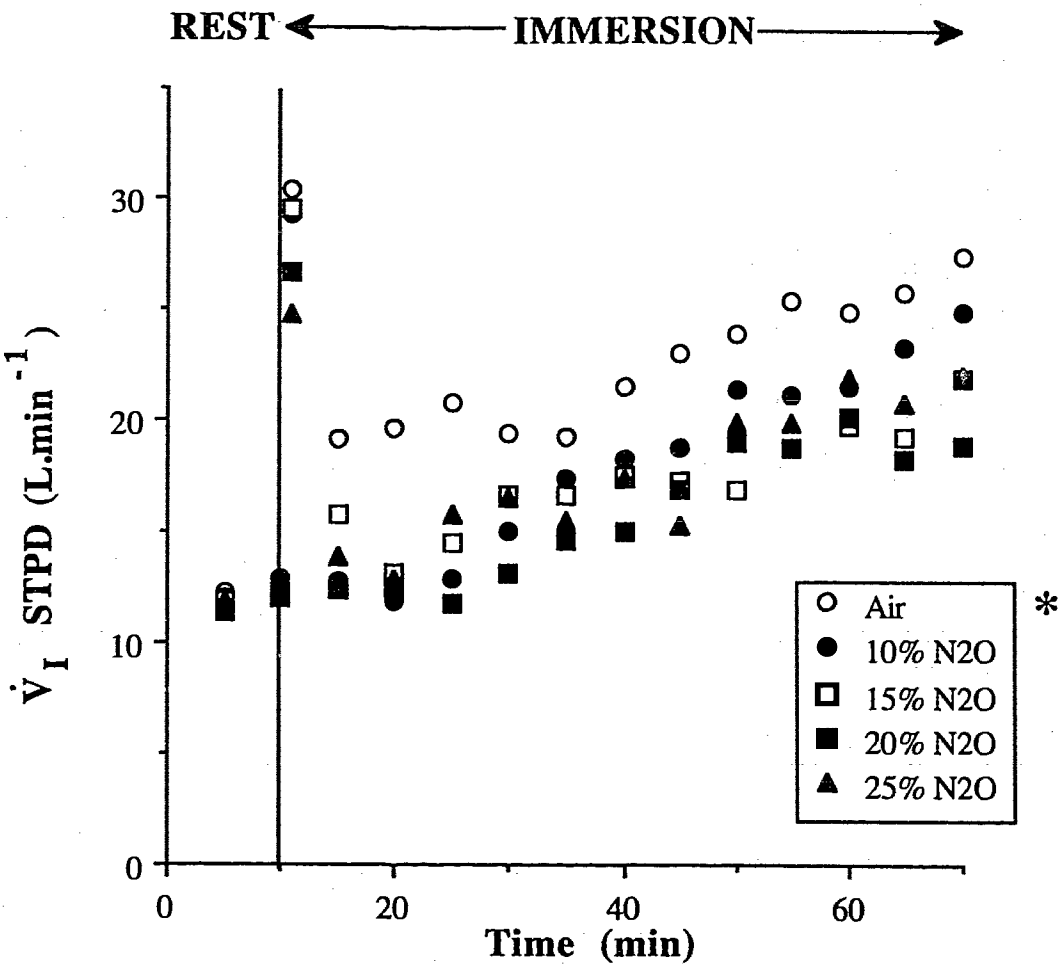

Fig. 4. Mean inspired ventilation ($\dot{V}_I$, STPD) during rest and immersion in AIR, 10, 15, 20, 25% N_2O. * $\dot{V}_I$ was significantly ($p \leq 0.05$) higher in AIR than in any of the N_2O conditions during the immersion phase.

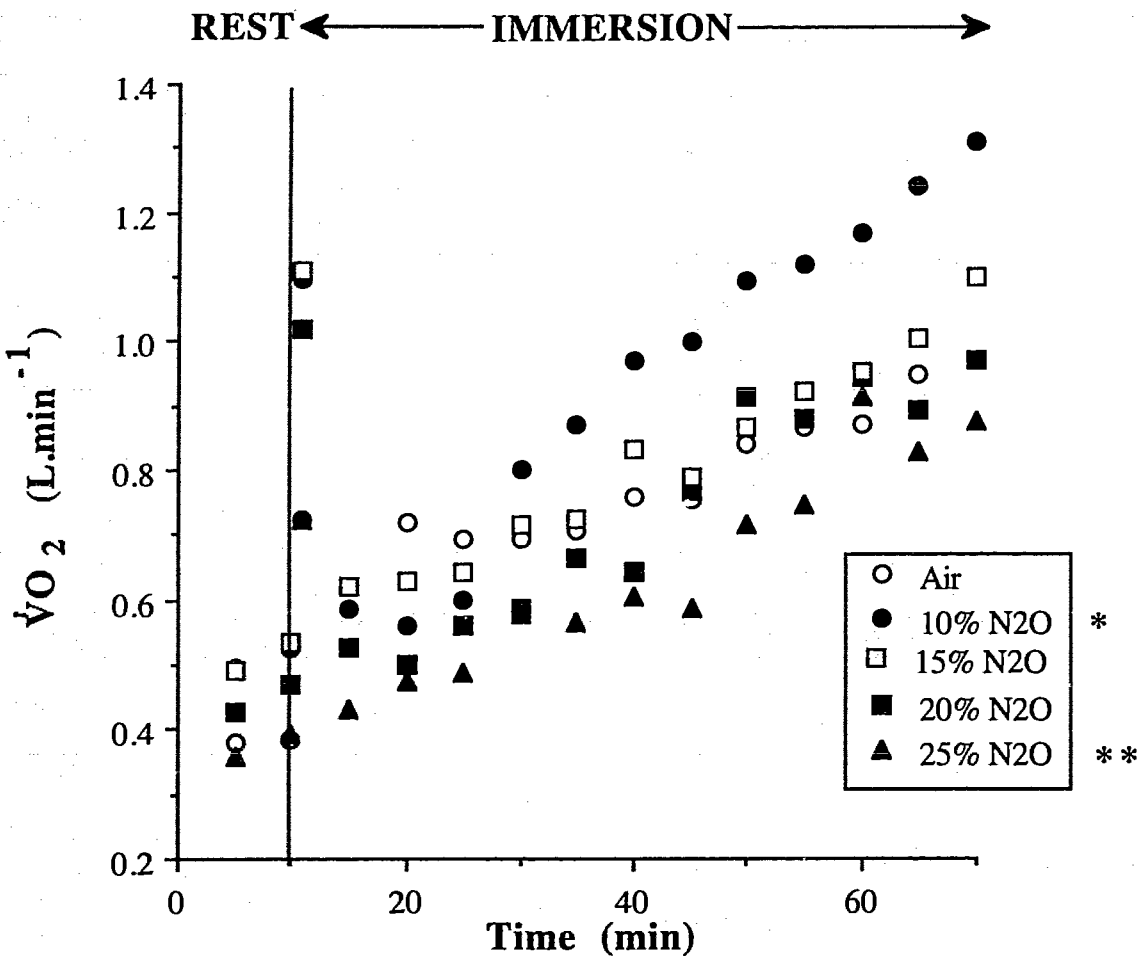

Fig. 5. Mean oxygen uptake ($\dot{V}O_2$) during rest and immersion in AIR, 10, 15, 20, 25% N_2O. * $\dot{V}O_2$ was significantly ($p \leq 0.05$) higher in 10% N_2O than in AIR. ** $\dot{V}O_2$ was significantly ($p \leq 0.05$) lower in 25% N_2O than in AIR. No difference was observed in the slope of the $\dot{V}O_2$ versus ΔT_{es} relationship among the conditions.

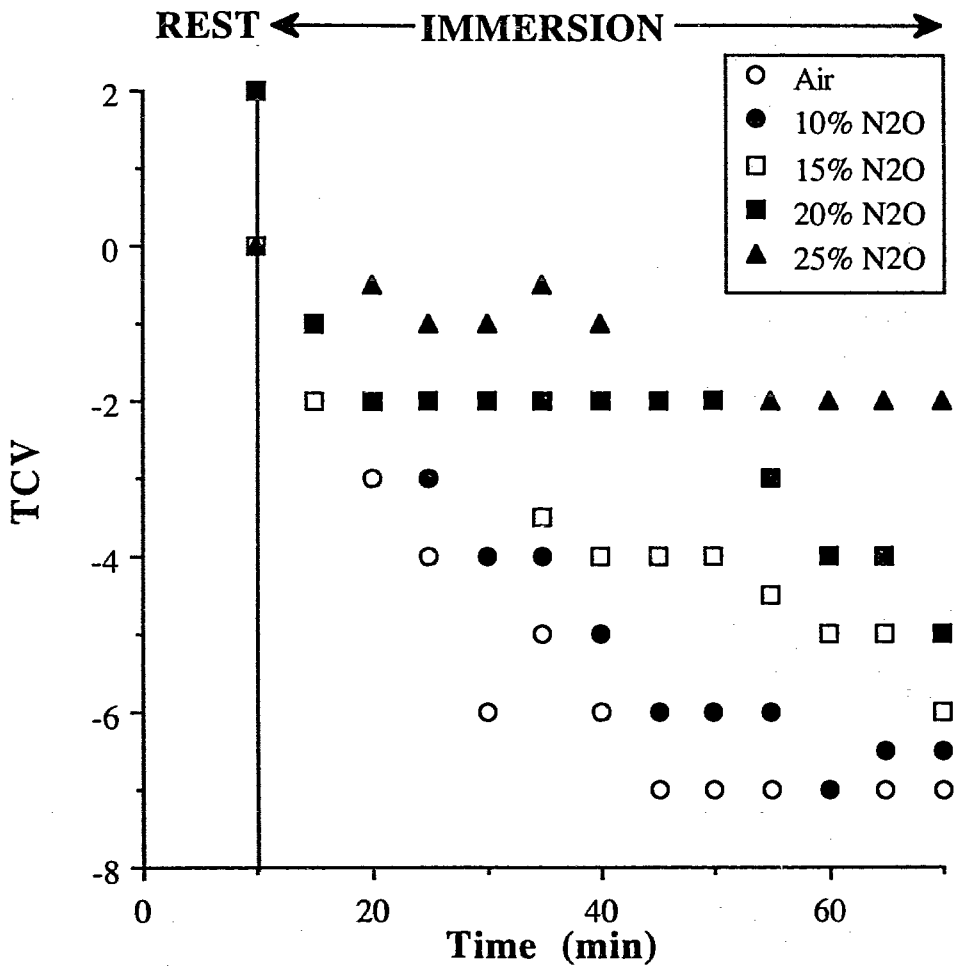

Fig. 6. Median values of thermal comfort (TCV) during rest and immersion in AIR, 10, 15, 20, 25% N_2O. A dose-dependent response of TCV to N_2O concentration was observed ($p \leq 0.001$), with each increase in N_2O concentration increasing TCV.

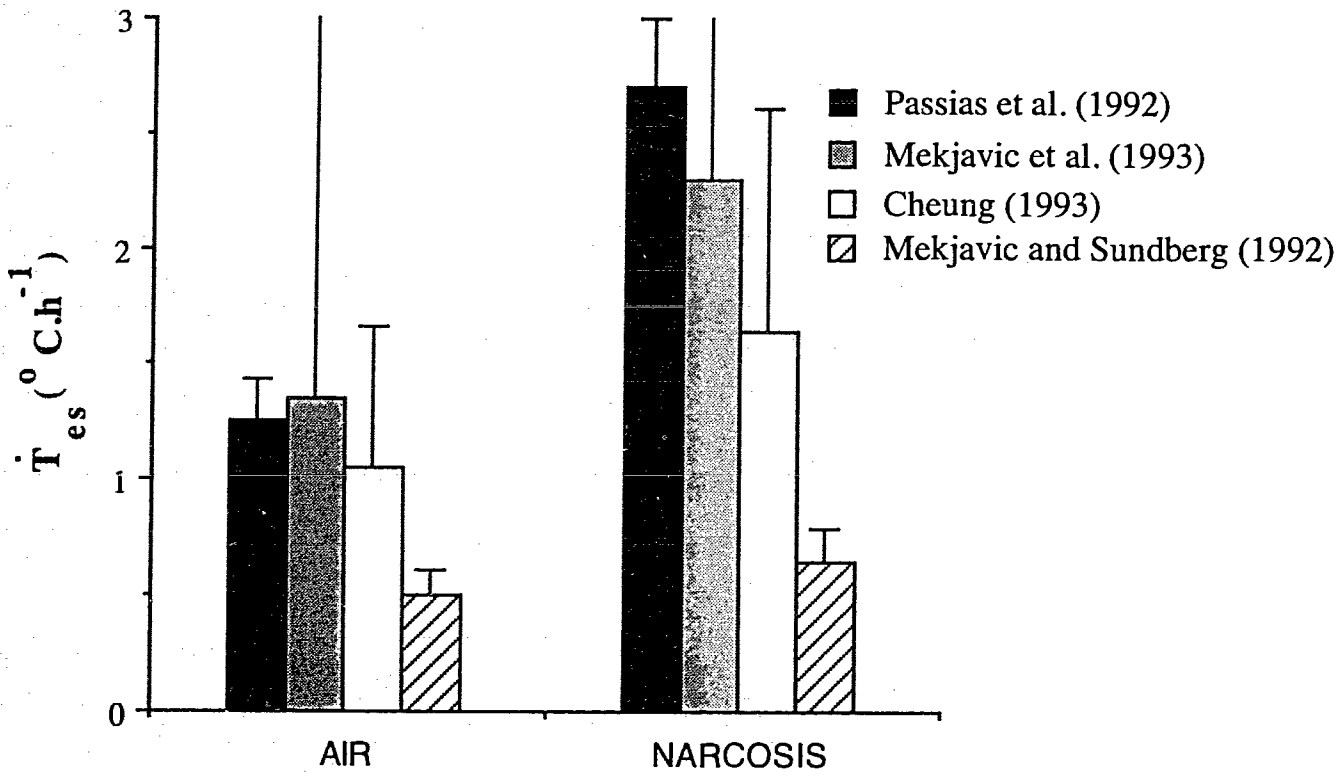

Fig. 7. Mean rate of core cooling ($\dot{T}_{es}$) in 20 °C water in both AIR and 25% N_2O conditions, compared with $\dot{T}_{es}$ as observed in nude head-out immersion in 15 °C (Passias et al. 1992, Mekjavic et al. 1993) and 28 °C (Mekjavic and Sundberg 1992) water. Narcotic conditions were either 30% N_2O (Passias et al. 1992, Mekjavic and Sundberg 1992) or 6 ATA (Mekjavic et al. 1993).