HUMAN THERMOREGULATORY RESPONSES TO COLD WATER IMMERSION DURING COMPRESSED AIR AND NITROUS OXIDE NARCOSIS

by

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HUMAN THERMOREGULATORY RESPONSES TO COLD WATER IMMERSION DURING COMPRESSED AIR AND NITROUS OXIDE ANALGESIA

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ABSTRACT

The thermoregulatory response to cold water immersion was studied in humans exposed to compressed air, and nitrous oxide. A total of 49 healthy subjects of both genders participated in 79 immersions in 4 different studies.

Results demonstrate that a compressed air environment of 6 atmospheres absolute pressure (ata), corresponding to 50.4 meters of sea water, significantly increased the rate of cooling of the body core in subjects immersed in 15°C water. Despite the increased rate of cooling, subjects perceived immersion in a hyperbaric environment as thermally more comfortable than at 1 ata. This suggests, that not only the autonomic response to cold but also perception of thermal comfort is affected in a hyperbaric environment. It was also shown that 100% oxygen breathing did not significantly alter the thermoregulatory response in subjects immersed in 20°C water at 1 ata. Since oxygen *per se* did not affect the thermoregulatory response, the increased cooling rate and improved thermal comfort at 6 ata were attributed to the nitrogen narcosis associated with compressed air breathing.

When subjects inspired air at 1, 3, 5 ata and 30% nitrous oxide (N_2O) at 1 ata while immersed in 15°C water, the core temperature precipitating the onset of shivering and the perception of thermal comfort were both related to the degree of narcosis. With an increase in narcotic potency of the breathing gas (measured as the partial pressure of N_2 and N_2O), a decrease in shivering threshold and an improved perception of thermal comfort was observed. There was no change in metabolic gain, $\Delta \dot{V}O_2/\Delta T_{es}$, (where $\Delta \dot{V}O_2$ and ΔT_{es} represent the change in oxygen consumption and the change in esophageal temperature respectively) in 3 and 5 ata air, but the gain was depressed in the 30% N_2O condition.

A linear regression model based on body physique, water temperature and the narcotic potency of the breathing gas was developed for predicting cooling rates during

diving. To identify the anthropometric measures which would give the best prediction of the core cooling rate, 43 raw and derived anthropometric measures from 49 subjects were subjected to regression analysis. The 4 anthropometric measures which together gave the best prediction were: medial calf skinfold thickness, medial calf girth, acromial height and tibial height. The linear regression model derived in this way was compared with a non linear model developed using an artificial neural network (ANN) having the same input variables. The non linear model did not perform better than the linear regression model. Using the experimental data a regression model was also developed to predict the survival time of nude humans during head out immersion in cold water, based on body physique and water temperature.

DEDICATION

To my parents Milica and Dragutin Savić,

for their love and support,

for believing in me,

and for letting me go after all my dreams.

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PREFACE

This thesis examines the effect of compressed air, and nitrous oxide breathing on the thermoregulatory response, and on the perception of thermal comfort of humans immersed in cold water.

This thesis is based on the following studies, which are referred to in the text by their Roman numeral (I-IV):

I: Breathing air at 6 ata increases the rate of core cooling and suppresses the perception of thermal discomfort in humans immersed in cold water

II: The thermoregulatory response of humans to cold water immersion during hyperoxia

III: The thermoregulatory response of humans to cold water immersion during compressed air breathing and inhalation of 30% nitrous oxide

IV: The prediction of body core cooling rate and survival time of humans immersed in cold water

ABBREVIATIONS

SSR	sum of square residuals
MSE	mean square error
atm	atmospheres of pressure (not a standard SI unit) 1 atm = 101.325 kPa
ata	atmospheres of absolute pressure
N_2O	nitrous oxide, laughing gas
ANN	artificial neural network
CG	medial calf girth
MCSF	medial calf skinfold thickness
ACHT	acromial height
TBHT	tibial height
msw	meters of sea water (10.08 msw = 1 atm)

INTRODUCTION

Hypothermia during diving is usually attributed to a convective/conductive heat loss from the body surface (Bridgman 1990, Webb 1982, 1970) and the respiratory tract (Piantadosi et al. 1981). In divers, mild hypothermia will produce fatigue and impaired cognition and, if it progresses into severe hypothermia, may ultimately result in death (Keatinge et al. 1980). In a high heat loss environment, such as a hyperbaric environment, an appropriate behavioral response, which relies on a subject's perception of thermal comfort (Fanger 1970), is essential for maintaining thermal balance. Padbury et al. (1987) observed that a diver conducting a simulated wet dive in a hyperbaric chamber was unaware of his falling body temperature and thus did not elevate the temperature of his breathing gas or exhibit any thermogenic response. Though this "silent" hypothermia has been suggested to be a consequence of the slow nature of core cooling and the inability of the core sensors to detect the slow cooling of the core (White et al. 1980, Hayward and Keatinge 1979), there is a paucity of data regarding the possible inhibition of the autonomic nervous system response, normally activated to maintain thermal stability of the core region.

Clinical studies indicate that volatile anesthetics produce a thermoregulatory inhibition in humans by decreasing the core temperature threshold for vasoconstriction and for shivering and thus affect a subject's ability to initiate an effective countermeasure which would prevent a progression to hypothermia (Giesbrecht 1994, Lopez et al. 1994, Vassilieff et al. 1994, Kurz et al. 1993, Sessler 1991, Hammel 1988). A similar observation of shivering suppression produced by a sub-anesthetic level of nitrous oxide in cold, immersed subjects has been made by other investigators (Cheung 1993, Mekjavic and Sundberg 1992, Passias et al. 1992).

In view of the above evidence, it is hypothesized that hypothermia among compressed air divers involves more rapid core cooling rates, attenuated heat production

and altered perception of thermal comfort due to inhibition by elevated partial pressure of nitrogen.

SCIENTIFIC BACKGROUND

I. Thermal problems during cold water immersion

Clinical hypothermia is defined as a body core temperature, measured rectally, below 35°C. An individual with a core temperature of 32°C to 35°C may be considered mildly hypothermic, with a core temperature of 28°C - 32°C moderately hypothermic and with a core temperature less than 28°C severely hypothermic (Ferguson et al. 1983). However, the chilling of the body depends on many circumstances: initial body thermal state, body shape, wet or dry conditions and whether the individual is protected or unprotected. Therefore any drop of temperature below the temperature which is considered normal for the particular situation and body state should be taken seriously.

There are four distinct modes of heat transmission which are recognized in the study of heat transfer in human physiology: conduction, convection, radiation and evaporation. Heat loss by convection from the body surface is a major pathway in normal air environments, and respiratory heat loss is usually no more than about 10% of metabolic heat production, even in very cold air. During head out water immersion, heat loss through the skin represents the major heat drain, enhanced by water movement, whereas radiant and evaporative heat loses are negligible.

Cold water exposure immediately increases the rate of heat loss from the skin, which causes a decrease in skin temperature. The physiological response to this is vasoconstriction of the cutaneous blood vessels, which causes the skin temperature to fall even faster, because it is no longer being warmed from within (Webb 1993). Peripheral vasoconstriction is not uniform and has been reported to be more pronounced in the extremities, than in the trunk and head region (Schvartz 1970, Nunneley et al. 1971). Besides vasoconstriction, which is mediated by sympathetic nerves releasing norepinephrine, there is also a direct effect of cold on the superficial blood vessels. The

result is conservation of heat as the result of smaller temperature gradient between the skin and water, reducing the heat flow (Ozaki et al. 1994, Sessler et al. 1990a). This is an important physiological response to cold exposure, presumably, because preserving heat is more efficient than generating it. Concomitantly, heat from the deep body tissues continues to pass by direct conduction towards the surface, aided by circulation from the deeper structures. In resting humans, the cooled shell becomes larger and larger and the relatively warm and stable core becomes smaller and smaller. A further response is an increase in metabolic heat production and an increase in muscle tension, which is soon detected as visible shivering. Shivering is believed to occur when maximal vasoconstriction and behavioral actions are insufficient to maintain thermal balance. If heat conservation through vasoconstriction and increased heat production from shivering are not sufficient to produce a thermal balance, the end result is a drop in core temperature, leading to hypothermia (Webb 1982, Bligh 1973, Hemingway 1963).

The initial hyperventilation at the onset of immersion is accompanied by a two- to three-fold increase in metabolic rate which declines to the resting value after one to three minutes (Martin and Cooper 1981, Cooper et al. 1976). This response is more marked at a lower water temperature (Cooper et al. 1976) and is attributed to the cold peripheral stimulus only, since no change in the core temperature is simultaneously observed. After this initial response, metabolic rate increases again, as core temperature begins to fall. Shivering is controlled by the sympathetic nervous system, as the descending tract of the shivering pathway originating from the posterior hypothalamus becomes activated.

When peripheral cooling is caused by cold water immersion, peripheral vasoconstriction is accompanied by an elevation in heart rate, together with elevation in arterial and venous blood pressure. The initial increase in the heart rate is followed by a decrease to a level slightly above the resting value. With the onset of shivering and increased need of oxygen by the muscles, the heart rate increases again. There is also a shift in blood volume from the periphery to the thorax, due to hydrostatic forces, causing

an increase of hyperosmolar fluid in the intravascular space (Khosla and DuBois 1981, 1979). This shift of blood from peripheral to central circulation is detected by low pressure receptors which initiate a reflex that suppresses vasomotor tone in the extremities and kidneys. Therefore, a hydrostatic expansion of the central blood volume tends to counteract the increased vascular resistance caused by the release of norepinephrine in response to stimulation of cutaneous cold receptors.

II. Thermal problems in a hyperbaric environment

During diving, the inspired gas becomes denser as pressure increases resulting in higher heat capacity and higher thermal conductivity, due to humidification and warming of the dry compressed gas obtained from a cylinder, which eventually becomes similar in temperature to the surrounding cold water (Webb 1970, Raymond et al. 1968). Respiratory heat loss increases many times during deep diving, where a helium-rich gas is breathed because of its high thermal coefficient (Piantadosi et al. 1981). However, during diving with compressed air the major heat loss is convective/conductive heat loss from the body's surface to the cold water (Webb 1982).

Narcotic effect of a hyperbaric environment

Breathing air at greatly increased ambient pressure results in signs and symptoms of narcosis such as euphoria, confusion, neuromuscular incoordination, and impaired performance (Adolfson 1965, Behnke et al. 1935). The extent of the narcosis at a given pressure is dependent on the relationship between the alveolar PCO_2, PO_2 and PN_2. In particular any increase in CO_2 level will potentiate narcosis (Hesser et al. 1978), as will increase in the PO_2 of the breathing mixture. Thus, at constant PN_2 an increase in PO_2

will produce greater narcosis and more impaired performance (Frankenhauser et al. 1963). Most of the studies have focused on the effect of narcosis on complex behavior such as cognitive processes, reaction time and dexterity and they were often performed at higher pressures than those used in compressed air diving (Abraini and Joulia 1992, Fowler et al. 1985).

Opinions differ regarding the causes and mechanisms of this narcosis. It has been suggested that the narcosis may be the result of pressure *per se* (Shilling 1937), the raised partial pressure of oxygen (Damant 1930, Bennett and Ackles 1969) or a raised CO_2 tension in the tissues due to hypoventilation and impaired CO_2 elimination (Bean 1950). However, most investigators consider the raised partial pressure of nitrogen and its affinity for lipid to be the principal cause (Bennett and Blenkarn 1974, Case and Haldane 1941, Behnke et al. 1935) on the basis of the Meyer-Overton hypothesis (Meyer 1899).

Nitrogen effect

In 1935, Behnke and coworkers attributed compressed air narcosis to the raised partial pressure of nitrogen. They characterized the narcosis as "euphoria, retardment of the higher mental processes and impaired neuromuscular coordination". Signs and symptoms begin to be noticed at about 30 meters of sea water (msw) and become increasingly more severe the greater the depth (Bennett 1993). Currently, the following are recognized as symptoms of nitrogen narcosis and are similar to those induced in anesthesia and hypoxia in aviators: slowing of mental activity, delay in auditory and olfactory stimuli, impairment of memory, change in sense of time, impaired ability to carry out fine movements, and at depths greater than 300 feet, possible loss of consciousness (Bennett 1993). The contribution of N_2 to the observed narcosis is demonstrated by the elimination of the signs and symptoms of narcosis, when nitrogen is substituted with helium (Behnke and Yarbourgh 1939) or hydrogen (Brauer et al. 1966).

Oxygen effect

Any compressed air environments is hyperoxic, such that breathing air at 5 ata (40.32 msw) is similar to breathing 100% O_2 at 1 ata (0 msw). The effects of hyperbaric oxygen at increased pressures have been recognized primarily as toxic rather than narcotic and may lead to convulsions or pulmonary damage. Indications of its narcotic properties have been based mainly on studies of isolated tissue or small animals (Perot and Stein 1959), which report an effect of PO_2 on transmission and a reversible block of action potential conduction at a high oxygen pressure (13 atm). Study of auditory responses in the brain of humans breathing hyperbaric oxygen in Heliox (He - O_2) mixtures at pressures not sufficient to produce convulsions, showed depression of auditory responses without affecting mental performance (Bennett and Ackles 1969). Since helium does not have narcotic properties, this decrement was attributed to oxygen. It was also demonstrated that oxygen and nitrogen have a synergistic interaction at elevated pressures, evidenced by deterioration of psychomotor performance (Hesser 1978, Bennett and Ackles 1969, Bennett 1965, Frankenhauser 1963, Damant 1930).

Carbon dioxide effect

One theory infers that due to the increased density of the breathing gas, there is respiratory insufficiency leading to carbon dioxide retention, and this increased carbon dioxide tension is the cause of narcosis (Bennett 1965, Diji 1959, Bean 1950). Other researchers, however, suggest that the combined effects of high partial pressures of CO_2 and N_2 are additive and much more severe than those of either alone (Hesser et al. 1971, Case and Haldane 1941). Hesser et al. (1971) have shown that carbon dioxide is not the cause of compressed air narcosis at alveolar CO_2 tensions below 40 mmHg. Lun (1992)

has also demonstrated that an isolated increase in PCO_2 in the breathing mixture under normobaric conditions has no demonstrable effect on the shivering response or cooling rate in cold immersed subjects.

Mechanisms and site of action of inert gas narcosis

Inert gases are defined as gases which exert their biological effect without undergoing any change in their own chemical structure or chemically modifying the biological system they are acting upon. Such gases are nitrous oxide, ethylene and cyclopropane as well as nitrogen, helium, neon, argon, krypton and xenon (Featherstone and Muehlbaecher 1963). Although several of those gases are anesthetic at less than 1 ata, all except helium and neon have been shown to produce "narcosis" at elevated pressure. Definition of the terms "narcosis" and "anesthesia" is not easy and as cited in (Featherstone and Muehlbaecher 1963) "... vagueness and multiplicity of meanings are so firmly established in the usage of 'narcotic' and 'anesthetic' as to render futile any insistence on rigid definitions, even for technical purposes." It would seem that such insistence belongs to the sphere of semantics. In this thesis, the terms narcosis and anesthesia are both used and, in most cases, the term used is that preferred by the author whose paper is reviewed.

The anesthetics used in clinical practice such as nitrous oxide, ethylene and cyclopropane are considered inert (Featherstone and Muehlbaecher 1963), and seem unlikely to have a different mechanism of action from N_2 (Carpenter 1954). However, the concentration of those anesthetics, used clinically, far exceeds the narcotic potency produced by the partial pressures of gases experienced in compressed air diving.

The site and mode of action of narcosis with N_2O may be quite distinct from that of hyperbaric N_2 and thus, studies examining the effect of anesthesia on autonomic function in humans may not be applicable to compressed air diving. Nevertheless, comparative behavioral studies using nitrous oxide and hyperbaric air have shown that

30% N_2O in a normoxic air mixture induces psycho-motor impairment similar to compressed air at 6.7 ata (Biersner 1987, Biersner et al. 1977). Also Fowler et al. (1980) and Biersner (1972) have demonstrated that N_2O and hyperbaric N_2 exert an identical narcotic effect on memory, auditory perception and other functions involved in skilled performance.

Due to the unreactivity of inert gases, biophysical, rather than biochemical mechanisms of inert gas narcosis have been studied. According to the Meyer-Overton hypothesis (Meyer 1899) the narcotic potency of nitrogen is related to its affinity for lipid or fat. It was suggested that narcosis is most probably due to the penetration of the cell membrane by the anesthetic substance. This led to the more recent theories of the 'critical volume hypothesis' (Miller et al. 1973) and the 'multisite expansion hypothesis' (Halsey et al. 1978) proposing that anesthesia is due to the expansion of a hydrophobic region beyond a certain critical volume, as a result of the absorption of the anesthetic substance. This theory also provides an explanation for the pressure reversal theory, which states that an increased pressure can reverse the signs and symptoms of narcosis. Thus, Lever et al. (1971) hypothesized that 0.4 % expansion of a neuronal membrane could cause narcosis and conversely a 0.4 % contraction of the membrane due to pressure alone could result in the effects described as HPNS (high pressure nervous syndrome). Others suggest that general anesthetics work by binding directly to a protein (which may or may not be membrane bound) and inhibit its normal function, by interfering with its catalytic or transport function or by competing for the binding with a neurotransmitter (Franks and Lieb 1982). Bennett et al. (1967) suggested an increased membrane permeability to cations (Na^+ and K^+) as the primary cause of anesthesia.

Carpenter (1954) has shown that N_2O at 12-13 ata caused decreased excitability, blocked conduction and produced a significant depolarization of isolated rat peripheral nerve. In contrast to Carpenter's findings, Jong and Nace (1967) have suggested that inhalation of an anesthetic has no significant effect on peripheral nerve conduction or the

generation of impulses in cutaneous receptors when an anesthetic is used in clinical concentrations much lower than the concentrations used in Carpenter's study.

These results suggest that anesthetics, similar to the inert gases inhaled at high pressures, most likely act at the synaptic junction, affecting the synaptic transmission within the nervous system. A sensory nerve impulse reaches the cortex either by a direct quick pathway (medial lemniscus, anterolateral system) or by a more central polysynaptic route via the reticular formation. The possibility of N_2O acting centrally is supported by Davis et al. (1957) who showed that by stimulating the nerve of an adult anesthetized cat, the evoked response, produced through the polysynaptic reticular system, was depressed to a greater degree by an anesthetic than a response transmitted through the medial lemniscal pathway. Thus, the more synapses involved in a particular pathway, the greater will be the distortion of the information and consequently the elicited response (Eger 1974, pages 48 - 50).

Effect of anesthetic agents on autonomic thermoregulation

It has been shown that anesthetic agents in general, and N_2O in particular, inhibit the thermoregulatory response in animals (Hammel 1988) and humans (Giesbrecht 1994, Lopez et al. 1994, Vassilieff et al. 1994, Kurz et al. 1993, Cheung 1993, Mekjavic and Sundberg 1992, Passias et al. 1992, Sessler 199, Sessler et al. 1988 a, b). Passias et al. (1992) and Mekjavic and Sundberg (1992) immersed subjects in 15°C and 28°C cold water respectively, breathing air and a 30% N_2O gas mixture. The attenuation of shivering thermogenesis was indicated by depression of oxygen uptake by 40% and a shift in the threshold for the onset of shivering towards a lower core temperature.

N_2O may increase the sympathetic outflow from the brain and inhibit removal of norepinephrine by the lung. In intact humans and animals this sympathetic stimulation, coupled with a mild capacity to produce direct depression, results in comparatively little

cardiovascular depression at both analgesic and anesthetic (1-1.5 atm) partial pressures. The absence of a marked depression of myocardial contractility and blood pressure distinguishes nitrous oxide from other more potent inhaled anesthetics.

Adding N_2O to a more potent anesthetic may reduce circulation, perhaps because narcotics block the sympathomimetic effects of nitrous oxide. Nitrous oxide may depress the heart directly while indirectly stimulating the heart by central activation of the brain nuclei that control beta - adrenergic activity (Fukunaga and Epstein 1973). Sympathetic stimulation also may result because N_2O inhibits the uptake of norepinephrine by the lung (Naito and Gillis 1973). Therefore, more of the norepinephrine released into the venous circulation will be available to act on the systemic circulation, causing vasoconstriction.

Although the evidence for and the importance of non shivering thermogenesis in adults remains scarce and inconclusive, the findings of Jessen et al. (1980) seem to support its existence in humans. An increase in oxygen uptake in curarized subjects exposed to cold observed by Jessen et al. (1980) was attributed to non shivering thermogenesis. Stjernstrom et al. 1985 showed that the catecholamines concentration in blood, which is correlated with shivering thermogenesis Jessen et al. (1980), was increased post operatively compared with the concentration during anesthesia, for the same core temperature. The increase of the catecholamine concentration during the post operative stage was concomitant with a 40% rise in oxygen uptake which probably reflected the thermogenic effect of the catecholamines. Since the authors did not comment on shivering during the post operative stage, a conclusion regarding the effect of anesthetics on catecholamine secretion and on the non shivering thermogenesis can not be drawn. Attenuation of nonshivering thermogenesis in humans during anesthesia have been also observed by Hynson et al. (1993) and Ohlson et al. (1994).

The fact that an anesthetic agent acts primarily on the synaptic connection suggests that higher centres would be impaired first due to their polysynaptic pathways

(Eger 1974) and the regulation of body temperature would be assumed by lower centres, which do not have the capability for fine, narrow band regulation because of their simpler neural arrangement (Satinoff 1978).

The effects of N_2 narcosis during compressed air breathing or inhalation of N_2O, could be mediated by the thermoreceptors, by the thermoregulatory centres in the CNS, by lower extrahypothalamic centres, by the polysynaptic pathway from the thermosensors to the thermoregulatory effectors or by the effectors itself, and could be expressed as an overall depression of neuronal conduction and synaptic activity (Fig. 1).

Besides the imposed cold thermal stress, there are other 'non thermal' factors that can affect the heat production pathway. Anesthesia has been discussed in detail. Other factors which are known to suppress shivering include: drugs (such as anti-pyretics), alcohol (Fowler et al. 1987), hypoglycemia (Passias 1993, Gale et al. 1981), isometric muscular contractions (Martin and Cooper 1981), increasing the intensity of exercise during shivering (Hong and Nadel 1979) and repeated exposure to cold (Rochelle and Horvath 1978).

III. Models of the human thermoregulatory system

Humans regulate temperature by comparing the afferent thermal input from the periphery i.e. skin surface, deep abdominal and thoracic tissues, and from regions of the central nervous system, i.e. the hypothalamus and spinal cord, with threshold values (analogous to a "set point" in an engineering control system). When an integrated thermal input exceeds the warm response threshold sweating and active capillary vasodilation are initiated in an effort to prevent further hyperthermia. Similarly, a body temperature lower than the cold response threshold triggers vasoconstriction, non shivering thermogenesis, and shivering, which act together to minimize further hypothermia. The

rate at which the intensity of response increases as body temperature deviates progressively from the triggering threshold is the thermosensitivity (analogous to the "gain" in an engineering system). At some point each response reaches its maximum and further deviation from the threshold temperature produces no increase in response intensity. The difference between the lowest warm and the highest cold threshold temperatures is the *inter threshold* range, typically 0.4°C (Sessler 1991). A thermoregulatory response does not occur within this range, although humans can detect a temperature change as small as 0.03°C.

Two approaches to modeling are possible. One consists of writing theoretical equations for the physiological processes of temperature regulation. The other approach is the empirical one, deriving a cause-effect relationship from experimental data, because the actual phenomena are not well understood. Alternatively a combination of these two approaches may be attempted. Neural phenomena are generally modeled by the empirical approach, but often there is not enough satisfactory experimental data for such modeling. For example, some data are available about the transfer characteristics of sensory neural receptors, but a model cannot yet be developed with the confidence that it will explain an observed phenomenon. Detailed knowledge and data about afferent pathways to CNS nuclei are even scarcer, and in general CNS integrative sites are represented by a "black box" in cybernetic systems. More experimental data are available about efferent signals from the CNS to sites such as muscles and glands, but there is still insufficient biophysical knowledge for *a priori* modeling.

Whereas most thermal models incorporate a single integrator, Satinoff (1978) proposed a hierarchical organization of thermoregulatory control, with multiple inputs and outputs, which developed a progressively more effective, complex and finer control during the course of evolution with the highest centre located in the hypothalamus. The hypothalamus is mainly described as responsible for regulating the threshold for the initiation of the thermoregulatory response, while thermosensitivity and maximal

intensity of the response could be regulated at a lower level within the central nervous system, possibly in the medulla and spinal cord, both of which have less complex synaptic connections (Sessler 1991). Satinoff has suggested that progressive widening of the thermoneutral zone may be expected with removal of higher structures in the thermoregulatory neuraxis, due to the hierarchical arrangement of parallel integrative systems involved in temperature regulation.

Neuronal model

In 1906 Sherrington introduced the concept of crossed inhibition in biological control systems. This concept may be represented by a simple neuronal model with two direct thermal pathways between temperature sensors and thermoregulatory effectors (Fig. 2). One of these direct pathways was from warm sensors to the heat loss effectors and the other was from cold sensors to the heat production effectors with crossed inhibitory connections between them (Bligh 1973). Thus, the observed response of heat production is a direct consequence of excitation from central and peripheral neural structures and crossed inhibition from heat loss centres which occurs in the afferent pathways. Such a model demonstrates that crossed inhibition of thermal afferent information will establish a threshold for the individual effector response. In this case a stabilized body temperature might be a consequence of the balance between opposing forces of heat loss and heat production thus eliminating the need for a comparator or "set point".

Mathematical models

Existing physical models for human temperature regulation describe the human body as either an infinite multilayer slab (Crosbie et al. 1961), one multilayer cylinder (Atkins and Wyndham 1969), or several interconnected cylinders (Tikuisis et al. 1988, Wissler 1964).

Mathematical models based on such assumptions involve highly nonlinear equations of heat and mass flow according to thermodynamic laws (Montgomery 1974, Nadel 1970, Wyndham and Atkins 1968, Stolwijk and Hardy 1966). Physical and mathematical models are essentially a description of transient adjustments in heat production, flow and distribution which operate to maintain thermal equilibrium at an approximately constant deep body temperature despite external temperature perturbations. However, even the most complex of these models is barely adequate to describe the relations between disturbance and response.

Engineering analogs, such as threshold (set point) and thermosensitivity (gain) are useful in describing the observed thermoregulatory response and predicting the intensity of it under a variety of circumstances.

Despite an extensive literature on body temperature regulation, the nature of the actual regulator, or set point determinant remains a subject of controversy. The hypothalamic structure of the brain concerned in the control of the body temperature is rather like the sealed control unit: it can not yet be examined in sufficient detail to reveal how it actually operates, but the relations between thermal disturbance and thermoregulatory response may be compared with the temperature controllers used in physical systems.

The essential features of a system which automatically regulates temperature at, or close to, a set level are shown diagrammatically in Fig. 3. The basis of regulation is the existence of a constant reference signal which constitutes a set point close to which the controlled variable is maintained. The disturbance to the controlled system (the balance between the rate of heat production and a heat loss) causes a change in the controlled variable (a core temperature sensed by hypothalamic temperature sensors). This change in the controlled variable is detected by temperature sensors which give rise to a signal which is fed to a comparator, where it is compared with the reference (or set point) signal.

Any error between the reference signal and that from the sensors of the controlled variable results in an adjustment in the rate of heat production and/or heat loss.

All these features except the set point are recognizable in a diagrammatic representation of the physiological thermoregulatory system by Cremer and Bligh (1969; Fig. 2). Here it is presumed that the controlled variable is the temperature of the arterial blood leaving the heart. Any alteration to the rate of heat production or heat loss has an immediate effect on the temperature of the venous blood draining from involved tissue. The venous streams at different temperatures become well mixed in the heart and lungs, and the shift in the balance between heat production and heat loss results in a rapid change in the temperature of the arterial blood which is distributed to all parts of the body. Wherever the temperature sensors are located, they will be affected by this shift in balance. Thus, the circulating blood provides information of the controlled variable to the sensors. The signal from the sensors is fed back to the hypothalamic controller via afferent neural pathways, and gives rise to an appropriate change in the efferent signals to the effectors.

Physical and mathematical model of the relation between disturbance and response in the autonomic system is a gross oversimplification. The relation between temperature sensors and thermoregulatory effectors is almost certainly influenced by a great number of circumstances not directly related to the temperature.

Models of physiological functions must be made as simple as possible in the first place in order not to obscure a basic features since all functions of the human body are interrelated to a greater or lesser extent. Linear regression models are simple descriptions of the relations between the disturbance and response in very restricted experimental circumstances, but they afford good insight into the nature of the neuronal control responsible for this relation and the resultant control of body temperature. Such models (Timbal et al. 1976, Hayward et al. 1975, Hall 1972, Smith and Hames 1962) can be applied in several ways. They assist in optimizing the design of laboratory experiments

and field studies and may be used in real time to help make a rational decision about termination of a hazardous search and rescue effort.

Modeling the cooling rate

The heat which is lost from the body to the environment during cold exposure, is conducted through the layers of muscle, subcutaneous fat and skin. The amount of heat loss depends on the temperature gradient between the skin and environment, the composition, and thickness of the peripheral layers of the tissue, and the geometric shape and surface area across which heat is dissipated. Thermal conductivity of fat is approximately half that of muscle. During a period of cold stress, thermal insulation is increased by reducing blood flow to the periphery, thus reducing the heat transfer from the core to the periphery. The bloodless muscles then act in series with subcutaneous fatty tissues and skin to provide maximal insulation (Ducharme and Tikuisis 1991, Park et al. 1984, Veicsteinas et al. 1982). Park et al. (1982) concluded that during a rest period muscle can contribute more than half of the total insulation. However, during exercise that insulation can be totally lost. The rate of core cooling is, therefore, very often modeled as being inversely related to the thickness of adipose tissue (White et al. 1991, Sloan and Keatinge 1973, Keatinge 1960). The relationship between surface area (A) and cooling rate depends on the way A is determined. Most investigators use the formula of DuBois and DuBois (1916) where A is a function of height and weight raised to a power and multiplied with a constant. Theoretically, subjects with a larger surface area should dissipate more heat in a cold environment and should cool faster. Also, subjects with greater surface area typically have greater mass, and more potential for heat generation with shivering as well as more insulation (McArdle et al. 1984). Kollias et al. (1974) used the surface area/mass (A/M) ratio to demonstrate that the increase in metabolic rate and cooling rate were significantly greater in persons with a higher A/M ratio. Therefore,

women with considerably higher A/M and similar percentage body fat than men, were found to cool more quickly. Others, however, have found that A/M affects the cooling rate minimally (White et al. 1992, Toner et al. 1986).

Predictive models of cooling rate maybe nonlinear (Wissler 1985, Tikuisis et al. 1988) or linear models (Timbal et al. 1976, Hayward et al. 1975, Hall 1972, Smith and Hames 1962). Tikuisis et al. (1988) demonstrated that the predictive ability of a model improved with inclusion of morphology as a variable in the model's structure. In this thesis two approaches were used in predicting the cooling rate of subjects immersed in cold water: a linear approach using linear regression and a nonlinear approach, using a neural network. Both models are based on body physique and water temperature.

IV: Summary

In the existing literature there is a paucity of data regarding the thermoregulatory response of a human exposed to cold water immersion in a compressed air environment. Studies on the narcotic effect of hyperbaric N_2 are mainly cncerned with psychomotor performance and there is little information on the effect of narcosis on thermoregulatory, autonomic and behavioural responses. Whether an altered thermal response can be attributed to the narcotic effect of hyperbaric N_2 and/or hyperoxia, associated with compressed air breathing, is not clear. Studies comparing the narcotic effects of hyperbaric N_2 and clinically used anesthetics, such as N_2O, are limited to psychomotor performance. The influence of these agents on the thermoregulatory, autonomic and behavioural response has not yet been established. Finally, since the cooling rate of subjects immersed in cold water will depend on body composition and shape as well as on the water temperature, a model for prediction of survival times in cold water should account for the effect of body physique.

AIMS OF THE PRESENT STUDIES

The four studies presented in this thesis examine the effect of compressed air and nitrous oxide on thermoregulatory response and the perception of thermal comfort of humans immersed in cold water.

The specific aims of the Studies I, II, III and IV were as follows:

- to investigate whether the autonomic thermoregulatory response and perception of thermal comfort are altered in a hyperbaric environment (I);
- to determine whether an increase in cooling rate and suppressed perception of thermal discomfort observed at 6 ata is due to the effect of an increased PO_2 associated with compressed air breathing (II);
- to assess whether an increase in atmospheric pressure affects shivering thermogenesis in subjects immersed in cold water (III);
- to assess whether the effect of increased PN_2 on shivering, cooling rate and perception of thermal comfort are dose dependent (III);
- to compare the narcotic effects of PN_2O and PN_2 on thermoregulation (III);
- to determine whether morphological and gender differences affect physiological reaction to thermal stress (IV);
- to develop a regression equation based on body physique, water temperature and narcosis level to predict the cooling rate of nude humans during diving (IV);

- to develop a regression equation based on body physique and water temperature to predict the survival time of nude humans during head out immersion in cold water (IV).

MATERIALS AND METHODS

This section outlines general methods common to all four experimental studies. Details of specific methods, protocols and instrumentation are given in each study.

Subjects

Healthy volunteers of both genders were used for the studies. Their participation in the experiment was subject to a doctor's approval. All subjects were familiarized with experimental protocol, which was approved by the institutional Ethics Review Committee. The experimental procedure was thoroughly explained to each subject prior to their participation and informed consent. Subjects were aware that they could withdraw from the study at any time. All subjects participating in a hyperbaric trial had previous experience with compression in a hyperbaric chamber.

Protocol

The same protocol was used in all studies, to simulate the conditions during compressed air diving where divers are not wearing a heated protective dry suit. Subjects dressed only in a swim suit, and sat quietly in a suspended chair in continuously stirred water, immersed up to their neck.

Hyperbaric chamber

The hypo/hyperbaric chamber at School of Kinesiology (Simon Fraser University) consists of 3 interconnected steel-walled pressure vessels: Entry Lock (7.23 m^3), Main Lock (13.8 m^3) and Wet Lock (9.6 m^3). The system is rated to approximately 300 meters of sea water pressure (300 msw or 30 ata) and to 12000 meters above sea level altitude. The chamber is 2 m in diameter and 7.5 m long overall. All immersions in studies I and III were conducted inside the Wet Lock. During the hyperbaric trials all compartments were

compressed. The water temperature was brought to the desired temperature using a cooling/heating unit. Throughout the experiment water temperature remained very close to the initial temperature due to high amount of water in the Wet Lock.

Compression and decompression

During compression, the subject sat on a chair, suspended above the wet lock, with all the probes in place and connected. Compression was conducted at a rate of approximately 1.2 $atm \cdot min^{-1}$. The decompression profile was determined for each dive separately, depending on the bottom time. The profile followed the DCIEM Air Diving Tables and Oxygen Decompression Tables protocol. Decompression time was never longer than the 244 minutes, required to decompress from 1 hour spent at a depth of 50 meters (I). During all decompressions done in Study III, pure oxygen was inspired intermittently at 20 minute intervals to reduce the risks of decompression sickness.

Personnel

During each hyperbaric experiment a qualified diver accompanied the subject inside the chamber. Other research personnel, including a medical doctor and technical staff - two chamber operators, and a back-up diver, assisted with the experiments from outside the chamber.

Rewarming procedures

Upon exiting the cold water, the hydrostatic pressure, which during immersion aids venous return and assists cardiac output, is withdrawn. Therefore the blood which is pooled in the central regions of the body during immersion, returns to the cold extremities, and comes back to the core much colder. The core region of the body continues to cool resulting in a phenomenon called afterdrop. The occurrence of afterdrop may also be explained as a result of heat transfer by physical means and need not to involve the circulatory system. If heat is applied to superficial tissues, the direction of heat flow will

not reverse immediately, and heat will continue to flow outward from warm core areas to cooler outer regions, resulting in an afterdrop. Rewarming in a hot bath (39°C - 41°C) increases the hydrostatic pressure and supports cardiac output. This method of rewarming was possible in normobaric trials. During decompression after a hyperbaric trial, subjects were rewarmed passively in a sleeping bag by endogenous heat produced by shivering. If necessary, subjects continued to be rewarmed in bath after completion of decompression.

Core temperature measuring sites

Core temperature was monitored sites in the present studies from the distal esophagus and 15 cm beyond the rectum. The esophageal probe insertion length was determined from the sitting height following the formula $\mathbf{L_{es} = 0.479 \cdot H_{sit} - 4.44}$ (Mekjavic and Rempel 1990). The distal esophagus is considered the most reliable core temperature monitoring site (Gerbrandy et al. 1954), reflecting the temperature in the pulmonary artery where any change of thermal state of the body is evident within seconds (Rowell 1986, Cooper and Kenyon 1957, Cranston et al. 1954). The rectal temperature is not so sensitive to temperature change and seems higher during the cooling phase than the esophageal temperature (T_{es}) (Mather et al. 1953), and responds more slowly (Molnar and Read 1974) perhaps due to the lower blood flow and better insulation in the visceral area. The temperature reading from the rectal site depends on the insertion length of the probe, the water temperature and the amount of insulation of each subject. T_{es} is able to track a fast change in temperature but fluctuates due to cooling from the alternate expiration of warm air and the flow of cooler air inspired at each breath (Molnar and Read 1974). The validity of prediction of survival time in study IV requires that the core temperature monitoring sites in the distal esophageal and the visceral region be well correlated.

Immersions

All immersions in Studies I and III were conducted inside the Wet Lock of a hyperbaric chamber. Water mixing and flow around the subject, was achieved by placing a loop of perforated Tygon tube on the chamber floor around the subject. The tube was connected to the external cylinder with compressed air. Bubbles of air produced water movement around the subject and maintained a minimal thermal gradient between the skin and water throughout the experiment. The immersions in Study II took place in a water tank measuring 210 x 105 x 210 cm. Water temperature was maintained constant with a cooling/heating unit. Water in the tank was continiously agitated throughout the experiment by a battery powered propeller.

Anthropometric measurements

Anthropometric measurements were made on each subject by a trained anthropometrist. Compressed adipose tissue thickness was determined using the caliper technique at each skinfold site using the same caliper closing pressure. Each measurement was made twice and a mean measure was reported. Anthropometric indexes of ectomorphy, mesomorphy and endomorphy were calculated from a regression equation. Body surface area (A) was estimated from known body height (HT) and weight (WT) using the formula of DuBois and DuBois (1916):

$$A = WT^{0.425} \cdot HT^{0.725} \cdot 71.84 \qquad (cm^2)$$

Measured anthropometric variables were used to calculate the proportinal amount of skin, adipose, muscle, bone and residual tissue mass in each subject according to Kerr (1988).

Perception of thermal comfort

In the present thesis, subjects were asked to rate the magnitude of their thermal discomfort. The thermal comfort vote in these studies reflects a subject's change in perception of thermal comfort as a function of T_{es}, since skin temperature was constant

during each immersion. Subjects rated their perception of their thermal state at 5 minute intervals, on a 21-point scale (Enander et al. 1979), with a middle point 0 defined as thermo-neutral (+10 = very very hot, +8 = very hot, +6 = hot, +4 = moderately hot, +2 = warm, 0 = neither warm nor cold, -2 = cool, -4 = moderately cold, -6 = cold, -8 = very cold, -10 = very very cold). In addition, a 5-point scale (Chattonet and Cabanac 1965) was used for sensation of thermal comfort, where +2 indicates "very pleasant", +1 = pleasant, 0 = neutral, -1 = unpleasant and -2 = very unpleasant. Subjects were first asked to choose a number from a 21-point scale in response to question "how cold are you". In response to second question "how do you feel", subjects chose a number from a 5-point scale. Whereas the first scale evaluates each subject's sensation of thermal comfort, the purpose of the second scale was to evaluate the possible effect of narcosis on perception of cold.

Prediction of core cooling using a nonlinear artificial neural network (ANN)

Heat loss and the metabolic rate of humans exposed to cold depends mostly on the temperature gradient, body surface area and body shape and composition. To develop a predictive model of core cooling as a function of body physique, a nonlinear relationship between the anthropometric variables (i.e. between surface area and height and weight) may be explored. Therefore, two approaches to modeling the cooling rate were used: a linear approach using linear regression and a nonlinear approach, using a neural network.

The theory of the ANN is to define a nonlinear relatinship which is usually hard to define or represent by a mathematical equation. A neural network consists of several layers of artificial neurons with a local memory. The layers connect those neurons that receive the input signals and those that generate the outputs. An example of a neural network with three layers and interconnections between the neurons in those layers is represented in Fig. 4. Each neuron in this network receives signals from all those in the previous layer, reacts to those signals and sends its output to all neurons in the next layer.

The ANN represents a parallel structure since the computations of the components are independent of each other. The way in which a neuron reacts depends upon a weighting factor assigned to each input. The weights define the behaviour of the network but do not have to be specified in advance. Instead, the network is trained on sets of sample data and adjusts its own weights until its responses are judged to be correct (until the error for the entire training set reaches the minimum or when a predetermined number of iterations had been performed). The ability to adjust the input weights gives the neural network learning capability. By training the ANN, a non-linear system can be modeled by properly adjusting weights of connections among nodes in the network.

Back-propagation (of error) is one of the most commonly used learning rules for the layered unidirectional - feedforward neural network (FFNN). Back propagation is an iterative gradient algorithm designed to minimize the mean square error between actual output and the target output. The difference between the output and target vector is fed back through the network and the weights are readjusted in such a way as to reduce the error. This new set of network weights is used to produce a new output vector, which is compared again with the target vector. The weights are readjusted until the error for the entire training set reaches an acceptably low level.

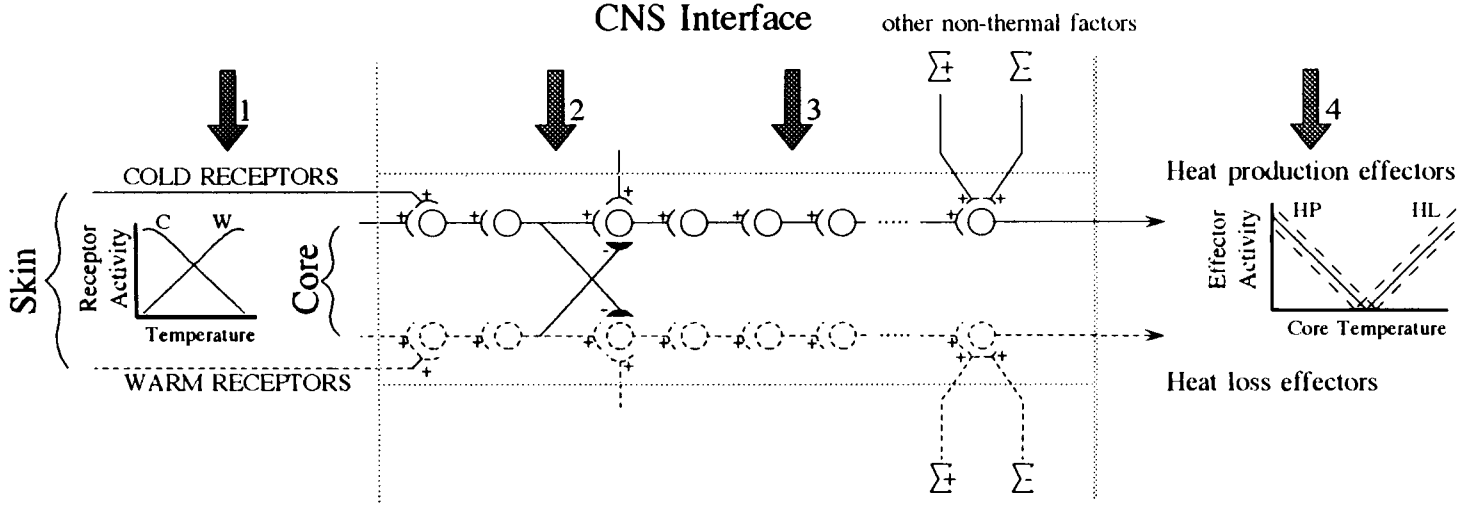

Fig. 1: A composite neuronal model of temperature regulation incorporating the inhibitory influence of anesthesia (adapted from Bligh, 1984). Model presents direct and cross-inhibitory pathways of neural coded information from cold and warm sensors to thermoregulatory effectors. Solid lines represent the afferent pathway to heat production effectors. Σ indicates the summed influence of a large number of converging excitatory and inhibitory influences which, by changing the relationship between sensors and effectors, may cause a change in the width of the thermoneutral zone, as shown on the graph of effector activity vs. core temperature. Big arrows represent possible sites of action of an anesthetic: 1- at the receptor site; 2- at the point of central processing and integrative unit in the hypothalamus; 3- anywhere along the polysynaptic pathway in the CNS outside the hypothalamus; 4- on the effectors (the systemic vessel, skeletal muscle and sweat gland).

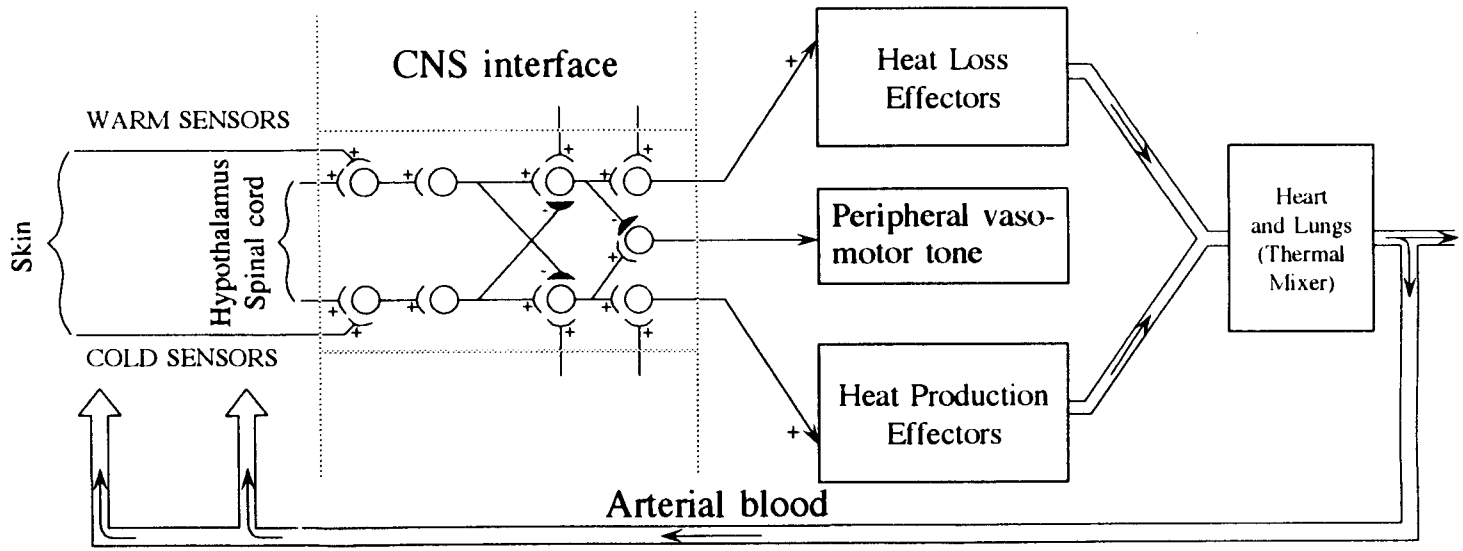

Fig. 2: A diagrammatic representation of the components and pathways of a thermoregulatory system. Single connecting lines indicate nervous pathways. Double lines indicate circulatory pathways (Cremer and Bligh 1969).

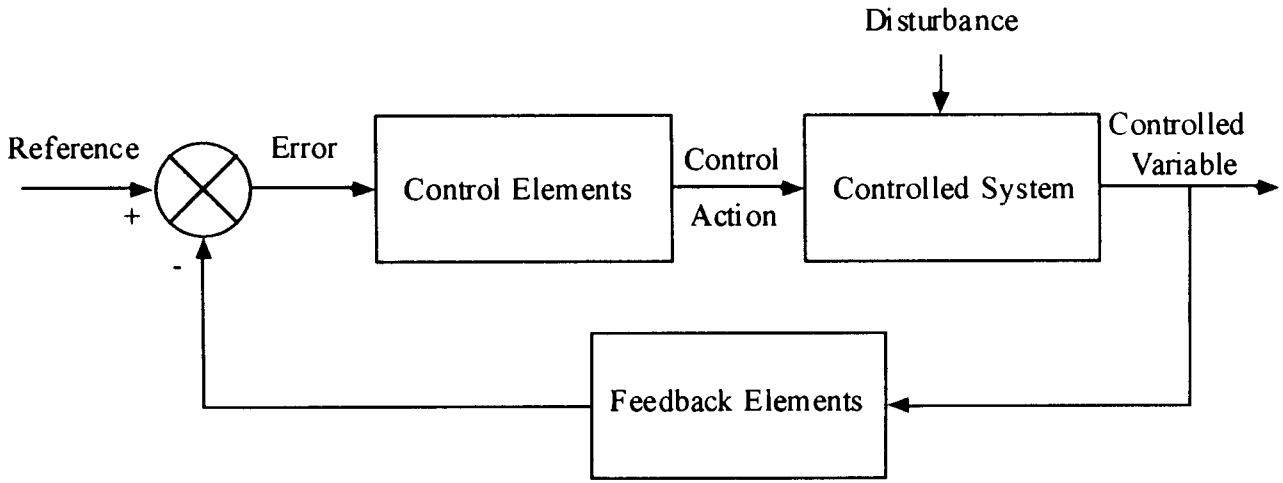

Fig. 3: General negative feedback control system with a reference signal.

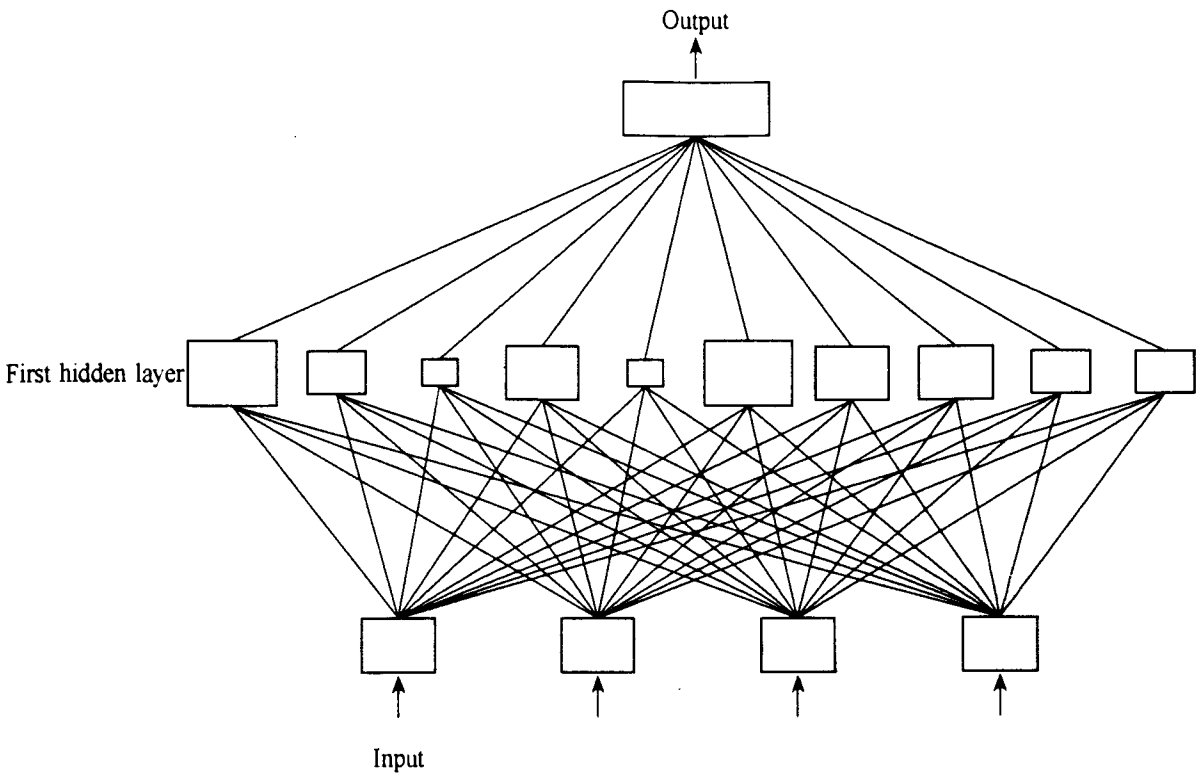

Fig. 4: An example of a neural network with 6 inputs, 1 hidden layer with 10 neurons and 1 output with all interconnections. The various size of the boxes in the hidden layer represent different weights.

STUDY I

BREATHING AIR AT 6 ATA INCREASES THE RATE OF CORE COOLING AND SUPRESSES THE PERCEPTION OF THERMAL DISCOMFORT IN HUMANS IMMERSED IN COLD WATER

ABSTRACT

Thermoregulatory responses of eight healthy subjects, six men and two women, were compared at 1 and 6 ata during head out immersion in 15°C water. Both trials were conducted in a hyperbaric chamber. During immersion, esophageal temperature (T_{es}) and skin temperature (T_{sk}) at two sites (chest and calf) were recorded at minute intervals. Oxygen uptake ($\dot{V}O_2$) was determined at 5 minute intervals. The order of the two trials was alternated randomly among subjects. The rate of core cooling ($\dot{T}_{es}$) was 20.1% greater during the 6 ata trial (mean ± SE, -2.34 ± 0.4 °C·h^{-1}) than during the 1 ata trial (-1.87 ± 0.6 °C·h^{-1}; $p \leq 0.05$). Subjects perceived that immersion at 6 ata was less cold than immersion at 1 ata despite significantly greater $\dot{T}_{es}$. There was no evidence from the $\dot{V}O_2$ data of change in heat production between the two conditions.

INTRODUCTION

During diving in cold water, divers may be exposed to a high rate of convective/conductive heat transfer and a low temperature of the aqueous environment, which can induce a drain of heat from the body's surface (Webb 1982). During deep ocean diving the heat loss from respiratory tract is also increased (Piantadosi et al. 1981). Therefore, research has focused primarily on thermal protection of divers and minimizing respiratory heat loss. Furthermore, a blunted appreciation of cold in divers (White et al. 1980) during the onset and progression of hypothermia may be a reason for diving accidents.

In two previous studies, Mekjavic and Sundberg (1992) and Passias et al. (1992) have demonstrated that a narcosis induced by inhalation of a normoxic gas mixture containing 30% nitrous oxide (N_2O) shifts the core temperature threshold for the onset of

shivering to a lower level and significantly attenuates oxygen uptake a criterion measure of shivering response. The observed increase in cooling rate during narcosis has been attributed primarily to attenuation of shivering thermogenesis by the anesthetic action of N_2O. Accordingly, it was hypothesized that narcosis induced by hyperbaric nitrogen, might also attenuate shivering thermogenesis and might therefore be a contributing factor in the development of hypothermia in compressed air diving.

The present study (I) was designed to investigate the effect of compressed air on thermoregulation of humans immersed in cold water. The objective was to assess whether nitrogen narcosis attenuates shivering thermogenesis, alters perception of cold and contributes to an enhanced cooling rate of the deep body core.

METHODS

Eight subjects (six men and two women) participated in the study. Their age, weight and height were 28 ± 2 years, 74 ± 6 kg and 178 ± 3 cm (mean ± SD), respectively. The subjects were familiarized with the protocol and instrumentation before the immersion trials, and all had previous experience of diving in a hyperbaric chamber. The schematic of the experimental setup is presented in Fig. 1-1.

Protocol

Experiments took place in a hyperbaric chamber consisting of an entry lock, main lock and wet lock situated beneath the entry lock. All subjects performed two experimental trials, one at 1 ata and one at 6 ata. The two trials were separated by a minimum of 5 days and the order in which the trials were conducted was alternated randomly among subjects. Subjects wearing only a swim suit were instrumented and sat in a chair suspended above the wet lock of the hyperbaric chamber. In the 6 ata trials, the subjects were compressed

at the rate of a 1.2 atm·min^{-1}. After a 5 minute rest period at 6 ata, each subject was lowered rapidly via a pulley system into the wet lock, and remained immersed up to the neck in 15°C water for a maximum of 60 minutes during a trial at 1 ata, and for 45 minutes during a trial at 6 ata. The maximum immersion time at 6 ata was restricted by the maximum bottom time of the DCIEM Air Diving decompression table approved by the ethics committee. An experiment was terminated if the esophageal temperature (T_{es}) decreased to 35°C or by 2°C below the subject's pre-immersion temperature. Upon completion of each immersion at 6 ata, the subject was transferred into the main lock of the hyperbaric chamber and rewarmed passively in a well insulated sleeping bag. After each immersion at 1 ata, the subject was rewarmed in a hot tub.

Instrumentation

T_{es} was measured with a YSI 702A thermistor probe (Yellow Springs Instruments, Yellow Springs, OH) inserted through a nostril into the esophagus to the level of the left ventricle. Skin temperature (T_{sk}) was recorded from two sites, mid chest and medial calf, using YSI 701 thermistors. Oxygen uptake ($\dot{V}O_2$) was measured by collectin of respired gas in a meteorological balloon. Samples of expired gas were collected every 5 minutes throughout the course of an experiment. The subjects breathed through a two-way respiratory valve (Hans Rudolph, Kansas City, MO), the expiratory side of which was connected with corrugated respiratory tubing to a two way valve and a meteorological balloon. Expired gas was collected for 1 minute in the normobaric trials In the hyperbaric trials, the expired gas sample was collected for 30 seconds in order to allow for bag expansion during the decompression. Expired ventilation ($\dot{V}_E$) was determined from one minute readings of a Parkinson Cowan dry gas volume meter (Chatham, ON) throughout the experiment and after the experiment the values were confirmed by exhausting the balloons through the same volume meter. The concentration of O_2 and CO_2 in the expired gas was analyzed with an Ametek Applied Electrochemistry S-3A (Pittsburgh, PA)

oxygen analyzer and a Beckman (Schiller Park, IL) carbon dioxide analyzer. During the hyperbaric trials filled meteorological balloons were kept inside the hyperbaric chamber (Fig. 1-1) and gas analysis of the contents of each was completed after the decompression. During rest and throughout an immersion at 5 minutes intervals, subjects were asked to give rating of their thermal state. They were asked to choose a number from a 21 point scale (Enander et al. 1979), where the middle point of 0 indicated 'thermoneutrality' (+10 = very very hot, +8 = very hot, +6 = hot, +4 = moderately hot, +2 = warm, 0 = neither warm nor cold, -2 = cool, -4 = moderately cold, -6 = cold, -8 = very cold, -10 = very very cold). In addition, a 5-point scale (Chattonet and Cabanac 1965) was used to determine subject's sensation of thermal comfort, on a scale on which +2 indicated "very pleasant", +1 = pleasant, 0 = neutral, -1 = unpleasant and -2 = very unpleasant.

Data analysis

The rate of core cooling was obtained by performing a regression analysis on the linear portion of the cooling curve. The linear portion of the T_{es} cooling curve was determined from the point in immersion at which a steady fall in T_{es} was observed until the end of immersion. Regression analysis of the linear portion of the T_{es} response for each subject yielded the slopes of the T_{es} response ($^{o}C \cdot h^{-1}$) which was compared between the conditions (1 and 6 ata) using a Student paired t-test. Significance was established at the 5% level. The perception ratings of thermal comfort reported by the subjects in each condition were compared using a non-parametric Wilcoxen signed rank test at each 0.5°C decrement of T_{es}.

RESULTS

Skin temperature

During the resting period in air prior to immersion and throughout the immersion, the unweighted group mean skin temperature ($\overline{T}_{sk}$) from the two measuring sites had similar values. The resting $\overline{T}_{sk}$ of 31.6 ± 0.2°C decreased to a stable value of 16.9 ± 0.4°C after immersion for 1 hour at 1 ata. At 6 ata $\overline{T}_{sk}$ decreased from 31.3 ± 0.2°C during rest to 15.9 ± 0.5°C during immersion. The difference in immersion $\overline{T}_{sk}$ between the trials was not significant. Following an initial drop on entry to the water, $\overline{T}_{sk}$ did not vary throughout the immersion and maintained a stable value slightly above the water temperature.

Esophageal temperature

Immersion in a hyperbaric trial was shorter due to the restraint imposed by the decompression table and the ethics committee constraints. The average dive duration was 44 minutes compared with a 56 minute normobaric trial. Despite this, the mean end-immersion T_{es} was lower at 6 ata compared with 1 ata, although the difference was not significant (Fig. 1-2). The onset of continuous cooling started earlier in the hyperbaric trial (mean ± SE, 12 ± 1.6 min) compared with 1 ata trial (14.3 ● 1.4 min; $p \leq 0.05$; Fig. 1-2). In all trials core temperature never decreased below 35°C. A linear regression was conducted on the linear portion of the T_{es} response for each subject, and the slope and coefficient of correlation (R^2) is hown in Table 1-1. The rate of core cooling ($\dot{T}_{es}$) was greater at 6 ata (-2.34 ± 0.41 $^{o}C \cdot h^{-1}$; $p \leq 0.05$) compared with the 1 ata trial (-1.87 ± 0.59 $^{o}C \cdot h^{-1}$).

Thermal Comfort Vote

When subjects rated their perception of comfort on a 5 point scale there was no significant difference between the 1 and 6 ata trial. In contrast, there was a significant difference between 1 and 6 ata when perception of thermal state was rated on a 21 point scale ($p \leq 0.05$, see Fig. 1-3). Subjects perceived their thermal state consistently colder at 1 ata than at 6 ata for the same value of ΔT_{es}. Statistical analysis was not attempted at $\Delta T_{es} = -1.5°C$ since only 3 subjects cooled to that degree in both trials.

Oxygen consumption

The oxygen uptake measurement was very variable between subjects. Due to technical problems with data collection which is detailed in Appendix, 5 subjects out of 8 had to be excluded from the analysis. For this reason results of only 3 subjects are presented. The removal of 5 subjects from analysis was determined from analysis of their $\dot{V}CO_2$, $\dot{V}O_2$ and $\dot{V}_I$ (ATPS) data. The respiration exchange ratio (RER) obtained for the group for $\dot{V}CO_2/\dot{V}O_2$ showed an unreasonably high (above 2) or low (below 0.5) value in excluded subjects. Fig. 1-4 shows the expired ventilation as a function of time and $\dot{V}O_2$ as a function of T_{es} for 3 subjects. The amount of data presented was not sufficient for statistical analysis of the group mean. The results of 3 subjects in Fig. 1-4 do not show an effect of N_2 narcosis at 6 ata on shivering thermogenesis.

DISCUSSION

The finding that hyperbaric exposure increased the cooling rate of T_{es} in response to cold water immersion may be due to an increased heat loss and/or decreased heat production. Despite the greater cooling rates, subjects perceived immersion at 6 ata as less cold than at 1 ata. Similarly Passias et al. (1992) and Mekjavic and Sundberg (1992) observed a greater

cooling rate and warmer rating of thermal state by subjects of similar age during cold water immersion while they inhaled normoxic gas mixture containing 30% N_2O. Although the effect of nitrogen narcosis on psychomotor performance is similar to that of the narcosis induced by inhalation of N_2O (Hesser et al. 1978), there is no evidence so far of the effect of nitrogen narcosis on the thermoregulatory response of humans immersed in cold water. It has been shown, however, that anesthetic agents in general, inhibit the thermoregulatory response in animals (Hammel 1988) and humans (Sessler et al. 1988 a, b, Sessler 1991). Since N_2, like anesthetics used in clinical practice such as nitrous oxide, ethylene and cyclopropane, are all considered biologically inert, N_2 could be expected to act on the thermoregulatory system by a similar mechanism as a general anesthetic gas (Carpenter 1954). The nitrogen inert gas theory is based on the Meyer-Overton hypothesis (Meyer 1899) who established a parallel between the affinity of an anesthetic for lipid and its narcotic potency. It was suggested that narcosis is most probably due to the penetration of the cell membrane by the anesthetic substance (Meyer and Hopff 1923).

It is difficult to conclude from the present study whether there is any difference in oxygen consumption between the 1 and 6 ata immersion. Results from three subjects presented in Fig. 4 do not show an effect of N_2 narcosis at 6 ata on shivering thermogenesis. However, the amount of data presented is not sufficient for any statistical analysis.

Passias et al. (1992) and Mekjavic and Sundberg (1992) showed an attenuation of shivering thermogenesis in subjects breathing normoxic gas mixture containing 30% N_2O, represented by a depression of oxygen uptake by approximately 40% in two studies despite a difference in the water temperature (15°C and 28°C, respectively). They also observed a shift of the threshold for the onset of shivering towards lower core temperatures when subjects breathed 30% N_2O with oxygen. The authors concluded that 30% N_2O normoxic gas mixture had no effect on thermoregulatory vasoconstriction, and that any possible depressant effect had been overridden by the intense peripheral cold

stimuli. They based their conclusion on the observation that there was no difference in heat flux, or forearm-fingertip temperature gradient between the N_2O/O_2 and air inhalation.

It has been shown previously that general anesthetics substantially reduce the temperature for the onset of vasoconstriction (Sessler et al. 1988 a, b) and increase the sweating threshold (Washington et al 1993, Kurz et al. 1993). An - anesthesia induced withdrawal of the vasoconstrictor tone of skin blood vessels would result in an increased skin blood flow and enhanced heat dissipation. However, in the present study the mean value of T_{sk} was 1°C lower at 6 ata (although not significantly) compared to 1 ata ($p > 0.05$). At the same water temperature Passias et al. (1992) observed only a 0.1°C lower mean T_{sk} during N_2O inhalation ($p > 0.05$). This suggests, that neither $PN_2 = 4.8$ atm nor $PN_2O = 0.3$ atm has enough anesthetic potency to supress vasomotor tone, and may have an opposite effect, especially at increased PN_2. This agrees with a study of Eisele and Smith (1972), who observed that a subanesthetic concentration of inhaled 40% N_2O produced a sympathomimetic action of N_2O. N_2O may increase the sympathetic outflow from the brain and inhibit removal of norepinephrine by the lung (Naito and Gillis 1973). Therefore, more of the norepinephrine released into the venous circulation will be available to act on the systemic circulation causing vasoconstriction.

A further observation of Passias et al. (1992) was that the thermosensitivity (gain) of the shivering response (expressed as $\Delta \dot{V}O_2/\Delta T_{es}$) was unaffected by N_2O during cooling, and the slope of $\Delta \dot{V}O_2/\Delta T_{es}$ was shifted in parallel towards the reduced threshold for shivering by 0.95°C in 30 % N_2O. Unfortunately, comparison with the present study is not possible, due to insufficient $\dot{V}O_2$ data. However, a similar parallel shift of $\Delta \dot{V}O_2/\Delta T_{es}$, rather than a change in the gain was observed in Study III of this thesis.

Direct comparison between different studies is difficult, as such comparison relies on the assumption that the narcotic potencies of an anesthetic gas and N_2 at elevated gas

pressure are equivalent, which may not be valid. As in clinical studies, the effect of N_2 narcosis on thermoregulatory function has not been investigated adequately enough to draw any substantive conclusion regarding whether the increased susceptibility to hypothermia arises due to enhanced heat loss or a decreased heat production. Furthermore, a variety of well known anesthetics are not simply reversible depressants of cellular function. They can also sensitize and stimulate, particularly in low concentration (Paton and Speden 1965). This was demonstrated by Cheung (1993) who cooled subjects in 20°C water and observed a significantly higher $\dot{V}O_2$ response when breathing 10% N_2O and a significantly depressed $\dot{V}O_2$ when breathing 25% N_2O compared to air breathing. Similarly, in study III of this thesis, the $\dot{V}O_2$ at 5 ata of air (PN_2 = 4 atm) was significantly ($p \leq 0.05$) higher compared to $\dot{V}O_2$ in air at 1 ata, when 5 subjects with the highest cooling rates were analyzed.

During diving the provision of heat for the diver becomes increasingly important as depth increases, and the precision of control also becomes more critical with increasing depth. At all depths however, the control is ultimately based upon the diver's subjective sensation of heat and cold. In the present study, subjects were not given the opportunity to respond behaviorally to the imposed thermal stress, but were asked to quantify their thermal state. The results at 6 ata reflect a change in the perception of cold as a function of T_{es}, since T_{sk} was constant during the immersion. Immersion at 6 ata was perceived as less cold ($p \leq 0.05$) despite the significantly greater cooling rates. However, the differences were not significant with a 5 point scale which might be due to its lower level of discrimination. For the same drop in T_{es} subjects could choose from 10 levels on the 21 point scale (from 0 "neutral" to -10 "very very cold") compared to 2 levels on the 5 point scale (from 0 "neutral" to -2 "very unpleasant"). Therefore, for the significant difference of 3 points in average at ΔT_{es} = 0.5°C from the 10 point scale is 30% of the whole range. That shift of 3 points is below the discrimination threshold on the 5 point scale.

In conclusion, this study shows that T_{es} cooling rate in human subjects during immersion in 15°C water is accelerated in hyperbaria compared with 1 ata. Since oxygen *per se* does not have a marked effect on thermoregulation (Study II), the more rapid onset of hypothermia is most likely due to increased PN_2. It is also concluded, that an altered perception of the thermal state observed during nitrogen narcosis may play a significant role in the development of hypothermia of compressed air divers.

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TABLES AND FIGURES

	1 ata		6 ata	
Subject	$\dot{T}es$ (°C·h^{-1})	R^2	$\dot{T}es$ (°C·h^{-1})	R^2
1	-0.45	0.51	-1.15	0.67
2	-1.88	0.98	-2.37	0.85
3	-4.96	0.98	-4.24	0.89
4	-0.54	0.68	-1.71	0.87
5	-0.22	0.20	-1.14	0.75
6	-1.42	0.80	-1.51	0.72
7	-3.61	0.99	-3.42	0.96
8	-1.83	0.96	-3.23	0.94
Mean	-1.87	0.76	-2.34	0.83
±SE	0.59	0.10	0.41	0.04

Table 1-1: Individual cooling rates ($\dot{T}_{es}$) during 1 and 6 ata trials. Cooling rates were greater ($p \leq 0.05$) during the hyperbaric trials.

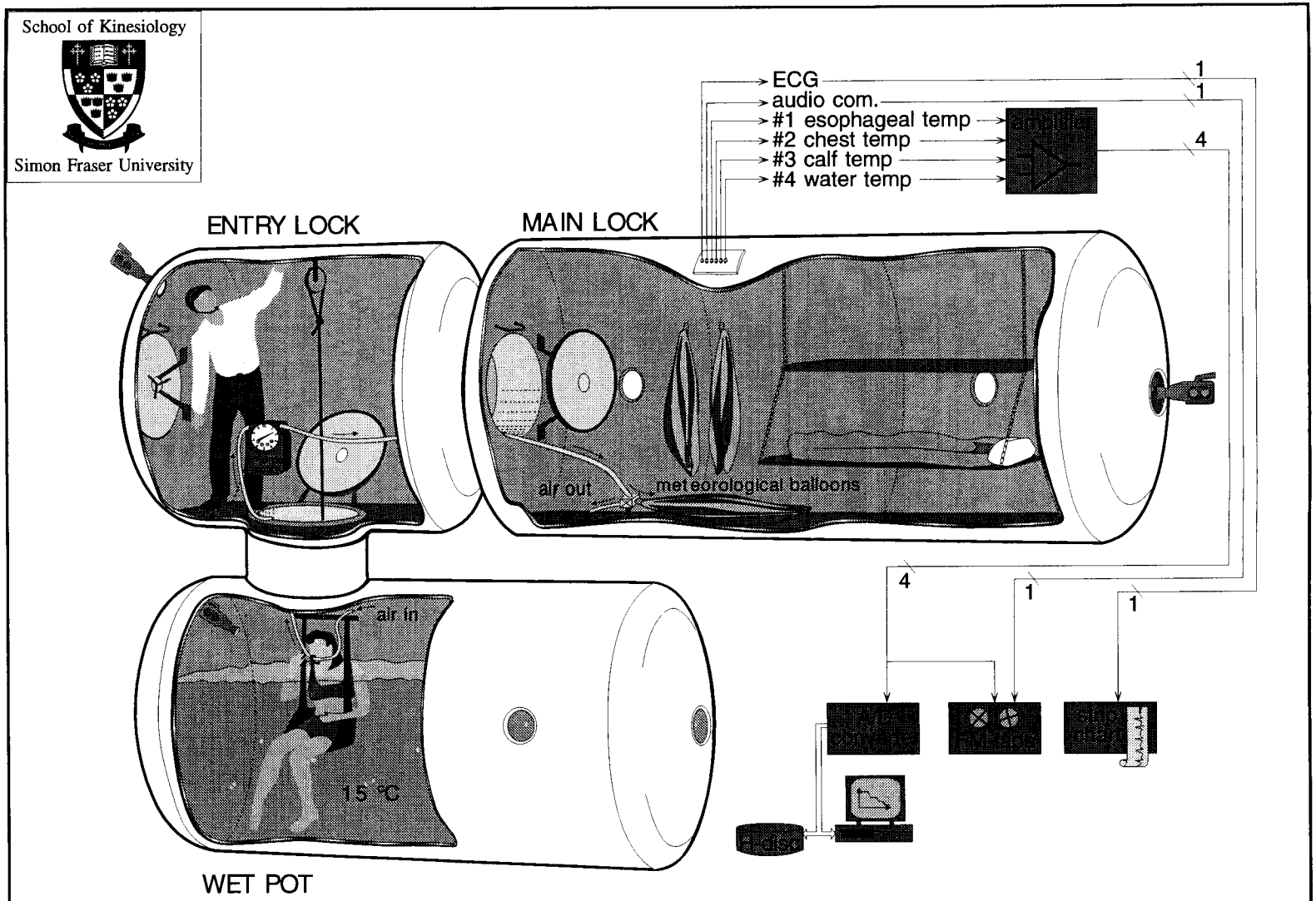

Figure 1-1: Schematic of experimental setup

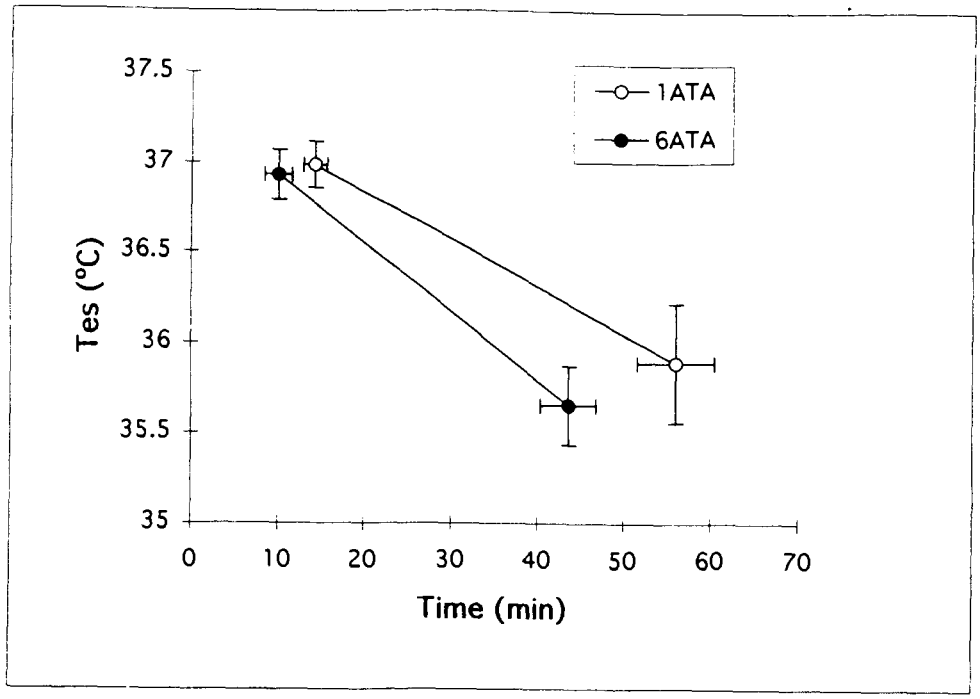

Fig. 1-2: Esophageal temperature response during the linear phase of core cooling during immersion in 15°C at 1 ata and 6 ata. Values are means (± SE) for 8 subjects. Mean T_{es} cooling rate (slope) was greater in 6 ata immersions (-2.34 ± 0.4 °C·h^{-1}) compared with 1 ata immersions (-1.87 ± 0.6 °C·h^{-1}; $p \leq 0.05$).

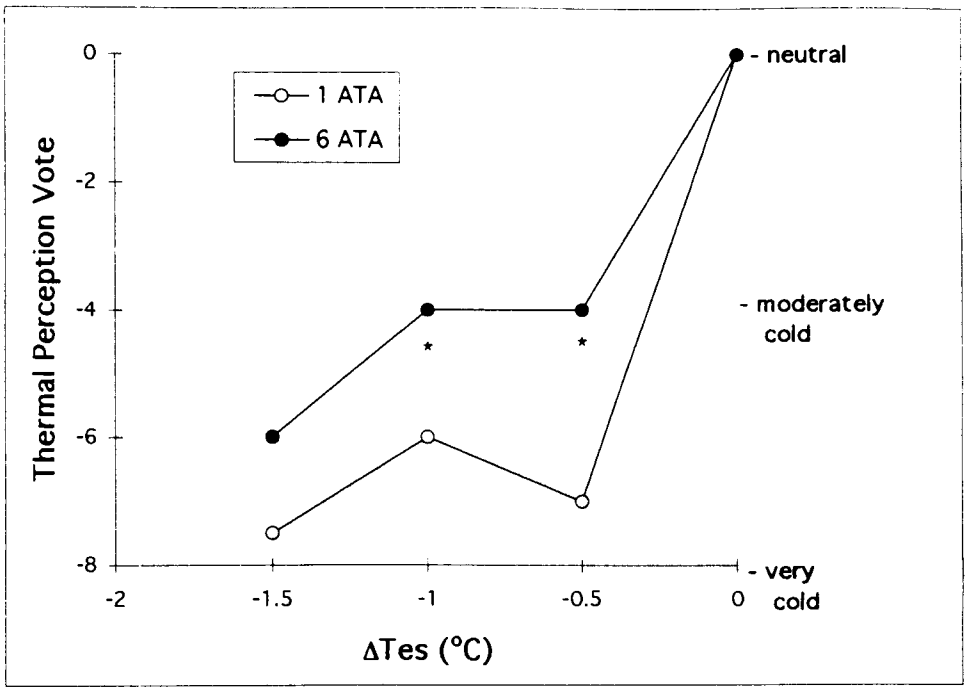

Fig. 1-3: Thermal perception vote reported by subjects during immersions in 15°C water at 1 and 6 ata. Values are means of n = 8; except for ΔT_{es} = -1°C and ΔT_{es} = -1.5°C, where n = 5 for 1 ata trial and 5 and 3 subjects, respectively for 6 ata trials.
*Significantly different from 1 ata ($p \leq 0.05$).

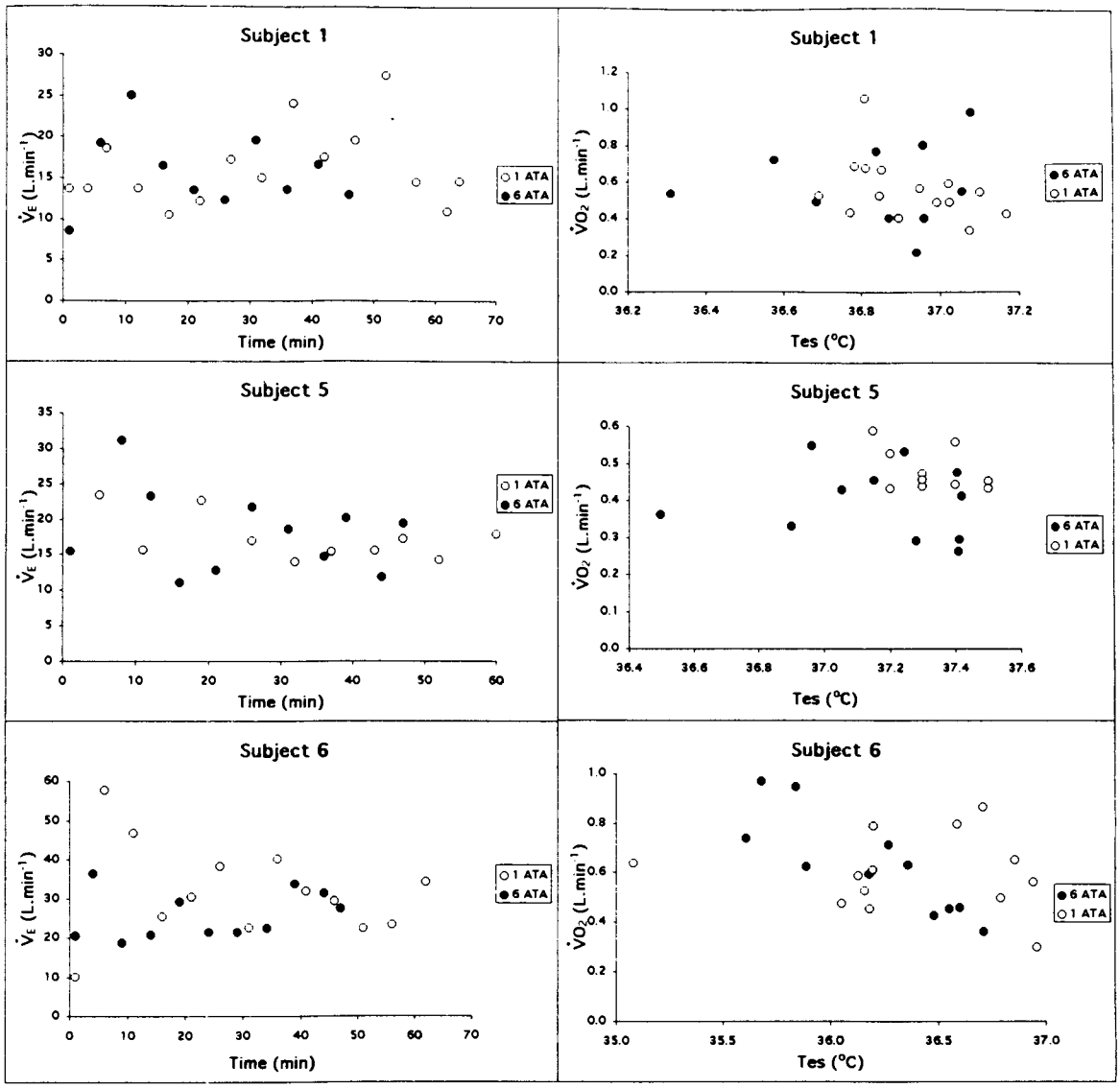

Fig. 1-4: Expired ventilation as a function of time ($L \cdot min^{-1}$ATPS) -left and oxygen consumption ($L \cdot min^{-1}$) as a function of T_{es} (°C) - right for 3 subjects during immersion at 1 and 6 ata both in 15 °C water.

APPENDIX 1

OXYGEN CONSUMPTION MEASUREMENTS IN HYPERBARIC CONDITIONS

Problems were encountered in Study I with $\dot{V}O_2$ and $\dot{V}CO_2$ data collection and analysis and the potential for error in $\dot{V}O_2$ due to insufficient accuracy when measuring the O_2 difference between two very similar fractions. This was detected in the form of unreliable respiration exchange ratios. Hence a new method was introduced in Study III. In the following text both methods used in this thesis: a bag collection of expired gas (I) and a mixing box with on line measurement (III) are compared and analyzed for accuracy. An experiment was conducted in a hyperbaric chamber at 1 and 5 ata with 2 subjects resting and lightly exercising on a bicycle. Both methods of $\dot{V}O_2$ measurements were used and compared for accuracy. Methodologies that were used in both studies are explained in details in the 'Methods' section of both studies.

When breathing compressed air at 6 ata, the partial pressure of oxygen has a value of 1.2558 atm ($PO_2 = 6 \cdot 0.2093$ atm). When the expired gas samples collected at 6 ata are analyzed at 1 ata, as in study I, the difference between inspired and expired fractions of O_2 (F_IO_2 and F_EO_2 respectively) is approximately 6 times smaller, requiring special care and high accuracy of measurement. This includes multiple calibrations, stable recording conditions and equipment capable of detecting small differences ($F_IO_2 - F_EO_2 = 0.3\%$ to 0.6%). Any small error in analyzing the expired gas composition is magnified in the calculation of $\dot{V}O_2$ and $\dot{V}CO_2$ by subtraction of two similar quantities.

INSTRUMENTATION

In Study I, the experimental setup consisted of following instrumentation: meteorological balloons, dry gas volume meter, O_2 and CO_2 analyzers. Subjects breathed through a two-way respiratory valve, the expiratory side of which was connected with corrugated respiratory tubing to a two way valve and a meteorological balloon. Expired gas was collected every 5 minutes during the trial. Expired ventilation was determined from one minute readings of a Parkinson Cowan dry gas volume meter throughout the experiment. Concentration of O_2 and CO_2 in the expired gas was analyzed with an oxygen analyzer and a carbon dioxide analyzer after the each trial.

In Study III, two gas mixing boxes, a ventilation meter (Alpha Technologies Ventilation Module), O_2 and CO_2 analyzers, a computer (Macintosh II), a data acquisition system (Hewlett - Packard Model 3497A data acquisition and control unit) and LabView 2.1 software (LabView, National Instruments) were used. Inspired ventilation was measured by a flow meter connected to the inspiratory side of an oronasal mask (see Fig. 1 and 2 in Study II). The signal from the turbine was directed through the chamber wall to a serial port of the computer, for display and $\dot{V}O_2$ calculation with a LabView program. Expired gas was directed to a gas mixing box. A continuous sample of expired gas was drawn from the mixing box and analyzed using an O_2 and CO_2 analyzer. In each hyperbaric trial an additional gas mixing box was introduced on the expiratory side outside the chamber to ensure that a steady gas flow was drawn at constant pressure to the gas analyzers. The output from the O_2 and CO_2 analyzers was directed to the data acquisition system from where data were sent to the LabView program for display, analysis and storage.

Ventilation meter

The meter used in Study I was a Parkinson Cowan dry gas volume meter (Chatham, ON) which gives a cumulative reading of volume. Calibration of the volume meter was performed using the syringe of 7.82 L of volume. Calibration was conducted at normal atmospheric pressure and at 5 ata. The average difference between two readings of the dry gas meter from the known syringe volume of 7.82 L in 10 trials was -0.04 L at 1 ata and +0.02 L at 5 ata.

The ventilation meter used in studies II and III was an Alpha Technologies Ventilation Module, Model VMM110 (Laguna Hills, CA, USA). The ventilation meter consists of a turbine allowing gas flow in both directions. The light emitted from four infrared (IR) diodes is intermittently blocked by the rotating turbine producing a digital signal which is subsequently transferred through the wall of the hyperbaric chamber to the serial port of the computer. The process is as follows. When the turbine rotates once, 2 ml of gas is passed through the turbine, producing 4 pulses from the IR diodes. The pulses are counted by a chip which sends the count to a microcontroller. Every 2 seconds the count is sent by the microcontroller to the serial port of the computer. Therefore, if at the end of the two second interval there are 800 counts, or 200 rotations of the turbine, which would be equivalent to 400 ml of gas. The digital signal is then processed by LabView 2.1 software for display of ventilation and calculation of oxygen consumption. The ventilation meter was calibrated at 1 ata and 5 ata using a syringe of a known volume (7.82 L). The measurement of the gas flow by the ventilation meter was insensitive to the speed and rotation of the turbine during emptying or filling of the syringe. The average difference from the known volume in 10 trials was 0.01 ± 0.002 L at 1 ata and 0.02 ± 0.003 L at 5 ata.

It is evident, therefore, that the turbine (Ventilation Module) and Cowan ventilation meter were sufficiently accurate during normobaric and hyperbaric calibrations.

However, when using the Parkinson Cowan ventilation meter during the experiment, minute ventilation data were obtained from a visual reading taken from the volume meter at one minute intervals, timed with a stop watch. In this technique the precise timing is crucial as well as accurate visual readings, since the needle may be rotating during the readings. The average error made by visual readings from dry gas meter when compared with turbine was 3.1%.

Meteorological balloons

In Study I, meteorological balloons were used to collect respired gas before the estimation of the expired gas volume and O_2 and CO_2 content were analysed. After all gas samples were collected in the meteorological balloons during the immersion, the balloons remained inside the hyperbaric chamber until the end of the decompression procedure. Therefore, the time elapsed between the sample collection and actual expired gas composition and volume analysis averaged 3.5 hours. Experimental testing of this technique has shown that this time span did not affect the volume content nor O_2 and CO_2 concentration inside the meteorological balloons.

Oxygen and carbon dioxide analyzers

The oxygen analyzer used in the Study I was an Ametek (Applied Electrochemistry, Pittsburgh, PA) Model S-3A. The accuracy of that O_2 analyzer is ± 0.01 % O_2 and sensitivity is ± 0.001 % O_2. The oxygen analyzer used in the Studies II and III was also an Ametek analyzer (same model). The carbon dioxide analyzer used in Study I was a Beckman carbon dioxide analyzer (Schiller Park, IL). In Studies II and III, an Ametek carbon dioxide analyzer Model CD-3A was used. The accuracy of both CO_2 analyzers is ± 0.02 % CO_2 and sensitivity is ± 0.01 % CO_2. As shown, the accuracy of these

analyzers is adequate to detect differences of 0.3% to 1% expected in fractions of expired O_2 and CO_2 during each hyperbaric experiment.

Data acquisition system

In Studies II and III the Hewlett - Packard Model 3497A data acquisition and control unit was used for data acquisition (DAQ). The electrical signals generated by the transducers or gas analyzers must be converted into a form that the DAQ system can accept. This was done by signal conditioning that can amplify a low level signal, linearize, isolate and filter it for more accurate measurements before reaching a DAQ system. The specifications of the DAQ system determines the accuracy of the signal conversion such as: number of channels, sampling rate, resolution and input range.

Multiplexing is a common technique for measuring several signals with a single analog to digital converter (ADC). The ADC samples one channel, switches to the next channel, samples it, switches to the next channel and so on. The HP3497A can accept a maximum of 20 channels of input. Sampling rate determines how often the conversion takes place. Maximum sampling rate on the 5½ digits displayed is 20 readings · sec^{-1} for 20 channels. In this thesis a maximum number of input channels was 7, thereby allowing the DAQ system to sample each channel at almost 3 Hz. Since the change in temperature is rather slow, except for skin temperature upon immersion, the maximal sampling rate was 0.17 Hz. According to the Nyquist sampling theorem the sample rate must be at least twice the rate of the maximum frequency component in the signal. It is evident that the sampling rate of the DAQ system is not a limiting factor, since it is 17 times the frequency of the input signal (0.17 Hz x 17 = 3 Hz).

Resolution was determined by the number of bits that the DAQ system uses to represent the analog signal. The higher the resolution, the smaller the detectable voltage

change. Range refers to the minimum and maximum voltage level which the DAQ system can quantify. The range, resolution, and gain available on a DAQ system determine the smallest detectable change in voltage. According to the system specifications of the HP 3497A for the 10 V input range and a gain of 10, the sensitivity is 100 μV. Therefore the resolution for the HP 3497A must be a minimum of 14 bits. A 14-bit converter divides the analog range into 2^{14} steps. At 100 % O_2 the gas analyzer is generating 5 V at the input of the DAQ. One step of the coded signal corresponds to a minimal resolution of 0.002 % O_2. Since the minimal resolution of the DAQ is smaller than the specified accuracy of the O_2 analyzer (0.01 % O_2), it is evident that the DAQ is not a limiting factor in the accuracy of the measurements. Similarly, at a maximal concentration of 15 % CO_2 the output of the analyzer is 7.5 V, giving a resolution of 0.0002 % CO_2. This is again much smaller than the specified accuracy of the CO_2 analyzer (0.02% CO_2).
The digital signal is then used by LabView 2.1 software for display of ventilation and calculation of oxygen consumption. For calculation of oxygen consumption this software also receives the data from an HP3497A in strings of ASCII code. These data are converted into numeric values without truncation. Therefore, the LabView software was not a limiting factor in accuracy.

EXPERIMENTAL TEST OF METHODOLOGY

Protocol:

Two subjects familiar with hyperbaric exposures performed sub-maximal exercise on a cycle ergometer inside a hyperbaric chamber at 1 ata and at 5 ata. Five minutes of resting was followed by 30 minutes cycling. Data were collected during rest and throughout the exercise period. The rest of the protocol and decompression procedures during the hyperbaric trials were as outlined in the 'Methods' section of the 'General introduction'. Oxygen uptake was analyzed using two methods:

a) using the $\dot{V}_I$ from the turbine and F_EO_2 and F_ECO_2 from a subject's expirate in the gas mixing box

b) using the $\dot{V}_I$ from the turbine and F_EO_2 and F_ECO_2 from a subject's expired gas collected into a meteorological balloon.

Experimental setup:

The inspiratory side of an oronasal mask was connected to a turbine (Alpha Technologies Ventilation Module, Model VMM110; Laguna Hills, CA, USA) for measurements of inspired ventilation. The turbine was connected through the wall of the hyperbaric chamber to a serial port of a Macintosh computer. A LabView 2.1 program sampled the digital signal from the turbine every 10 seconds and recorded inspiratory ventilation in real time. The turbine was connected in series with a short piece of corrugated tubing to a Parkinson Cowan dry gas volume meter, such that the subject inspired via the dry gas meter and turbine. Readings from the Parkinson Cowan meter were taken every minute. The expiratory side of an oronasal mask was connected to a 2 way valve, which was in one direction connected to a meteorological balloon and in the other direction to a 5 L

expired gas Plexiglass mixing box. Every 5 minutes the 2 way valve was switched and 1 minute of expired volume was collected in the meteorological balloon. The gas collection to the balloon was 30 sec long in the 5 ata trial, to compensate for the gas expansion upon decompression. Otherwise, the expired gas was passed through the mixing box and a continuous sample (200 $ml \cdot min^{-1}$) of expired gas was drawn from the mixing box through the analyzers by the means of a pump, connected in series with the O_2 and CO_2 analyzers, respectively. The excess of expired gas was exhausted from the mixing box through a one-way valve to the chamber atmosphere. In the hyperbaric trial, the sample of expired gas drawn from the mixing box was passed through the chamber wall by means of a special through hull penetrator and entered a second 5 L Plexiglass mixing box. A sample of the exhaled gas from the second mixing box was then drawn through the gas analyzers. This arrangement ensured a steady flow to the gas analyzers at atmospheric pressure. The analog output from the analyzers was fed to the HP 3497A DAQ system. F_EO_2 and F_ECO_2 were recorded every 10 seconds using a LabView 2.1 program.

Results:

Inspired ventilation measured by the turbine matched the Parkinson Cowan volume meter measurements. The difference between the two methods was 2.3% at 1 ata and 3% at 5 ata. F_EO_2 and F_ECO_2 were, on average, slightly higher when measured with a mixing box compared with the bag analysis (0.013 % O_2 and 0.018 % CO_2, respectively, at 1 ata and 0.018 % O_2 and 0.023 % CO_2 at 5 ata). This difference could be due to a timing error, matching samples which were not taken at exactly the same time. The sample from the meteorological balloon was matched with a sample from a mixing box after the valve was switched to the mixing box and the F_EO_2 and F_ECO_2 values stabilized (approximately 1 minute). Overall, the $\dot{V}O_2$ results obtained by these two methods matched well and it

does not seem that the difference in methodology in Study I and Studies II and III could have influenced the $\dot{V}O_2$ results significantly.

CONCLUSIONS

In view of the tests of methodology of measuring $\dot{V}O_2$ in hyperbaric conditions it seems unlikely that ventilation measurements have influenced the $\dot{V}O_2$ results. The tests also show that the $\dot{V}O_2$ measured with meteorological balloon method compared accurately with a mixing box method. The difference in reading was the result of switching the valve from the meteorological balloon after collecting the expired gas sample to a mixing box. The data show that after switching the valve to a mixing box, a 30 second period was required for the mixing box to be flushed. During that time the F_EO_2 and F_ECO_2 would have changed since a subject can not maintain exactly the same level of exercise and ventilation throughout the experiment.

However, underestimation of $\dot{V}O_2$ in Study I could be due to overestimation of F_EO_2 and to a lesser extent due to underestimation of F_ECO_2. Table 1-2 line 1 shows an example of 20.29 % expired O_2 at 6 ata from Study I. Line 2 Table 1-2 shows an average expected expired O_2 of 20.6% during cold water immersion (simulated with sub-maximal exercise on a cycle). Calculation shows that if F_EO_2 is overestimated by 0.31% the resultant $\dot{V}O_2$ will be 0.35 ($L \cdot min^{-1}$) which is one third of the expected value (0.91 $L \cdot min^{-1}$), depressed by 63%. Published data from Study I [1] report an average of 30% attenuation in $\dot{V}O_2$ at 6 ata. Such a difference can not be explained with the present methdology. However careful consideration of the data from Study I showed a drift in the calibration lines of the O_2 analyzer which may cause such an error. Unfortunately, the

[1] Mekjavic IB, Savic AS, Eiken O: Nitrogen narcosis attenuates shivering thermogenesis, *J App Physiol*, 78(6):2241-2244, 1995.

same analyzer could not be obtained for the tests described here since it had been replaced in Study II and III with a different Ametek type O_2 analyzer.

In conclusion, the test of methodology of $\dot{V}O_2$ measurements proved that in Studies II and III the reliable $\dot{V}O_2$ data was obtained. When 5 subjects showing unreasonable values of respiratory exchange ratio were eliminated from Study I, the remaining 3 subjects showed no evidence of attenuation of the $\dot{V}O_2$ response at 6 ata. These results agree with the findings at 5 ata in Study III.

Pb	$\dot{V}_I$	O_2exp.	CO_2exp.	STPD	$\dot{V}O_2$	$\dot{V}CO_2$
3773	31.7	**20.29**	0.70	4.5410	**0.91**	0.96
3773	31.7	**20.60**	0.70	4.5410	**0.35**	0.97

Table 1-2: Resultant $\dot{V}O_2$ if F_EO_2 is manipulated.

Where: $F_IO_2 = 0.2093$; $F_ICO_2 = 0.0003$; $\dot{V}_I = 31.7$ ($L \cdot min^{-1}$), $T_{amb} = 24°C$, $P_{H2O} = 18.47$ mmHg; $Pb_{1ata} = 733$ mmHg

STUDY II

THE THERMOREGULATORY RESPONSE OF HUMANS TO COLD WATER IMMERSION DURING HYPEROXIA

ABSTRACT

The effect of hyperoxia on the human thermoregulatory response was investigated in 7 male subjects during head-out immersion in 20°C water for one hour. Each subject completed two trials, breathing air and 100% O_2 respectively. Esophageal temperature (T_{es}), skin temperature (T_{sk}), oxygen uptake ($\dot{V}O_2$) and heart rate (HR), were recorded at minute intervals. Perception of thermal comfort was assessed every 5 minutes of the resting and immersion periods respectively. No significant difference was observed in the rate of core cooling ($\dot{T}_{es}$) or in $\dot{V}O_2$ between the trials. The average decrease in T_{es} (ΔT_{es}) was 1.05 ± 0.29°C when breathing air and 1.08 ± 0.21°C when breathing 100% O_2. The average $\dot{T}_{es}$ obtained from the linear portion of the T_{es} response was -1.27 ± 0.09 °C·h^{-1} when breathing air and -1.14 ± 0.07°C·h^{-1} when breathing 100% O_2 ($p > 0.05$). Group mean $\dot{V}O_2$ was 0.89 ± 0.45 L·min^{-1} in the oxygen trial and 1.00 ± 0.49 L·min^{-1} in the air trial ($p > 0.05$). Regression analysis of $\Delta\dot{V}O_2/\Delta T_{es}$, which represents the gain of the shivering response, did not show any significant difference between the slopes in the two experimental conditions. Unweighted mean skin temperatures ($\bar{T}_{sk}$) attained a similar end immersion value in both trials (air: 20.7 ± 1.3°C; hyperoxia: 20.9 ± 1.3°C). Inspired ventilation and perception of thermal comfort showed no significant difference between the trials. In contrast, heart rate was consistently and significantly lower ($p \leq 0.05$) in the hyperoxic trial (air: 79 ± 20 min^{-1}; hyperoxia: 71 ± 18 min^{-1}).

It is concluded, that thermal balance during cold water immersion is not affected by hyperoxia, and that hyperoxia does not contribute to the attenuation of shivering thermogenesis during compressed air diving.

INTRODUCTION

The incidence of hypothermia, prevalent among compressed air divers has been attributed primarily to the potentiation of heat loss due to cold water and the cold compressed breathing gas (Webb 1970). Hypothermia in diving has been termed "silent" hypothermia (Hayward and Keatinge 1979). It develops without previous warning and can progress into a severe type of hypothermia if precautions are not taken immediately. Though this silent hypothermia has been suggested to be a consequence of the slow nature of core cooling and the inability of the core sensors to detect it, there is a paucity of data regarding the possible inhibition of a regulating autonomic response, which would be activated to maintain core region thermal stability. Mekjavic and Sundberg (1992) and Passias et al. (1992), found that attenuation of heat production during inhalation of 30% N_2O significantly contributed to the progression of cold water immersion hypothermia. The observed magnitude of attenuation in heat production and increased core cooling in the above studies suggests that a causative factor inducing an increased cooling rate during compressed air diving could be the narcotic effect of an elevated PN_2.

In the first study (I) eight subjects immersed up to the neck in 15°C water showed greater cooling rate ($p \leq 0.05$) of esophageal temperature (T_{es}) at 6 ata compared with 1 ata. The immersion at an increased pressure was also consistently perceived as less cold ($p \leq 0.05$). A possible explanation was, that due to the narcotic property of hyperbaric N_2, an increased cooling would result from a depression of shivering, caused by inhibitory action of increased PN_2 on central nervous structures. The mechanism involved in depressing the heat production could also have an inhibitory effect on thermal perception. Unfortunately, due to difficulty in attaining consistent $\dot{V}O_2$ measures evidence for or against depression in heat production during hyperbaria could not be obtained. In

addition, other factors at that depth, such as increased PO_2 (1.2 atm) at 6 ata, and the effect of pressure *per se* could not be ruled out.

Froese (1958) reported that intermittent inhalation of 95% O_2 (PO_2 = 0.95 atm) caused a decrease in $\dot{V}O_2$ in subjects exposed to cold ambient air at 1 ata, and suggested the cause was a hyperoxia-induced suppression of cold sensor activity. This hyperoxia-induced depression of $\dot{V}O_2$ was also observed by MacCanon and Eitzman (1961) during prolonged hyperoxic exposure f humans to cold air. A common conditin in both above studies was the absence of any change in body temperature during cold exposure, despite a significant reduction in heat production. According to Froese (1958), thermal balance may have been maintained during the hyperoxic condition by the vasoconstrictive effect of O_2, which may have reduced heat loss from the skin.

The present study was undertaken to examine the hypothesis that hyperoxic gas breathing by subjects immered in cold water in a compressed air environment produces an increase in core cooling rate. It was alo hypothesized that a hyperoxia related alteration in thermal afferent information would be reflected in a subjects thermal perception.

METHODS

The present study was designed to examine the effect of hyperoxia, associated with compressed air breathing, on the human thermoregulatory response to immersion in cold water. In order to eliminate the effects of pressure and nitrogen narcosis, the hyperoxia present at 5 ata air breathing (PO_2 = 1 atm) was simulated by having the subject to inspire 100% O_2 at 1 ata.

Subjects

Seven healthy male subjects participated in the study, their participation was previously approved by an attending physician. Their age was 25.6 ± 2.8 years (mean ± SD), height 177.6 ± 8.5 cm and weight 73 ± 10.7 kg. All subjects were familiarized with experimental protocol, which was approved by an institutional review process, and each subject was aware that he could withdraw from the study at any time.

Protocol

All subjects participated in two experimental trials, one breathing air and the other breathing 100% O_2. The order of the two trials was random and immersions were spaced one week apart to avoid any effects of adaptation to hypothermia. In order to avoid the effect of circadian rhythm, subjects performed each immersion at the same time of day.

The subject wore only a swim suit and was instrumented and seated in a chair harness suspended above the immersion water tank. A twenty minute rest period before immersion was scheduled to allow tissue to saturate with oxygen in the hyperoxia trial. During this latter period, expired CO_2 and O_2 values were recorded and they stabilized within a maximum of 18 minutes. This is in accordance with the literature, which suggests that 10 minutes of pure oxygen breathing plus 5 minutes of light exercise is sufficient for nitrogen wash-out (Welch 1981). A twenty minute rest period was also incorporated in the air trials. Cylinders containing the compressed gas were masked and subjects were not informed of the breathing mixture administered. Four subjects received 100 % O_2 in the first trial, and air in the second trial, while the remaining three subjects received gas in the alternate order. Prior to the commencement of each hyperoxia trial, the respiratory circuit (mixing box, respiratory tubes and humidification system) was flushed with 100 % oxygen, and the integrity of the respiratory circuit was evaluated by monitoring the O_2

content within the circuit during the flushing phase. Precaution was taken to eliminate any possibility of air leaking into the respiratory circuit.

Following the 20 minute rest period, the subject was lowered rapidly into 20°C water up to the neck. The subject remained immersed in continuously stirred water for one hour. An immersions was terminated when esophageal temperature decreased to 35°C, or by 2°C from the preimmersion value. Upon completion of the immersion, all transducers were removed and the subject was assisted to a hot tub, for rewarming. The subject remained in hot (around 40°C) and stirred water until he rewarmed completely.

Instrumentation

Skin temperature

Skin temperature (T_{sk}) was monitored with thermistors (Concept Engineering, USA, model #FR-025-TH44018) attached to the skin with waterproof tape (Elastoplast, Smith and Nephew, Lachine, Quebec) to minimize movement of the sensors and prevent water from penetrating during immersion. Unweighted mean skin temperature ($\overline{T}_{sk}$) was determined from skin temperature measurement made at four sites: chest (left lateral, mid-clavicular line at the second intercostal space), left upper arm (upper anterior aspect, mid portion), left thigh (anterior surface, mid portion) and left calf (lateral aspect, mid portion).

Esophageal temperature

Esophageal temperature (Tes) was obtained with a YSI 401 thermistor probe (Yellow Springs Instruments, Yellow Springs, OH, USA) inserted through a nostril into the esophagus, to the level of the left ventricle. T_{es} was used to estimate body core temperature.

Ventilation and expired gas content

Both breathing gases, air (0.03% CO_2, 20.93% O_2, 79.04% N_2) and 100% O_2 were humidified prior to inspiration by passing them through a water bath at room temperature. The water bath was tightly covered with a meteorological balloon, in order not to allow leakage and to provide a steady flow of breathing gas to the inspiratory side of the breathing circuit. The top of the meteorological balloon was connected to a ventilation meter (Alpha Technologies Ventilation Module, Model VMM110, Laguna Hills, CA, USA) which was connected with 135 cm of corrugated respiratory tubing (Collins) to the inspiratory side of a one-way respiratory valve. Expired gas was directed via 225 cm of corrugated tubing to a 5 L fluted Plexiglass mixing box. A continuous 0.5 $L \cdot min^{-1}$ sample of gas was drawn from the mixing box for analysis of the O_2 and CO_2 content of the mixed expired gas using Ametek O_2 and CO_2 analyzers, respectively (Ametek Systems, Pittsburgh, PA, USA). $\dot{V}O_2$ was calculated based on measurements of $\dot{V}_I$ and the O_2 and CO_2 content of the expired gas at 10 second intervals. The 10 second values throughout each minute were averaged to provide a minute value.

Heartrate

Heart rate was recorded with a Physio-Control Systems (Washington, USA) electrocardiograph and assessed from an ECG trace obtained from three pre-gelled electrodes, two placed laterally on the chest and one on the mid portion of the right scapula.

Perception of thermal comfort

Each subject rated his perception of thermal comfort at 5 minute intervals, on a 21-point scale (Enander et al. 1979), where +10 was defined as "very very hot", 0 as "neutral" and -10 as "very very cold". In addition, a 5-point scale (Chattonet and Cabanac 1965) was

used for sensation of thermal comfort, where +2 indicates "very pleasant", 0 indicates "neutral" and -2 "very unpleasant".

Data acquisition

All variables including $\dot{V}_I$ were continuously sampled and recorded on-line at 10-sec intervals, using a data acquisition system (Hewlett Packard 3497A) and Labview 2.1 software (Labview, National instruments) on a Macintosh II computer (Apple Computer, Inc., Cupertino, CA, USA).

Data analysis

A repeated measures analysis of variance with two factors (subjects and condition) on each of the 6 variables: T_{es}, T_{sk}, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_I$ and HR were performed for the resting and immersion phase. During the resting phase the measurements were repeated 5 times, each observation corresponding to 1 minute of the rest period. During the immersion phase, the first observation was made during the sixth minute of immersion, after the initial dynamic response of all variables upon immersion had stabilized. The initial dynamic $\dot{V}O_2$ response was analyzed separately. The area under the curve of the initial increase in $\dot{V}O_2$ was analyzed for the maximal peak, width and surface area. Linear regression analysis of the linear portion of the T_{es} cooling response was performed separately for each subject. The individual slopes of the T_{es} response were then statistically compared between the experimental conditions with a Student paired t-test. The linear portion of the T_{es} cooling curve was determined from the time during immersion when a steady fall in T_{es} was observed until the end of immersion. The slopes of the $\Delta \dot{V}O_2/\Delta T_{es}$ relation for the two conditions, reflecting the gain of the shivering response, were also compared between the two experimental conditions with a Student

paired t-test. $\Delta \dot{V}O_2$ and ΔT_{es} represent the change relative to the preimmersion value. The difference between the rating of thermal perception and sensation of thermal comfort respectively for the two conditions, was compared with a Wilcoxon signed rank test.

RESULTS

Skin temperature

After a rapid drop immediately upon immersion, skin temperature stabilized quickly, attaining a similar end immersion value in both trials. $\bar{T}_{sk}$ was 20.7 ± 1.3°C when breathing air and 20.9 ± 1.3°C when breathing 100% O_2. There was no significant difference in $\bar{T}_{sk}$ between the trials during the rest period preceding immersion (air: 31.2 ● 0.2°C; hyperoxia: 30.5 ± 0.7°C).

Esophageal temperature

All immersions were 60 minutes duration and T_{es} never decreased below 35°C (Fig. 2-1). The average decrease in T_{es} in the air trial was 1.05 ± 0.29°C and in the hyperoxia trial 1.08 ± 0.21°C (Table 2-1). The rate of core cooling ($\dot{T}_{es}$, °C·h^{-1}), obtained from the linear portion of the T_{es} response was not different between the trials (air: -1.27 ± 0.09 °C·h^{-1}; hyperoxia: -1.14 ● 0.07 °C·h^{-1} ; $p > 0.05$; Table 2-2).

Inspired ventilation, carbon dioxide production and oxygen consumption

The group mean $\dot{V}_I$ showed a similar value during five minutes of rest ($p > 0.05$) before each trial. An initial hyperventilation due to the cold peripheral stimuli upon immersion was observed in all subjects. The group mean $\dot{V}_I$ after the first 5 min of immersion until

the end of the experiment attained the following values: 26.89 ± 11.81 $L \cdot min^{-1}$ during air breathing and 24.66 ± 10.23 $L \cdot min^{-1}$ in the hyperoxia trial (Fig. 2-2). The difference between conditions was not significant.

The group mean value of carbon dioxide production ($\dot{V}CO_2$) in the two trials was not significantly different (air: 0.86 ± 0.2 $L \cdot min^{-1}$; hyperoxia: 0.85 ± 0.1 $L \cdot min^{-1}$). Fig. 2-3 shows the mean $\dot{V}CO_2$ response of seven subjects in the air and hyperoxia trial until the end of immersion.

The group mean peak oxygen uptake $\dot{V}O_2$ immediately after immersion was 1.86 ± 0.67 $L \cdot min^{-1}$ in the air trial and 1.74 ± 0.57 $L \cdot min^{-1}$ in hyperoxia. The area under the curve of the initial dynamic $\dot{V}O_2$ response upon immersion was analyzed separately and yielded the following results: the mean length of the $\dot{V}O_2$ transient response was 2.0 ± 0.1 min in air and 1.91 ± 0.1 min in the hyperoxia trial; the mean oxygen uptake volume (area) was 9.93 ± 1.62 L in the air trial and 11.04 ± 3.2 L in the hyperoxia trial. No significant difference in the width, maximal peak nor volume of the dynamic $\dot{V}O_2$ response was found ($p > 0.05$). The group mean stable immersion $\dot{V}O_2$ was 0.89 ± 0.45 $L \cdot min^{-1}$ in the oxygen trial and 1.00 ± 0.49 $L \cdot min^{-1}$ in the air trial. There was no significant difference between these values ($p > 0.05$). The mean oxygen uptake for seven subjects during head out immersion breathing air and 100% O_2 is shown in Fig. 2-4.

The gain of the shivering response determined from the relation $\Delta \dot{V}O_2/\Delta T_{es}$, is shown in Table 2-3. The average slope of $\Delta \dot{V}O_2/\Delta T_{es}$ was not different between the trials (air: -0.41 ± 0.31 $L \cdot min^{-1} \cdot °C^{-1}$; hyperoxia: -0.36 ± 0.24 $L \cdot min^{-1} \cdot °C^{-1}$; $p > 0.05$).

Heart rate

Heart rate (Fig. 2-5) was consistently and significantly lower ($p \leq 0.05$) in the hyperoxia trial (71 ±18 min^{-1}) compared with the air trial (79 ± 20 min^{-1}).

Thermal perception and sensation of comfort

The thermal perception and sensation of comfort data was compared between the two trials at standard ΔT_{es}'s of 0.5 and 0.75°C decrease in core temperature. No significant difference in perception of thermal comfort was found for these degrees of temperature change ($p > 0.05$). Since only three subjects cooled by 1°C in both trials, statistical comparison for a 1°C decrease in core temperature was not possible. Fig. 2-6 represents the mean values for seven subjects of the thermal perception vote at $\Delta T_{es} = -0.5$°C.

DISCUSSION

The present study demonstrates that an imposed hyperoxia of 5 ata air breathing does not significantly affect shivering thermogenesis and perception of thermal comfort during cold water (20°C) immersion. This conflicts with previous reports, showing that both intermittent inhalation of 100% O_2 (Froese 1958) or prolonged hyperoxia (MacCanon and Eitzman 1961) reduce metabolism during cold air exposure and improve the perception of thermal comfort

While nitrogen has an anesthetic effect in air, even at normal atmospheric pressure (Winter et al. 1975) which is potentiated at increased pressure, hyperbaric oxygen is widely agreed to be toxic and to cause convulsions and pulmonary damage above 3 ata. Therefore, a possible mechanism by which O_2 may interfere with neural transduction of thermal information, axonal propagation rate and central processing of thermal afferent information must be discussed in terms of both the toxic and anesthetic properties of an elevated PO_2. The level and duration of the hyperoxic exposure in the present study, as well as in the studies of Froese (1958) and MacCanon and Eitzman (1961), was probably insufficient to give rise to a deleterious change in neural function and brain metabolism.

Based on relative lipid solubility, oxygen is about twice as soluble as nitrogen, and therefore should be at least twice as potent a narcotic. Unlike N_2 or N_2O, O_2 is used in oxidative processes of the metabolism in the body. Therefore, tissue PO_2 will not equilibrate with inspired O_2 or even arterial O_2 as in the case of PN_2 and PN_2O. Paton (1967) and Smith and Paton (1976) demonstrated in mice that the ratio of the partial pressures of O_2 and N_2 which produce anesthesia is 2.6, indicating a greater anesthetic potency of O_2. This has been shown in humans by Hesser et al. (1978) who demonstrated a 10% decrement in arithmetic performance of divers exposed to either air or PO_{22} = 1.7 atm. When the same group of divers was exposed to compressed air at 8 ata (PN_2 = 6.35 atm; PO_2 = 1.65 atm) the effect of N_2 alone on the performance caused a decrease of 10% compared with breathing pure oxygen at 1.7 ata (PO_2 = 1.7 atm). This suggests that for producing similar degrees of decrement in mental function, PN_2 must be 3 to 4 times greater than PO_2.

Froese (1958) showed that inhalation of 95% O_2 at normal room temperature (25°C) did not impair oxygen consumption in normally dressed subjects, but during exposure to cold room air (10°C), the intermittent inhalation of 95% O_2 significantly lowered oxygen consumption. Since the rectal temperature was not altered, peripheral vasoconstriction was suggested as the means for maintaining thermal balance. It was suggested that an increased oxygen pressure might modify the metabolic response to cold by affecting the temperature receptors of the skin. A study by MacCanon and Eitzman (1961) also showed a reduced oxygen consumption, produced less shivering and less thermal discomfort in prolonged hyperoxia during cold air exposure. The discrepancy of this result with the present $\dot{V}O_2$ results might be due to the Douglas bag method which the former authors used for gas collection. This method has been proven to underestimate the $\dot{V}O_2$ values in hyperoxia (Welch and Pedersen 1981). It is also possible that the greater thermal stimulus provided by immersion in 20°C water as in the present study compared with exposure to 10°C air, as in the above studies, may have overridden any

anesthetic effect of O_2. The results of the present study do not exclude the possibility of O_2 exerting a significant inhibitory influence on shivering at higher levels of PO_2.

The observation in the present study that hyperoxia does not alter the core temperature response to cold water immersion is supported by the studies of MacCanon and Eitzman (1961) and Froese (1958). They concluded that the maintenance of thermal balance, despite reduced heat production is most likely due to the vasoconstrictive effect of O_2 on the peripheral circulation, effectively increasing the core to skin temperature gradient, and thus reducing heat loss from the skin. Reduction of the peripheral circulation should result in a lower skin temperature, which will generate a greater peripheral drive for shivering, and be reflected in a greater $\dot{V}O_2$ response. A reduction in $\dot{V}O_2$ is attributed by the above authors to a decreased sensitivity of the cold sensors as a result of hyperoxia. In the present study, there was no significant difference in skin temperature between the two trials during the rest period or throughout the immersion in hyperoxia.

The most consistent change produced by breathing 100 % O_2 described in the literature is a reduction in heart rate. This was also observed in the present study, and is probably due to a reflex response to peripheral vasoconstriction caused by the cold stimulus and the direct effect of oxygen on vagal activity (Keatinge and Evans 1960, Barrat-Boyes and Wood 1958).

Ventilation usually increases upon cold water immersion due to a strong cutaneous cold stimulus. The initial increase is then followed by a rapid decrease due to rapid adaptation of skin thermoreceptors. An increased PO_2 would initially decrease ventilation due to the depressant effect of O_2 on the carotid body and chemoreflex drive. Respiratory depression however leads to a rise in central PCO_2 and hydrogen ion concentration which in turn will increase the ventilation (Lambertsen et al. 1953 a, b, c). Those two effects are opposing. However, Dejours et al. (1957) concluded that the chemoreflex stimulus was abolished when the inspired oxygen was above 33%. The

present results show an initial increase in $\dot{V}_I$ upon cold water immersion in both conditions, then a decrease, and an eventual end immersion value which is not significantly different between the conditions of the present experiment.

The present findings also show that at a PO_2 = 1 atm, the central drive for shivering, expressed by the relation $\Delta \dot{V} O_2/\Delta T_{es}$ is not affected by hyperoxia (Table 2-3). This study also demonstrates that perception of thermal comfort is not impaired during 100 % O_2 breathing. This is not in agreement with results of MacCanon and Eitzman (1961), whose subjects felt less thermal discomfort in hyperoxia, and Goldscheider and Ehrmann (1924), who reported that O_2 applied externally to the finger would lower the threshold for the sensation of warmth by 5 to 7°C.

In conclusion, though O_2 has been reported to impair the thermoregulatory response to mild cold exposure in air, the present results show no significant attenuation of thermoregulation during cold water immersion. Thus, it is unlikely that the attendant hyperoxia of compressed air, equivalent to the hyperoxia of the present study, would contribute significantly to impairment of the thermoregulatory response and perception of thermal comfort. Any depressant effect on heat production mechanisms in a compressed air environment, is more likely to be due to an increased PN_2 than an increased PO_2.

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TABLES AND FIGURES

	AIR	100% O_2
Subject	ΔT_{es} (°C)	ΔT_{es} (°C)
1	1.63	1.09
2	1.16	1.07
3	1.17	1.10
4	0.89	1.30
5	0.73	0.77
6	0.93	1.36
7	0.86	0.86
Mean	1.05	1.08
±SE	0.12	0.08

Table 2-1: Individual maximal decrease in T_{es} (ΔT_{es}) in 7 subjects when breathing air and 100% O_2 during head out immersion in 20°C water. The group mean difference between conditions was not significant.

	AIR		100 % O_2	
Subject	$\dot{T}_{es}$ (°C·h^{-1})	R^2	$\dot{T}_{es}$ (°C·h^{-1})	R^2
1	-1.39	0.96	-0.86	0.92
2	-1.56	0.96	-1.35	0.96
3	-1.48	0.96	-0.96	0.95
4	-1.04	0.97	-1.17	0.97
5	-1.20	0.96	-1.21	0.96
6	-1.05	0.94	-1.28	0.96
7	-1.16	0.89	-1.14	0.94
Mean	-1.27	0.95	-1.14	0.95
±SE	0.09	0.01	0.07	0.01

Table 2-2: Individual cooling rates ($\dot{T}_{es}$) in 7 subjects when breathing air and 100 % oxygen during head out immersion in 20°C water. The difference was not significant.

Subject	AIR	100 % O_2
1	-0.78	-0.77
2	-0.18	-0.36
3	-0.03	-0.24
4	-0.13	-0.11
5	-0.43	-0.12
6	-0.78	-0.59
7	-0.54	-0.32
Mean	-0.41	-0.36
±SE	0.13	0.10

Table 2-3: Group mean slopes of the relation $\Delta \dot{V}O_2/\Delta T_{es}$ ($L \cdot min^{-1} \cdot °C^{-1}$). $\Delta \dot{V}O_2$ and ΔT_{es} represent the change relative to the preimmersion value. The difference in slope between the air and 100% oxygen condition was not significant.

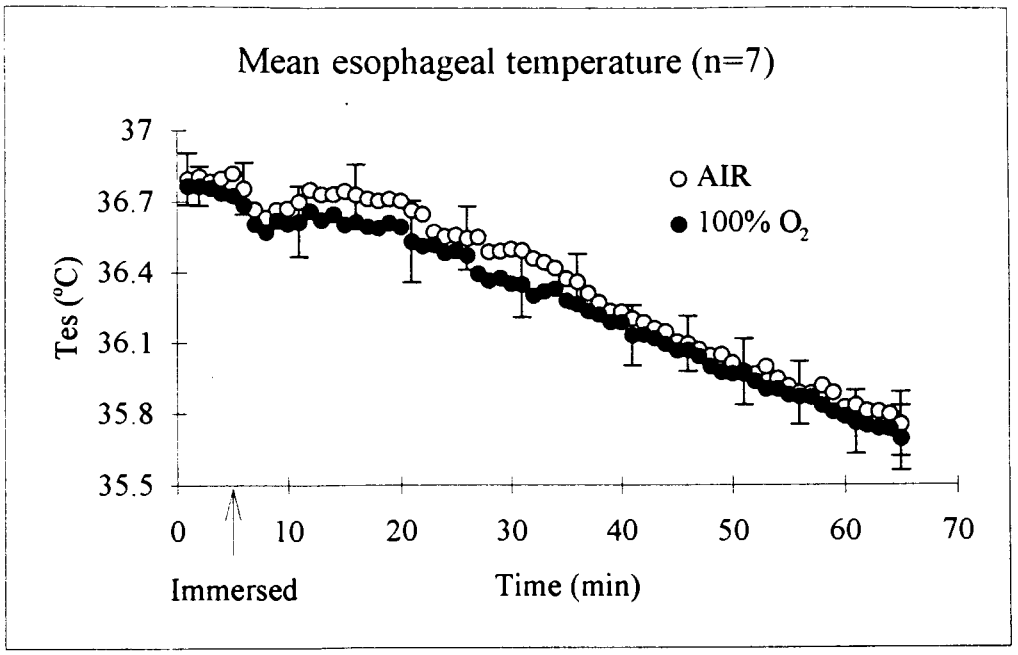

Fig. 2-1: The group mean T_{es} response during the last 5 minutes of rest and during one hour of immersion in 20°C water, breathing air and 100% O_2. The difference in cooling rate was not significantly different between the two conditions.

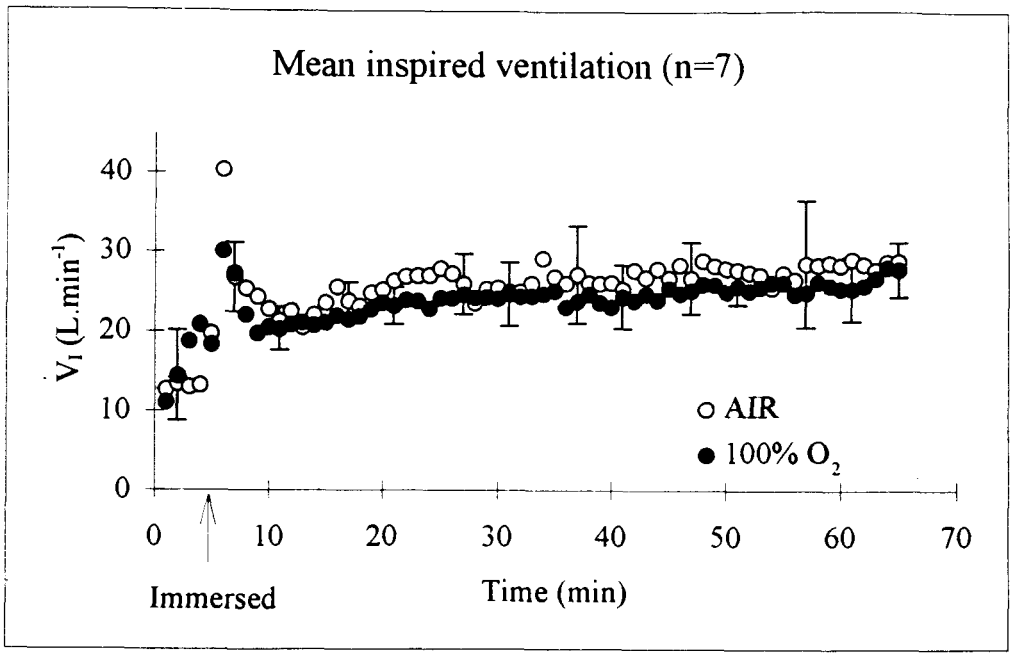

Fig. 2-2: The group mean inspired ventilation (n = 7) did not differ between trials during immersion period and attained similar end immersion values (p = 0.06) in the air (open circles) and the hyperoxic trial (closed circles).

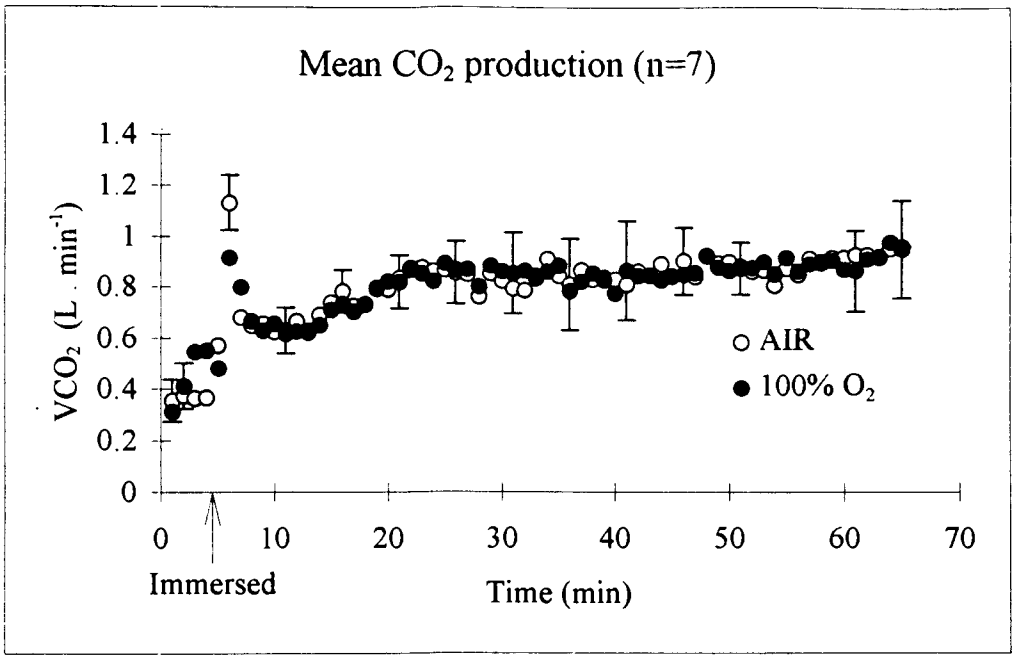

Fig. 2-3: The group mean CO_2 production ($\dot{V}CO_2$) for seven subjects during head out immersion breathing air and 100% O_2.

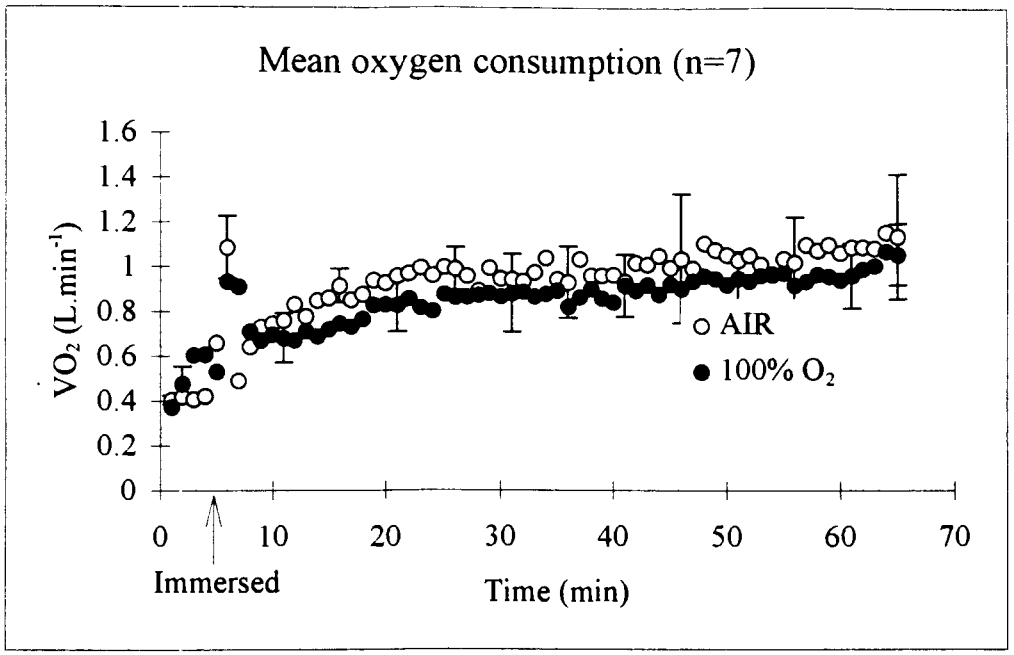

Fig. 2-4: The group mean oxygen uptake ($\dot{V}O_2$) for seven subjects during head out immersion breathing air and 100% O_2.

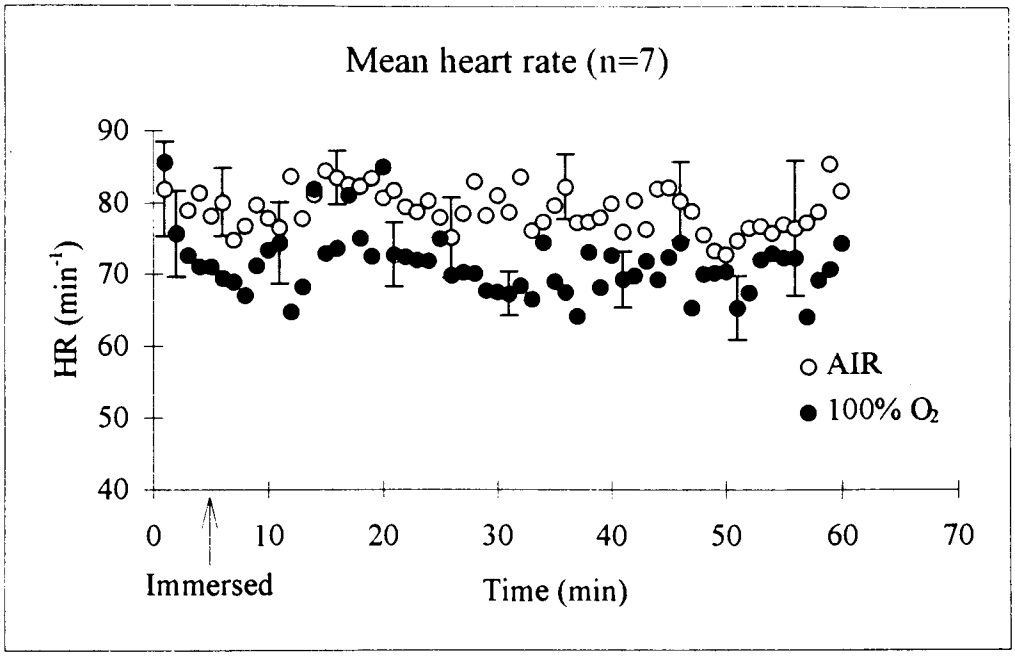

Fig. 2-5: The group mean heart rate (n = 7) was significantly lower ($p \leq 0.05$) in hyperoxia than in air.

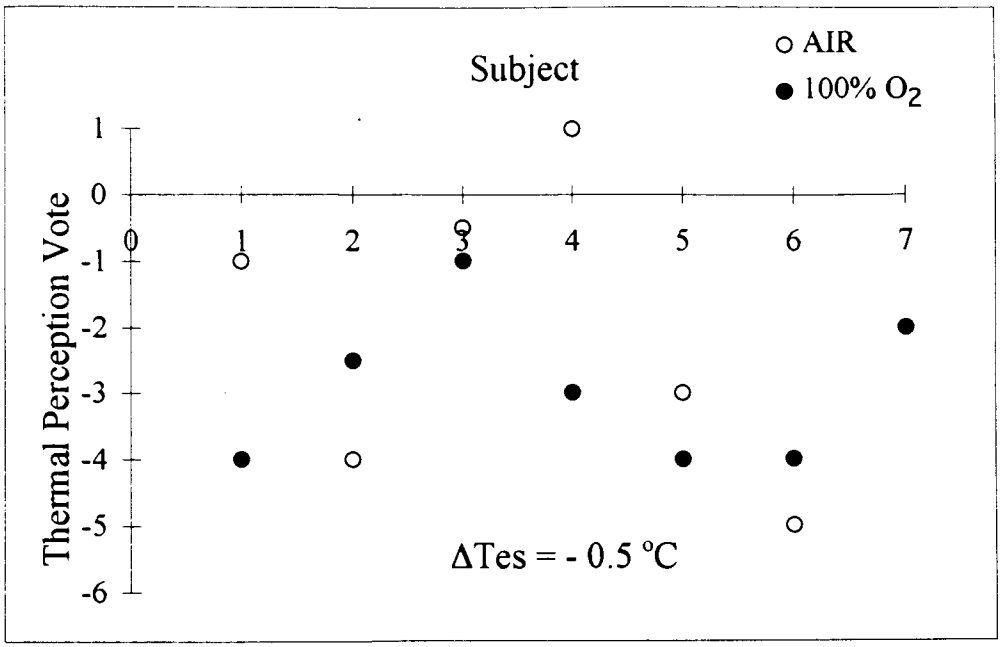

Fig. 2-6: Individual thermal perception vote at ΔT_{es} = -0.5°C for seven subjects immersed in 20°C water while breathing air and 100% O_2. There was no significant difference between the conditions.

STUDY III

THE THERMOREGULATORY RESPONSE OF HUMANS TO COLD WATER IMMERSION DURING COMPRESSED AIR BREATHING AND INHALATION OF 30% NITROUS OXIDE

ABSTRACT

Nine male subjects were immersed to the neck in 15°C water in the wet lock of a hyperbaric chamber on four separate occasions. Subjects inspired air at 1, 3 and 5 ata (PN_2 of 0.8, 2.4 and 4.0 atm, respectively) and a normoxic gas mixture containing 30% N_2O at 1 ata (PN_2O = 0.3 atm). Measurements of skin temperature (T_{sk}) from four sites, esophageal temperature (T_{es}), inspired ventilation ($\dot{V}_I$), oxygen uptake ($\dot{V}O_2$) and heart rate (HR) were recorded at minute intervals. In addition, the subjective perception of thermal comfort was evaluated every 5 minutes.

The perception of thermal comfort progressively improved with an increase in narcosis but the difference was significant only when the nitrous oxide trial was compared with air at 1 ata. Compressed air at 5 ata and PN_2O = 0.3 atm caused an increased cooling rate of T_{es} (5 ata: -2.63 ± 0.42°C·h^{-1}, N_2O: -2.65 ± 0.44 °C·h^{-1} ($p \leq 0.05$); compared with 1 ata: -2.05 ± 0.36°C·h^{-1} and 3 ata: -2.3 ± 0.4°C·h^{-1}). The core temperature for the onset of shivering (ΔT_{es}) was shifted to a lower value with an increase in PN_2 and the effect was dose dependent (-0.27 ± 0.07°C at 1 ata, -0.38 ± 0.15°C at 3 ata and -0.6 ± 0.13°C at 5 ata; $p \leq 0.05$ at 5 ata compared with 1 ata air breathing). The narcotic effect of nitrous oxide shifted the threshold for the onset of shivering to an even lower value than observed with compressed air (-1.08 ± 0.15°C, $p \leq 0.05$). $\dot{V}O_2$ increased upon immersion and also increased as T_{es} decreased. However, at any given T_{es}, the $\dot{V}O_2$ in the N_2O trial was significantly lower than in all air trials ($p \leq 0.05$). In contrast, among the air trials, for any given T_{es} the $\dot{V}O_2$ response during the 5 ata trial was higher compared with 1 and 3 ata, although this difference was significant only in 5 subjects with the highest cooling rate.

INTRODUCTION

Hypothermia in divers is one of the main hazards in deep commercial diving (Keatinge et al. 1980, Hayward and Keatinge 1979) and has been identified as a cause of fatalities. During diving, divers are exposed to the high convective/conductive heat capacity and a low temperature of the aqueous environment, which induces a major drain of heat from the body surface (Bridgman 1990, Webb 1982, 1970) and respiratory tract (Piantadosi et al. 1981). Padbury et al. (1987) observed that a diver performing a simulated wet dive in a hyperbaric chamber was unaware of his falling body temperature, thus he did not elevate the temperature of his breathing gas nor did he exhibit any thermogenic responses.

In Study I of this thesis, subjects perceived cold water immersion at 6 ata consistently more thermally comfortable than at 1 ata, despite the greater core cooling observed during the hyperbaric experiment. Other investigators have also observed that narcosis impairs a person's perception of thermal status (Pertwee et al. 1990, 1986) and thus their ability to initiate any effective countermeasure, exacerbating the progression to hypothermia (Keatinge, Hayward and McIver 1980, White et al. 1980, Hayward and Keatinge 1979).

Study II demonstrated, that breathing 100% oxygen at 1 ata did not alter thermoregulatory response (Savic and Mekjavic 1994). Hence this suggests that an accelerated core cooling rate and improved perception of thermal comfort observed in subjects immersed at 6 ata (Study I), are due to a pressure related narcotic effect of nitrogen. It has been shown that the alteration of thermal perception and shivering response are also induced by inhalation of a general anesthetic (Giesbrecht 1994, Lopez et al. 1994, Vassilieff et al. 1994, Kurz et al. 1993, Sessler 1991, Hammel 1988), and a sub-anesthetic concentration of nitrous oxide (Cheung 1993, Mekjavic and Sundberg 1992, Passias et al. 1992). The aim of the present study was to investigate whether the onset of

hypothermia among compressed air divers was accelerated due not only to an extensive heat loss, but also to an attenuated heat production.

Comparative behavioural studies using nitrous oxide and hyperbaric air have shown that 30% N_2O in a normoxic air mixture induces psycho-motor impairment similar to compressed air at 6.7 ata (Biersner 1987, Biersner et al. 1977). The anesthetics used in clinical practice such as nitrous oxide, ethylene and cyclopropane are considered inert (Featherstone and Muehlbaecher 1963), and seem unlikely to have a different mechanism of action than N_2 (Carpenter 1954). The concentration of anesthetics used clinically far exceeds the narcotic potency of N_2 in compressed air diving. There are, however, some reports which suggest that inhalation anesthetics act directly and negatively on cardiovascular thermoregulation by suppressing the onset threshold for initiation of an effective regulatory response (Kurz et al. 1993, Sessler 1991).

The oxygen consumption data from Study I were not sufficient to determine whether the observed increase in core cooling at 6 ata is due to increased heat loss or decreased heat production. This study was, therefore, designed to investigate whether an elevated level of PN_2 (2.4 and 4.0 atm) suppresses thermoregulatory shivering in the subject immersed in cold water. A second objective was to determine, whether the improvement of thermal comfort observed at 6 ata (Study I) occurs at lower levels of PN_2. It was postulated that if such an effect on autonomic and behavioural thermoregulation exists, it would be dose dependent. The study also compared the effect of 30% N_2O and hyperbaric N_2 on human responses to cold immersion. Their effect on thermoregulatory response and perception of thermal comfort is discussed.

METHODS

Nine healthy male subjects participated in a head out immersion in 15°C water on four separate occasions for a maximum of one hour. Their participation was previously approved by the attending physician. The experimental protocol was approved by the institutional Ethics Review Committee and the procedure was thoroughly explained to each subject prior to their participation and informed consent. Subjects were aware that they could withdraw from the study at any time. All subjects had previous experience with compression in a hyperbaric chamber. On one occasion subjects inspired a gas mixture of 30% N_2O, 20.93 % O_2 and 49.07 % N_2 at 1 ata. On other occasions they inspired air at ambient pressures of 1, 3 and 5 ata. The trials were conducted in a hyperbaric chamber.

Experimental trials were chosen randomly and were spaced one week apart, to avoid adaptation to hypothermia. To avoid the effect of circadian rhythm, subjects performed each immersion at the same time of the day. Once the subject was instrumented, he sat in a chair suspended above the wet lock of the hyperbaric chamber. A twenty minute resting period was incorporated in each normobaric trial (air at 1 ata and normoxic gas mixture with 30% N_2O) to allow saturation of the tissue with nitrous oxide. In hyperbaric trials (at 3 ata PN_2 is 2.4 atm, at 5 ata PN_2 is 4.0 atm) only a five minute resting period was allowed once the desired pressure was reached. This change in protocol was due to the restriction of the total bottom time (45 min at 5 ata and 55 min at 3 ata including compression) in order to limit the decompression requirement. After the resting period was completed, the subject was immersed in continuously stirred water while suspended by a pulley system and sat in the water. A normobaric immersion was terminated after 60 minutes, or when T_{es} dropped to either 35°C or 2°C below the pre-immersion value. The subjects was then rewarmed in a warm stirred water bath

maintained at 40°C. In all hyperbaric trials subjects were transferred to the main lock for rewarming in a sleeping bag before decompression commenced.

Skin temperature was measured from four sites (upper arm, chest, thigh, calf) with YSI 701 thermistor probes (Yellow Springs Instruments, Yellow Springs, OH). Mean T_{sk} ($\overline{T}_{sk}$) was obtained by taking the unweighted average of all four sites. A flexible YSI 704 thermistor probe was inserted through subject's nostril into the esophagus, to the level of the left ventricle, for monitoring the esophageal temperature. Inspired ventilation was measured by a flow meter (Alpha Technologies Ventilation Module, Laguna Hills, CA) connected to the inspiratory side of an oronasal mask. In hyperbaric trials the inspiratory side of the flow meter was open to the chamber atmosphere. In normobaric trials, the breathing mixture, either air or 30% N_2O, was delivered from compressed gas cylinders to a humidification system consisting of a water bath maintained at room temperature and covered with a Douglas bag (see Fig. 3-1). The outlet from the Douglas bag was connected to the flow meter. This ensured similar humidity and temperature of the gas in all trials and reduced respiratory evaporative heat loss to a similar degree in all four conditions. Expired gas was directed to a 5 L fluted Plexiglass mixing box. A continuous 0.5 $L \cdot min^{-1}$ sample of expired gas was drawn from the mixing box and analyzed using O_2 and CO_2 analyzers (Ametek Systems, Pittsburgh, PA). In hyperbaric trials an additional 5 L mixing box was introduced on the expiratory side outside the chamber to ensure that a steady gas flow was drawn at constant pressure to the gas analyzers (see Fig. 3-2). Heart rate was measured from an electrocardiogram (Physio - Control Systems, Washington, USA) obtained from two precordial electrodes placed laterally on the chest and a ground electrode on the mid portion of the right scapula. An electrocardiogram was examined for arrhythmias and heart rate was determined from the average R-R interval of seven consecutive beats. Subjects rated their perception of thermal comfort at 5 minute intervals, on a 21-point scale (Enander et al. 1979), where +10 was defined as "very very hot", 0 as "neutral" and -10 as "very very cold". The

narcotic potency (NP) of PN_2 and PN_2O was determined from the Bunsen coefficient (Bennett 1982, Carpenter 1954) multiplied by the pressure of the gas (atm). The Bunsen coefficient (Bc) determines to what extent the gas is soluble ($cc \cdot cc^{-1}$) in olive oil (representing the lipid biomembrane) at 37°C at 1 atmosphere (760 mmHg). Bc for N_2 is 0.067 and for N_2O is 1.6 ($cc \cdot cc^{-1}$). Therefore, the calculated NP of N_2 in air at normal atmospheric pressure ($PN_2 = 0.8$ atm) is $NP = 0.067 \cdot 0.8 = 0.0536$ $cc \cdot cc^{-1} \cdot atm$. The NP of 30% N_2O normoxic gas mixture inspired at 1 ata ($PN_2O = 0.3$ atm, $PN_2 = 0.5$ atm) is $NP_{N2+N2O} = NP_{N2} + NP_{N2O} = 0.51$ $cc \cdot cc^{-1} \cdot atm$, which is equivalent to the narcotic potency of nitrogen present in compressed air at 9.57 ata ($PN_2 = 7.66$ atm).

All variables were continuously sampled and recorded at 10-sec intervals, using a data acquisition system (Hewlett Packard 3497A) and LabView 2.1 software (LabView, National instruments) on a Macintosh II computer (Apple Computer, Inc., Cupertino, CA).

Data analysis

A one way analysis of variance ANOVA with repeated measures was performed on the mean of each of 6 variables: T_{es}, $\overline{T}_{sk}$, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_I$ and HR for four conditions (1, 3 and 5 ata air and 0.3 atm N_2O). Resting values for all variables were determined by averaging the values recorded during the resting phase. For the analysis during the immersion phase, the first observation was taken from minute four of immersion, after the initial dynamic response of all variables due to onset of immersion had stabilized. When a single significant difference among the mean values was found, a multiple comparison of means, using a modified Tukey's test, was performed to determine the source of the difference (Kleinbaum et al. 1988). Linear regression analysis was performed on the linear portion of the T_{es} response of each subject separately (Appendix 2, 3-14 and 3-15). The resulting slopes of the T_{es} response were statistically analyzed in a one way ANOVA.

The linear portion of the T_{es} cooling curve was determined from the time of immersion when a steady fall in T_{es} was observed until the end of immersion (Appendix 2, Fig. 3-14 and 3-15). Also a logarithmic regression was performed on the T_{es} cooling curve and tested for parallelism. Similarly, a linear regression and logarithmic regression were performed on the $\dot{V}O_2$ response and the slopes were tested for parallelism. The onset of shivering was determined from the increase in $\dot{V}O_2$, and the shivering threshold defined as drop in T_{es} relative to the resting phase, beyond which all minute $\dot{V}O_2$ measures were greater than the median $\dot{V}O_2$ value of the subject at rest (Appendix 2, Fig. 3-14 and 3-15). The shivering threshold values obtained were compared using a one way ANOVA. Ratings of thermal comfort for the four conditions were compared with a Friedman non parametric test. For all analyses, the 5% level was chosen as the level of statistical significance.

Graphical presentation of the data

Due to the restricted immersion time in the hyperbaric exposure some subjects of higher mass did not establish a steady cooling rate. Therefore, for graphical presentation of the relationship $\Delta\dot{V}O_2/\Delta T_{es}$ only 5 subjects (1, 3, 4, 6 and 9 from Table 3-3) who cooled more than 1°C during the time of the shortest immersion (25 minutes) were selected. Other mean data were also plotted over the time of the shortest immersion.

RESULTS

The immersions at 3 and 5 ata were shorter (40 and 30 minutes maximum respectively) than in normobaric trials, due to the restriction of decompression table and ethics committee regulations for hyperbaric exposure. All subjects experienced mild euphoria during N_2O breathing, which in some subjects persisted throughout the 20 minutes of rest and most of the immersion. None of the subjects experienced nausea with nitrous oxide breathing. The physical characteristics of the subjects are given in Table 3-1.

Resting data

The mean values of physiological data collected while the subjects rested prior to immersion are provided in Table 3-2. There was no difference between the pre-immersion data variable values and any condition except for $\dot{V}O_2$ and $\dot{V}_I$. Resting $\dot{V}O_2$ was higher ($p \leq 0.05$) during the 5 ata and N_2O trial than in the control trial at 1 ata. Resting $\dot{V}_I$ was also higher in the 3 ata and during the N_2O trial when compared with 1 ata ($p \leq 0.05$).

Immersion data

$\bar{T}_{sk}$ dropped quickly upon immersion to a level slightly above the water temperature and did not vary between the trials (Table 3-2). Mean $\dot{V}_I$ during immersion was significantly lower in the N_2O trial than in the air trials at 1 ata, 3 ata or 5 ata, but there was no significant difference between any of the air trials. Mean HR and $\dot{V}CO_2$ during immersion were not significantly different between any two trials.

Linear regression analysis of the linear portion of the T_{es} response showed significantly higher cooling rates at 5 ata and during nitrous oxide analgesia ($p \leq 0.05$) than when breathing air at 1 ata (Table 3-3). Fig. 3-3 (see also Appendix 2 Fig. 3-12). presents

the change of mean T_{es} with time for all four conditions. The ability to present the mean data of all 9 subjects in the time domain is limited by the time period of the shortest immersion (25 minutes). On the graph, air trials are noted as 1 ata, 3 ata and 5 ata (PN_2 = 0.8 atm, 2.4 atm and 4.0 atm, respectively), and the nitrous oxide trial is noted as 0.3 atm N_2O. The first point represents the mean resting value.

In order to be able to analyze the effect of temperature change ΔT_{es} in all 9 subjects, the limiting ΔT_{es} was 0.4 °C (subject 2 from Table 3-3). That drop in T_{es} caused a mean increase in $\dot{V}O_2$ from the pre-immersion value ($\Delta \dot{V}O_2$) of 0.37 ± 0.15 L· min^{-1} at 1 ata, 0.45 ± 0.18 L· min^{-1} at 3 ata, 0.47 ± 0.06 L· min^{-1} at 5 ata and 0.2 ± 0.18 L· min^{-1} in the N_2O trial ($p \leq 0.05$ in N_2O compared with 1 ata). The $\Delta \dot{V}O_2$ response was significantly lower in the N_2O trial only ($p \leq 0.05$). In this trial two subjects did not shiver at all (subjects 3 and 9). However, when analyzing the five subjects who showed the greatest cooling rates (subjects 1,3,4,6 and 9 from the Table 3-3), a significantly higher $\dot{V}O_2$ was found in the 5 ata trial compared with the 1 ata ($p \leq 0.05$). Fig. 3-4 presents the mean $\dot{V}O_2$ response of all nine subjects during the first 25 minutes of immersion at 1, 3, 5 ata and 30 % N_2O (see also Appendix 2 Fig. 3-13).

Once the shivering commenced, the gain of the shivering response (expressed as the ratio $\Delta \dot{V}O_2/\Delta T_{es}$) showed a similar tendency between ΔT_{es} of 0.3°C to 0.7°C during all air conditions but the slope was depressed in the N_2O condition. This data is shown in Fig. 3-5, where each point represents the mean value of ΔT_{es} and $\Delta \dot{V}O_2$ calculated at each minute up to 25 minutes. Since the dynamic response took place up to approximately 0.2°C of T_{es} and the substantial cooling in the subjects of higher mass did not occur in the first 25 min of immersion, additional analysis was performed on the 5 subjects who obtained a minimum drop of 1°C in all four experimental conditions. This allowed data to be extended to ΔT_{es} of -1.2°C and showed the effect of PN_2 on the gain of the shivering response more clearly. From Fig. 3-6 it is evident that there is no difference in the slopes between the air conditions (supported with statistical analysis; $p > 0.05$),

and that shivering is significantly suppressed in the N_2O condition ($p \leq 0.05$). Although there was no difference in the gain of the shivering ressponse, the estimated T_{es} threshold for the onset of shivering decreased progressively with elevated PN_2 and was significantly lower in the 5 ata, as well as in the N_2O trial (Table 3-4). Subjects perceived the immersions during N_2O breathing as thermally more comfortable (Fig. 3-7) when compared with 1 and 3 ata for the same drop in T_{es} (ΔT_{es}; $p \leq 0.05$). There was no significant difference in thermal comfort vote among the air conditions. The relationship between the shivering threshold and atmospheric pressure is presented in Fig. 3-8. According to the calculated narcotic potency, breathing 30% N_2O at 1 ata ($PN_2O = 0.3$ atm, $PN_2 = 0.5$ atm) would have narcotic potency equivalent to N_2 in air at 9.6 ata ($PN_2 =$ 7.7 atm). Fig. 3-9 shows the relationship between the thermal comfort vote at $\Delta T_{es} =$ 0.5°C and atmospheric pressure. Fig. 3-10 (top) reveals a linear relationship between the threshold for shivering and narcotic potency of the breathing gas ($R^2 = 0.99$). The mean thermal comfort votes at $PN_2 = 0.8$, 2.4 and 4 atm and $PN_2O = 0.3$ atm are again very linear ($R^2 = 0.99$; Fig. 3-10 bottom).

DISCUSSION

The present study suggests that during cold water immersion the shivering response does not depend on the PN_2 within the normal pressure range of air diving The perception of coldness appears to be progressively attenuated with an increase in narcosis (Fig. 3-9), but the effect was not significant between 1 and 5 ata. In contrast, an increase in PN_2 caused a lower esophageal temperature threshold for the onset of shivering thermogenesis and a greater cooling rate $\dot{T}_{es}$, suggesting that nitrogen narcosis contributes to a delayed thermoregulatory response and faster development of hypothermia.

Mild nitrous oxide anesthesia (30% N_2O) showed a greater effect on the threshold for shivering and perception of thermal comfort in accordance with its higher lipid solubility and narcotic potency (Carpenter 1954, Meyer and Hopff 1923). As shown in Fig. 3-10 there is a linear relationship between the shivering threshold as well as thermal comfort vote with narcotic potency of N_2 in air at 1, 3 and 5 ata and 30% N_2O at 1 ata.

An increased rate f core cooling ($\dot{T}_{es}$), a lower shivering threshold and a depressed shivering response, were also the observed response to breathing 30% N_2O (Passias et al. 1992). Passias et al. immersed subjects in 15°C water, breathing either air or 30% N_2O and observed that for any drop in T_{es} during cooling, the $\dot{V}O_2$ response was lower in the N_2O trial than in the air trial. The situation is similar for the 5 subjects in Fig. 3-6. For any ΔT_{es} between -0.5 and -1.2°C the change in the $\dot{V}O_2$ from the pre-immersion value ($\Delta \dot{V}O_2$) was lower for the subject breathing N_2O gas mixture than air at any pressure. The same method of clamping skin temperature in 20°C water and measuring the thermoregulatory response during air and various levels of N_2O analgesia (10, 15, 20 and 25% N_2O) was conducted by Cheung in 1993. He observed a greater drop in T_{es} from the pre-immersion value and a lower $\dot{V}O_2$ response when 15 - 25% N_2O was inspired, but the effect did not appear to be dose dependent (Fig. 3-11). The lowest concentration of N_2O (10% N_2O, 70% N_2, 20% O_2) caused a significantly higher $\dot{V}O_2$ response, similar to the increase observed with 5 ata in the present study, when only 5 subjects with the highest cooling rate were analyzed. However, since the drop in T_{es} was greater during 10% N_2O compared with air, the gain of the shivering response (slope $\Delta \dot{V}O_2/\Delta T_{es}$) did not differ between those two conditions. The mixture of $PN_2O = 0.1$ atm and $PN_2 = 0.7$ atm is similar in narcotic potency to $PN_2 = 3.1$ atm or air at 3.86 ata. When Cheung's data were reanalyzed (1993), there was also no difference in $\Delta \dot{V}O_2/\Delta T_{es}$ among the various conditions. Similarly, in the present study, a higher $\dot{V}O_2$ response was observed at 5 ata (Fig. 3-4) due to greater T_{es} cooling (Fig. 3-3). However, the slope of the relationship $\Delta \dot{V}O_2/\Delta T_{es}$ for 5 ata did not differ ($p > 0.05$) from the slope at 1 ata (Fig. 3-

6) in five subjects who cooled for more than 1°C T_{es} during first 25 minutes of immersion. In contrast, for 30% N_2O the $\Delta \dot{V}O_2$ response as a function of ΔT_{es} was depressed (Fig. 3-6).

It is possible that the increased core cooling rate measured at 5 ata and 30% N_2O conditions result from an increased heat loss from the periphery. However, the $\overline{T}_{sk}$ during immersion did not vary among trials, which suggests that there was no change in the core - skin temperature gradient due to narcosis. Also, Cheung (1993) and Passias et al. (1992) showed no change in skin heat flux during any N_2O trial, which indicates that the amount of heat loss is similar during N_2O and air breathing. It is possible, that a strong cutaneous stimulus from immersion in cold water and the increased central drive due to falling core temperature, act together to override any vasodilatory effect of the anesthetic. However, it has been demonstrated, that in contrast to many inhaled anesthetics, N_2O may increase the sympathetic outflow from the brain (Fukunaga and Epstein 1973) and inhibit removal of norepinephrine by the lung (Naito and Gillis 1973). Therefore, norepinephrine released into the venous circulation would be available to act on the systemic circulation producing some vasoconstriction.

Other effects, such as that exerted by N_2O on cutaneous thermoreception and the peripheral conduction of thermal stimuli, are reported to be negligible (Jong and Nace 1967, Somjen 1967). Narcosis produced with an inhaled anesthetics impairs synaptic transmission at either pre- or postsynaptic junctions (Bennett 1967, Thesleff 1956). Similarly, compressed air inhibits synaptic transmission (Bennett 1982), decreases the frequency of the action potentials (Carpenter 1954), decreases the magnitude and increases the duration of action potentials (Rosenberg and Heavner 1980), suggesting that both peripheral and central neural structures are affected by inert gas narcosis imposed at high pressures.

Shivering is believed to occur only when maximal vasoconstriction and behavioural manoeuvres are insufficient to maintain an appropriate mean body temperature.

According to Lopez et al. (1994), vasoconstriction occurs at ΔT_{es} = -0.2°C, whereas shivering occurs after a much greater change in core temperature (ΔT_{es} = -1.4°C) (also Kurz et al. 1993, Sessler 1991). The observation, that initiation of shivering is controlled less well than vasoconstriction would also suggest, that shivering may be, in large part, mediated by phylogenetically older centers (Satinoff 1978) particularly the spinal cord (Herdman 1978). Satinoff (1978) has proposed a hierarchical organization of thermoregulatory control in which the signal is successively processed in the spinal cord, medulla and hypothalamus. In this system the phylogenetically "older" centres subserve "newer" centres dominated by the hypothalamus, responsible for finer thermoregulatory control. Experimental evidence supports the view, that the areas of highest complexity, involving polysynaptic pathways, are most affected by anesthetics (Poterack et al. 1991) and that the control then passes to a lower centre, possibly in the spinal cord which would exert a coarser regulation, first decreasing the vasoconstriction threshold then the shivering threshold. Satinoffs' concept can be used to explain the results of the present study. Thus, greater impairment of the activation threshold for shivering is caused by inhibition of the higher level integration at the hypothalamus with both N_2 and N_2O narcosis. The regulation is preserved at a lower level, less susceptible to narcotic impairment, thus preserving the thermosensitivity and gain of the shivering response.

The conclusion from this study is, that a compressed air environment and N_2O inhalation increase the core cooling rate ($°C \cdot h^{-1}$) of subjects immersed in 15°C water, and that the effect depends on the narcotic potency of the inspired gas mixture. Perception of thermal comfort is progressively attenuated by an increased narcotic potency of the breathing mixture and the effect is linear (R^2 = 0.99). The core temperature threshold for the onset of shivering is related to the narcotic potency of the inhalate and the relationship is also linear (R^2 = 0.99). Although no difference was found in the gain of shivering response at 1, 3 and 5 ata of air, there was evidence of an attenuated gain in the N_2O condition in 5 subjects.

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TABLES AND FIGURES

Subject	Height (cm)	Weight (kg)	Age (years)
1	182	76.3	24
2	186	88.8	40
3	178	69.5	37
4	180	78.3	23
5	182	92	24
6	182	67.5	20
7	186	74.8	19
8	184	92.3	30
9	175	70.8	30
Mean±SD	181.7 ± 3.6	78.9 ± 9.7	27.4 ± 7.4

Table 3-1: Subjects' physical characteristics

REST

	1 ata	3 ata	5 ata	N_2O
$\dot{V}O_2$ (L· min^{-1})	0.44 ± 0.02	0.54 ± 0.07	0.52 ± 0.02	0.57 ± 0.05
T_{es} (°C)	37.0 ± 0.11	37.07 ± 0.11	37.12 ± 0.13	37.05 ± 0.05
$\bar{T}_{sk}$ (°C)	33.88 ± 0.31	33.33 ± 0.37	33.71 ± 0.56	34.33 ± 0.45
$\dot{V}_I$ (L· min^{-1})	13.2 ± 0.8	23.30 ± 0.43	19.80 ± 0.43	16.50 ± 0.40
$\dot{V}CO_2$ (L· min^{-1})	0.39 ± 0.02	0.52 ± 0.08	0.41 ± 0.03	0.45 ± 0.04
HR (min^{-1})	78 ± 6	76 ± 3	75 ± 3	75 ± 3

IMMERSION

	1 ata	3 ata	5 ata	N_2O
$\bar{T}$ sk (°C)	16.21 ± 0.17	16.52 ± 0.21	16.37 ± 0.4	16.3 ± 0.21
T_{es} (°C)	36.41 ± 0.03	36.51 ± 0.03	36.33 ± 0.04	36.29 ± 0.03
$\dot{V}_I$ (L· min^{-1})	26.6 ± 0.64	28.76 ± 0.52	29.08 ± 0.52	22.56 ± 0.35
$\dot{V}O_2$ (L· min^{-1})	0.95 ± 0.02	1.01 ± 0.02	1.14 ± 0.03	0.85 ± 0.02
$\dot{V}CO_2$ (L· min^{-1})	0.84 ± 0.03	0.87 ± 0.03	0.93 ± 0.02	0.72 ± 0.01
HR (min^{-1})	82 ± 2	73 ± 3	74 ± 3	75 ± 10

Table 3-2: Group mean values of physiological variables while resting prior to immersion (top) and during immersion (bottom). Data is given as mean ± SE.

Subject	1 ata AIR	3 ata AIR	5 ata AIR	0.3 atm PN_2O
1	-3.62	-3.25	-3.97	-3.77
2	-0.80	-0.89	-0.86	-1.88
3	-2.98	-3.45	-2.97	-4.43
4	-2.83	-4.18	-4.64	-4.14
5	-1.33	-1.58	-2.49	-1.68
6	-3.09	-2.81	-3.21	-3.48
7	-1.45	-1.86	-1.33	-2.31
8	-0.72	-0.56	-1.36	-0.94
9	-1.66	-2.09	-2.83	-1.26
Mean±SE	-2.05±0.36	-2.3±0.4	* -2.63±0.42	* -2.65±0.44

Table 3-3: The rate of T_{es} cooling ($°C \cdot h^{-1}$) obtained from the linear portion of the T_{es} cooling curve for nine subjects. (*) significantly different from 1 ata ($p \leq 0.05$)

Subject	1 ata AIR	3 ata AIR	5 ata AIR	0.3 atm PN_2O
1	-0.64	-0.34	-0.79	-1.05
2	-0.08	-0.21	-0.14	-1.08
3	-0.38	-0.54	-1.17	† -1.70
4	-0.59	-1.09	-1.14	-1.09
5	-0.10	0.14	-0.34	-0.66
6	-0.27	-0.79	-0.79	-1.79
7	-0.24	-0.58	-0.05	-0.78
8	-0.05	0.33	-0.47	-0.46
9	-0.09	-0.31	-0.47	† -1.08
Mean±SE	-0.27±0.07	-0.38±0.15	* -0.60±0.13	** -1.08±0.15

† no shivering observed

* significantly different from 1 ata ($p \leq 0.05$)

** significantly different from 1, 3 and 5 ata ($p \leq 0.05$)

Table 3-4: Individual estimated thresholds for the onset of shivering as drop in Tes from the pre-immersion value (ΔT_{es}; °C) for four experimental conditions (1, 3, 5 ata air and 30% N_2O).

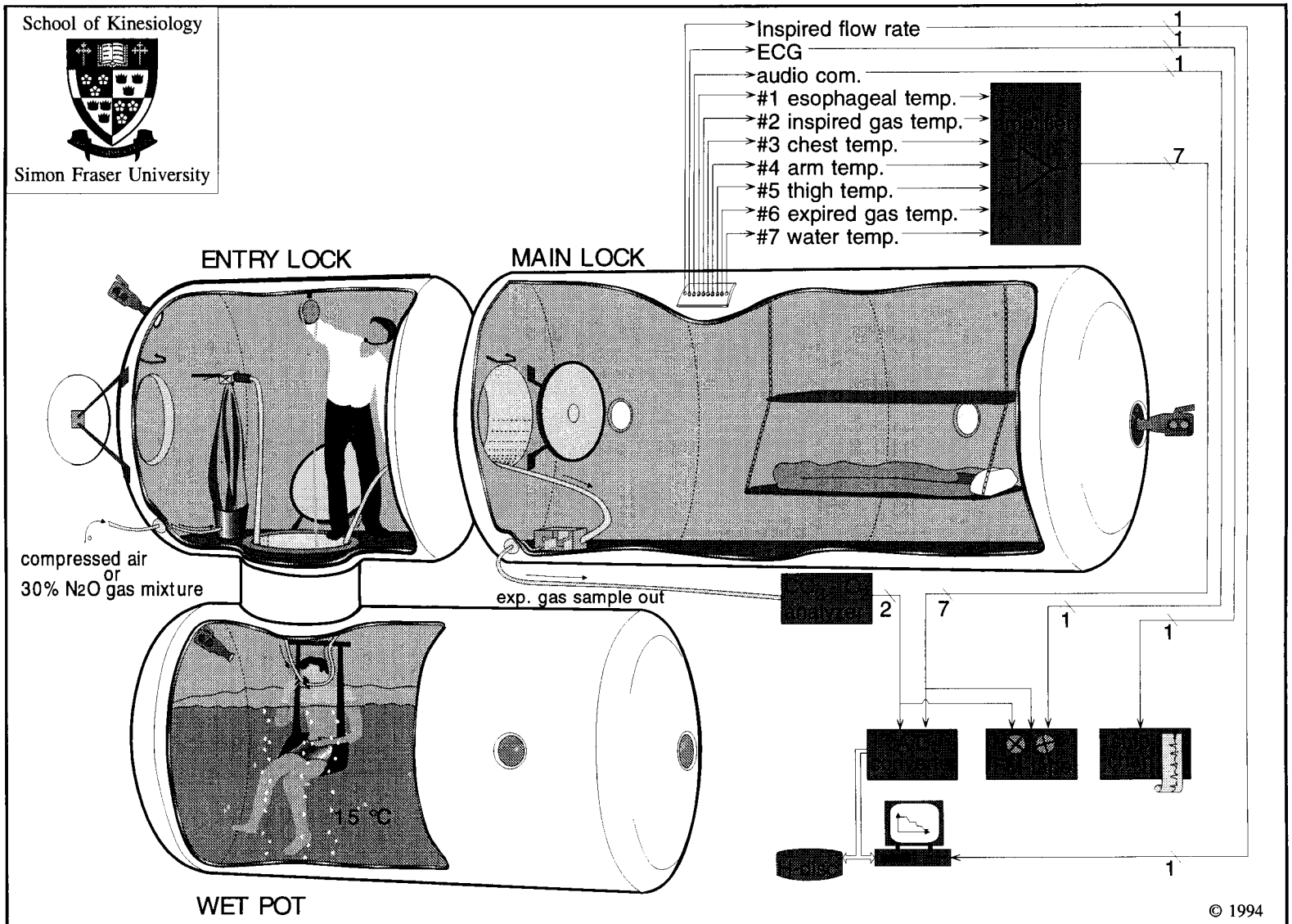

Figure 3-1: Schematic of the experimental setup in normobaric conditions. Subjects cooled in 15°C water inspiring either air or 30% N_2O normoxic gas mixture delivered from pressure cylinders and humidified.

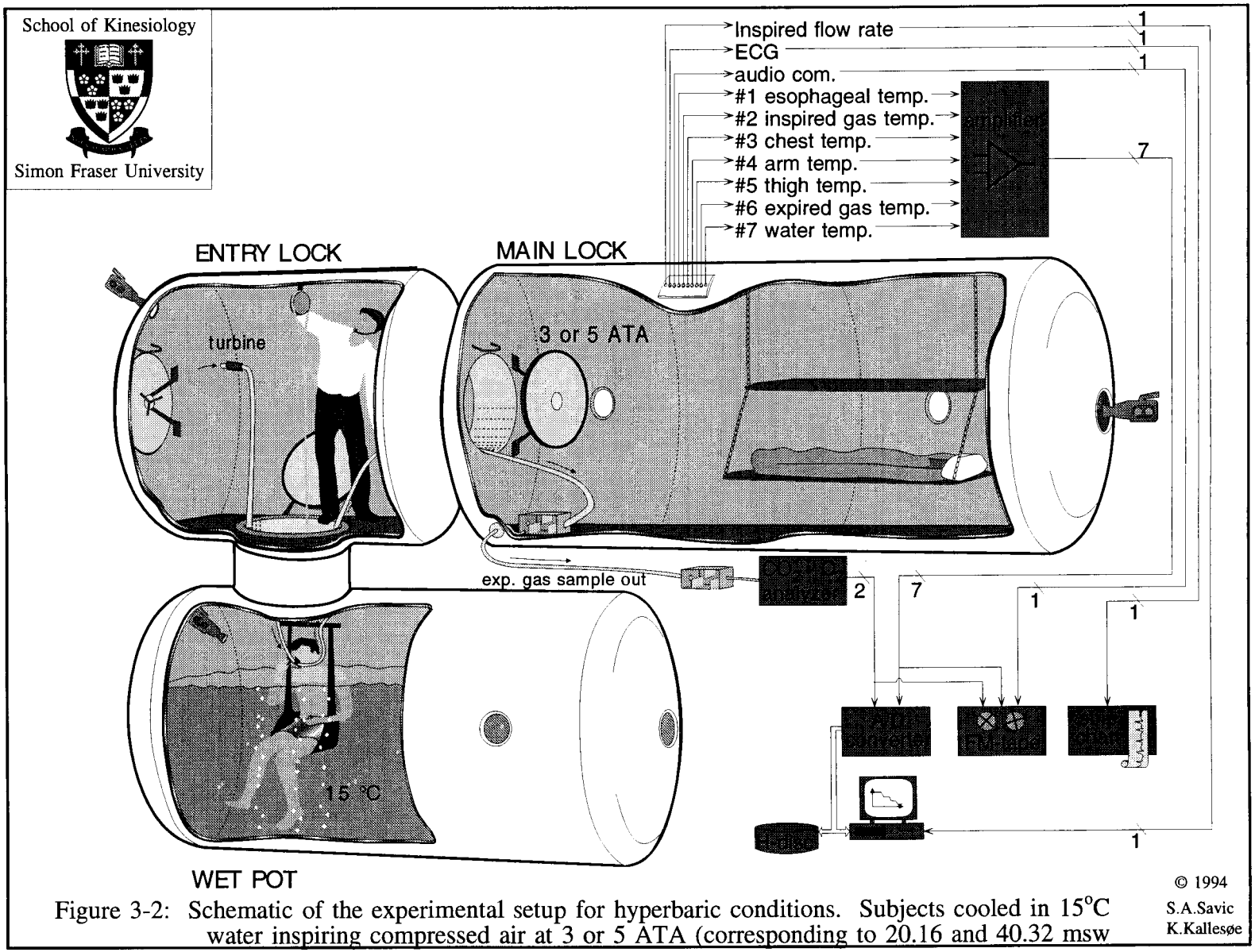

Figure 3-2: Schematic of the experimental setup for hyperbaric conditions. Subjects cooled in 15°C water inspiring compressed air at 3 or 5 ATA (corresponding to 20.16 and 40.32 msw

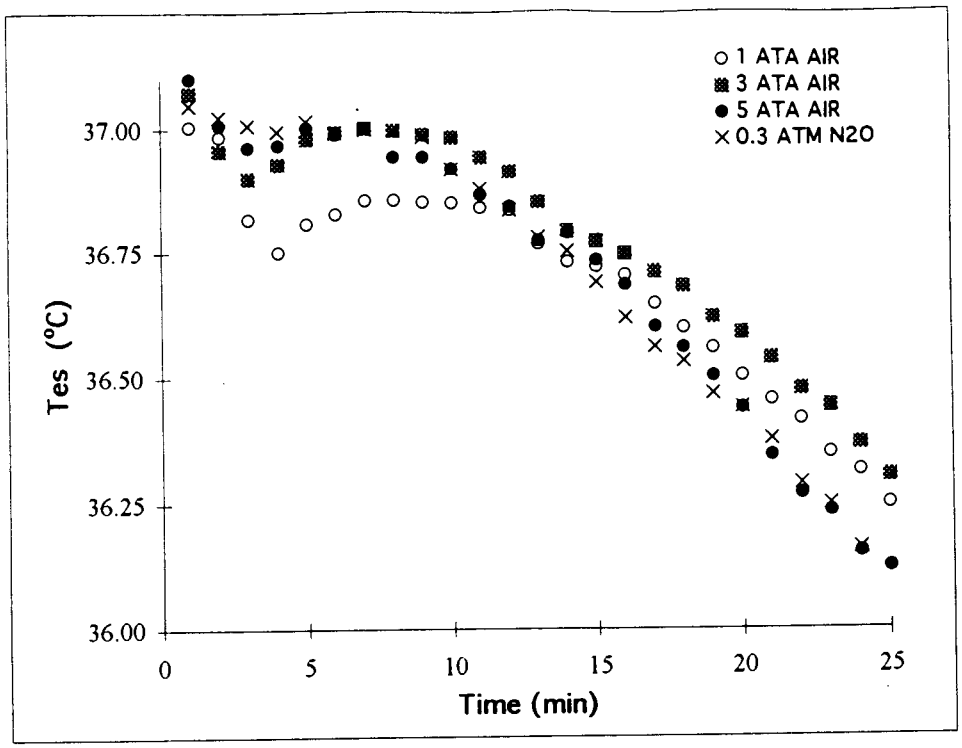

Fig. 3-3: Group mean T_{es} response for nine subjects during the first 25 minutes of immersion in 15°C water at 1, 3 and 5 ata breathing air, and breathing 30 % N_2O at 1 ata. Minute 1 represents resting T_{es} prior to immersion.

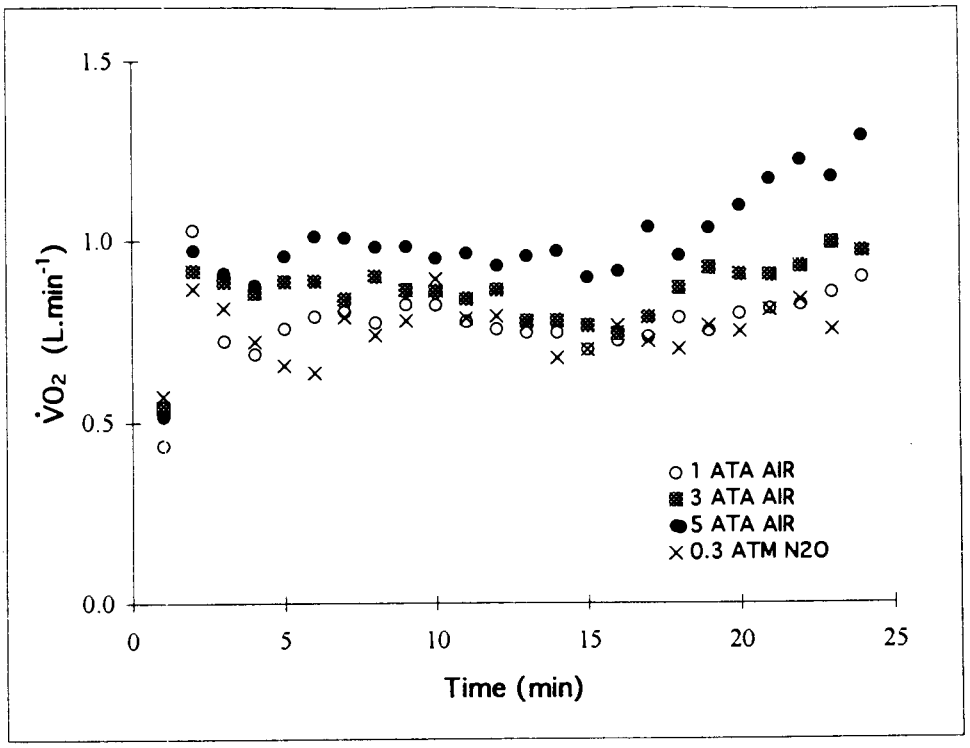

Fig. 3-4: Group mean $\dot{V}O_2$ response to core cooling for nine subjects immersed in 15°C water at 1, 3 and 5 ata breathing air, and breathing 30 % N_2O at 1 ata. Minute 1 represents resting $\dot{V}O_2$ prior to immersion.

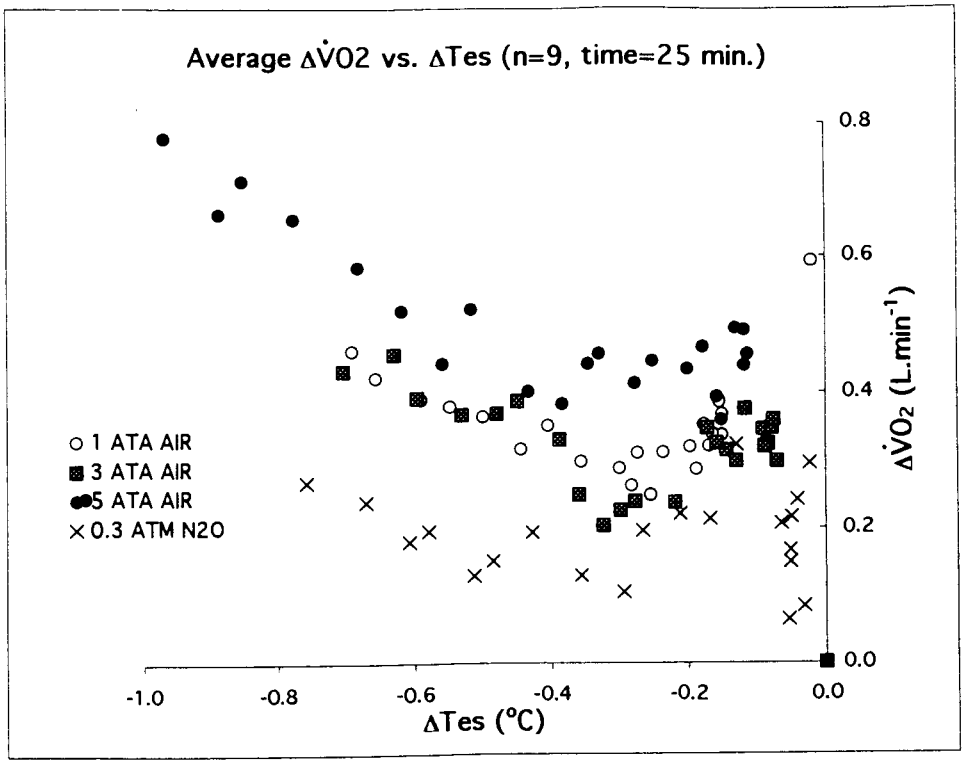

Fig. 3-5: Relative change in the oxygen uptake ($\Delta \dot{V}O_2$) from the pre-immersion value as a function of relative change in T_{es} (ΔT_{es}) from the pre-immersion value for all nine subjects during immersion in 15°C water at 1, 3, 5 ata air and 0.3 atm PN_2O.

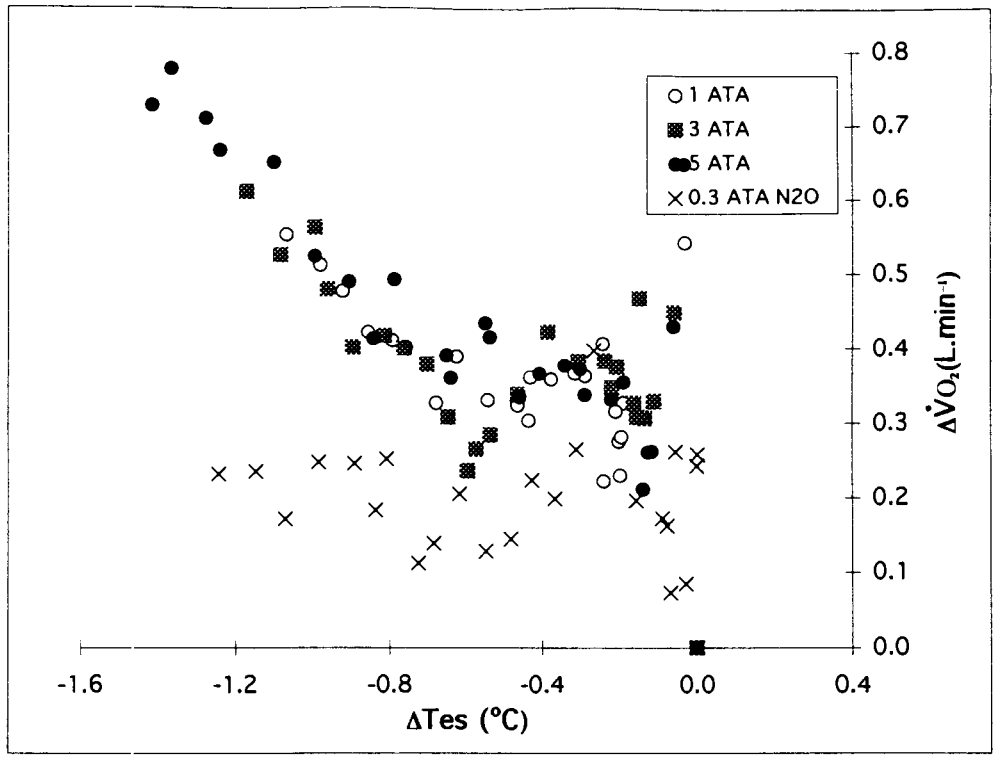

Fig. 3-6: Relative change in the oxygen uptake ($\Delta \dot{V}O_2$) from the pre-immersion value as a function of relative change in T_{es} (ΔT_{es}) from the pre-immersion value for five subjects with the highest cooling during immersion in 15°C water at 1, 3, 5 ata air and 0.3 atm PN_2O.

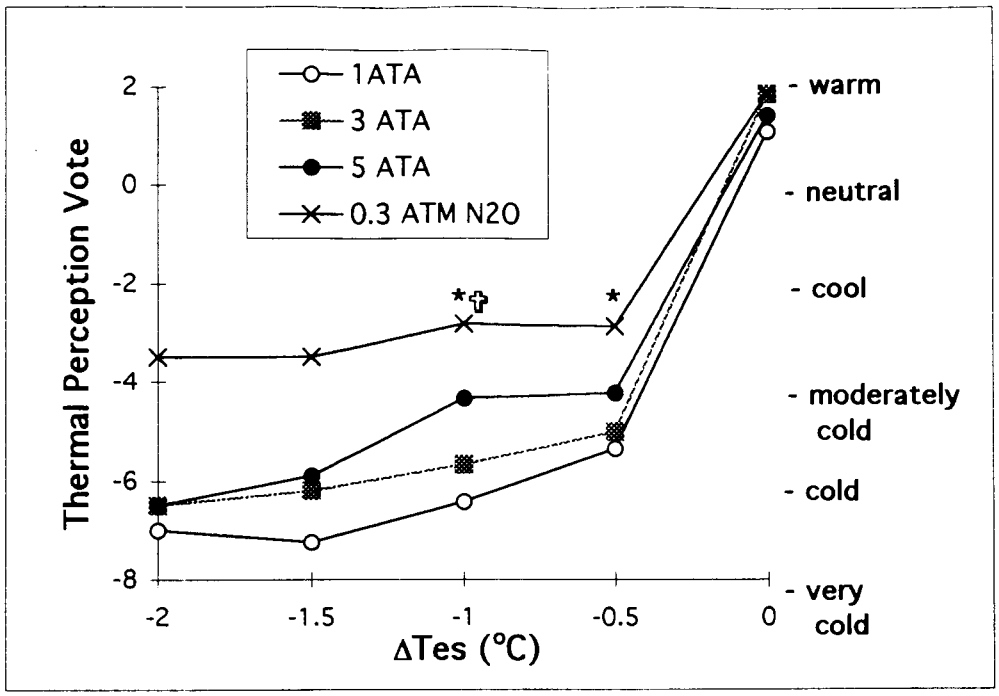

Fig. 3-7: Mean thermal perception vote reported by subjects during immersions in 15°C water at 1, 3, 5 ata air and 0.3 atm PN_2O. Values are the mean of n = 9 at ΔT_{es} = 0°C, n = 8 at -0.5°C, n = 6 at -1°C, n = 4 at -1.5°C and n = 3 at -2°C. The N_2O trial was significantly different compared with 1 ata (*), and 3 ata (⇧).

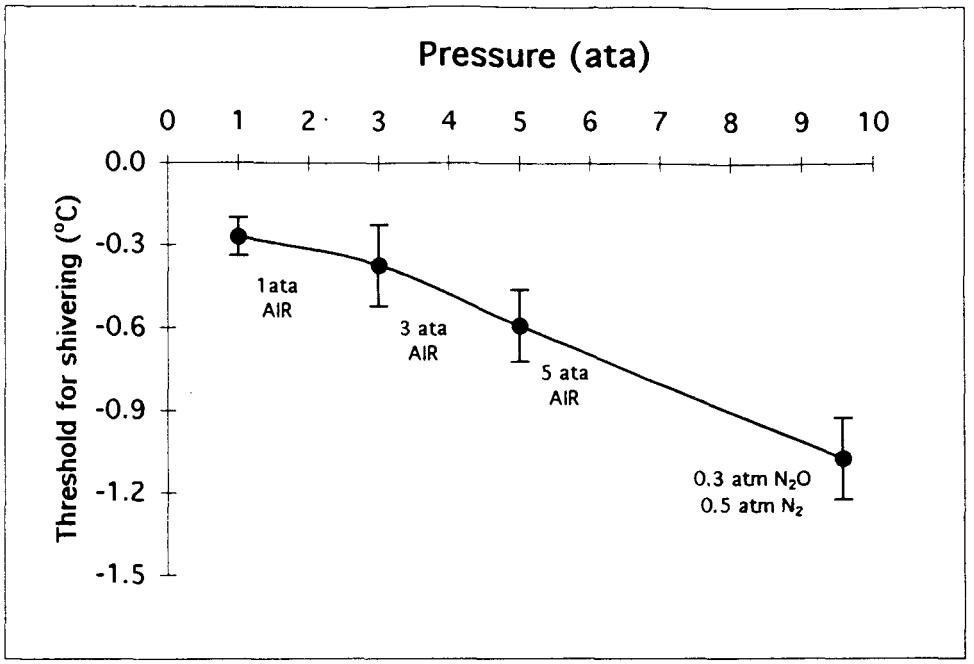

Fig. 3-8: Threshold for the onset of shivering thermogenesis (ΔT_{es}; °C) vs. atmospheric pressure. Calculated narcotic potency of 30% N_2O breathing mixture (PN_2O = 0.3 atm, PN_2 = 0.5 atm) is equivalent to N_2 in compressed air at 9.6 ata (PN_2 = 7.7 atm). Graph presents the mean ± SE for 9 subject.

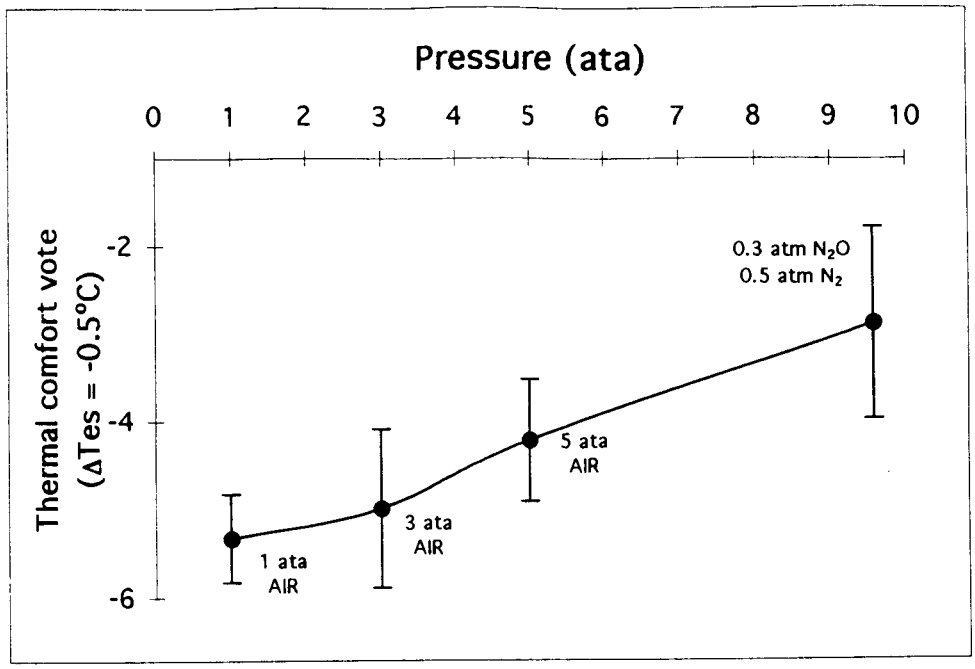

Fig. 3-9: Group mean thermal comfort vote as a function of atmospheric pressure. Calculated narcotic potency of 30% N_2O breathing mixture (PN_2O = 0.3 atm, PN_2 = 0.5 atm) is equivalent to N_2 in compressed air at 9.6 ata (PN_2 = 7.7 atm). Graph presents the mean ± SE for 9 subject.

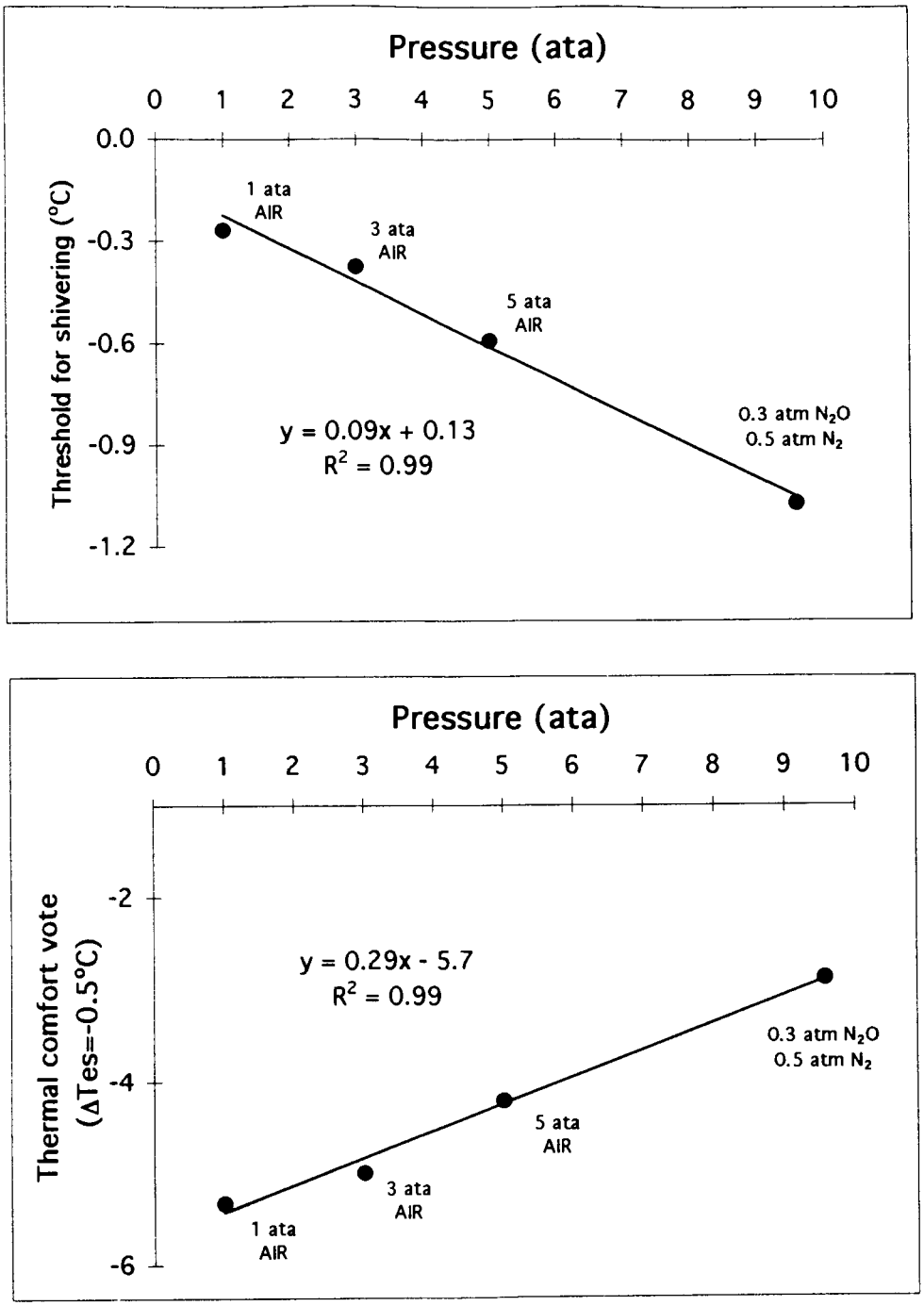

Fig 3-10: Linear regression applied to the relationships of threshold for shivering (top, n = 9) and thermal comfort vote (bottom, n = 8) as a function of the narcotic potency of N_2 at increased atmospheric pressure.

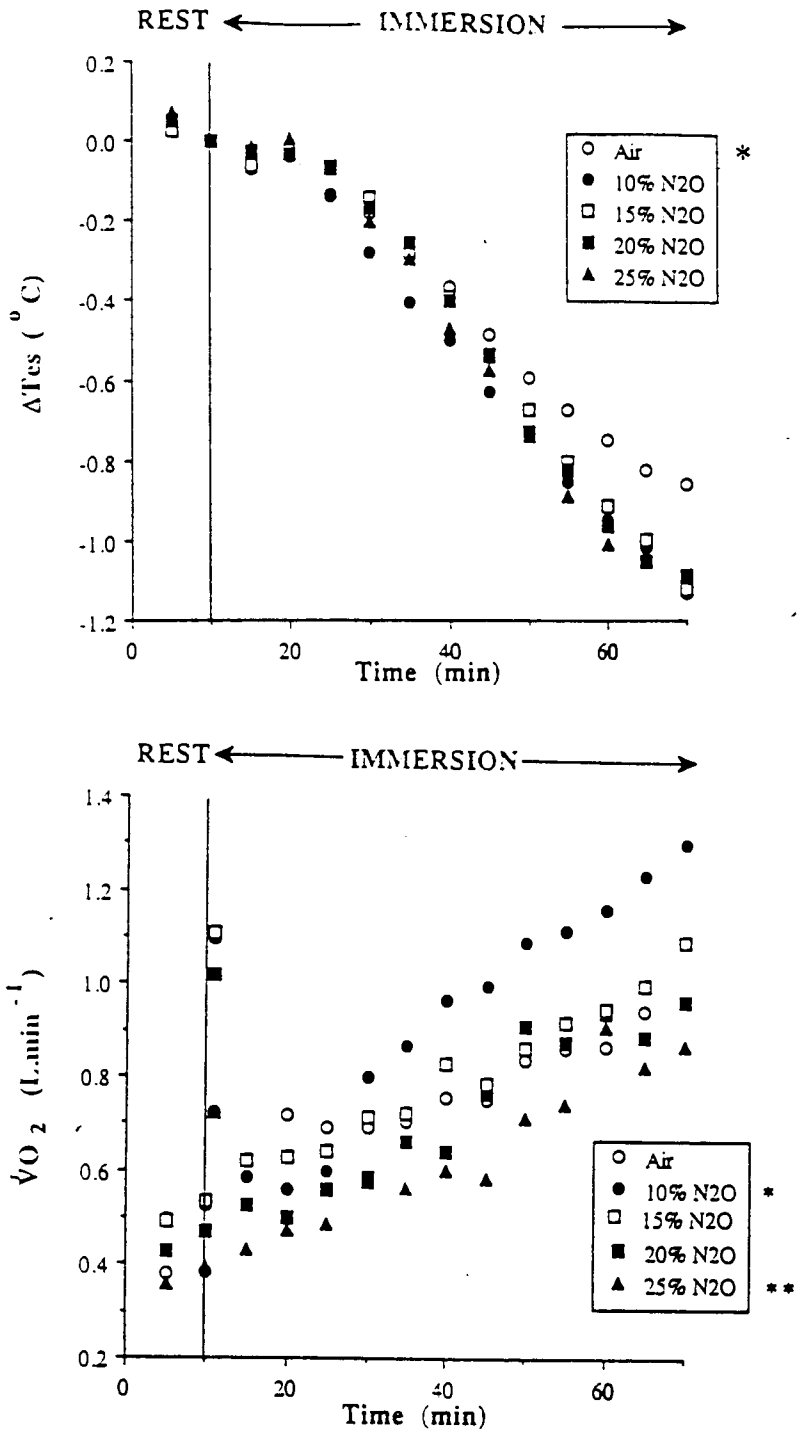

Fig. 5. Mean oxygen uptake ($\dot{V}O_2$) during rest and immersion in AIR, 10, 15, 20, 25% N_2O. * $\dot{V}O_2$ was significantly ($p \leq 0.05$) higher in 10% N_2O than in AIR. ** $\dot{V}O_2$ was significantly ($p \leq 0.05$) lower in 25% N_2O than in AIR. No difference was observed in the slope of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

Fig. 3-11: $\dot{V}O_2$ and ΔT_{es} results from Cheung (1993) with permission

APPENDIX 2

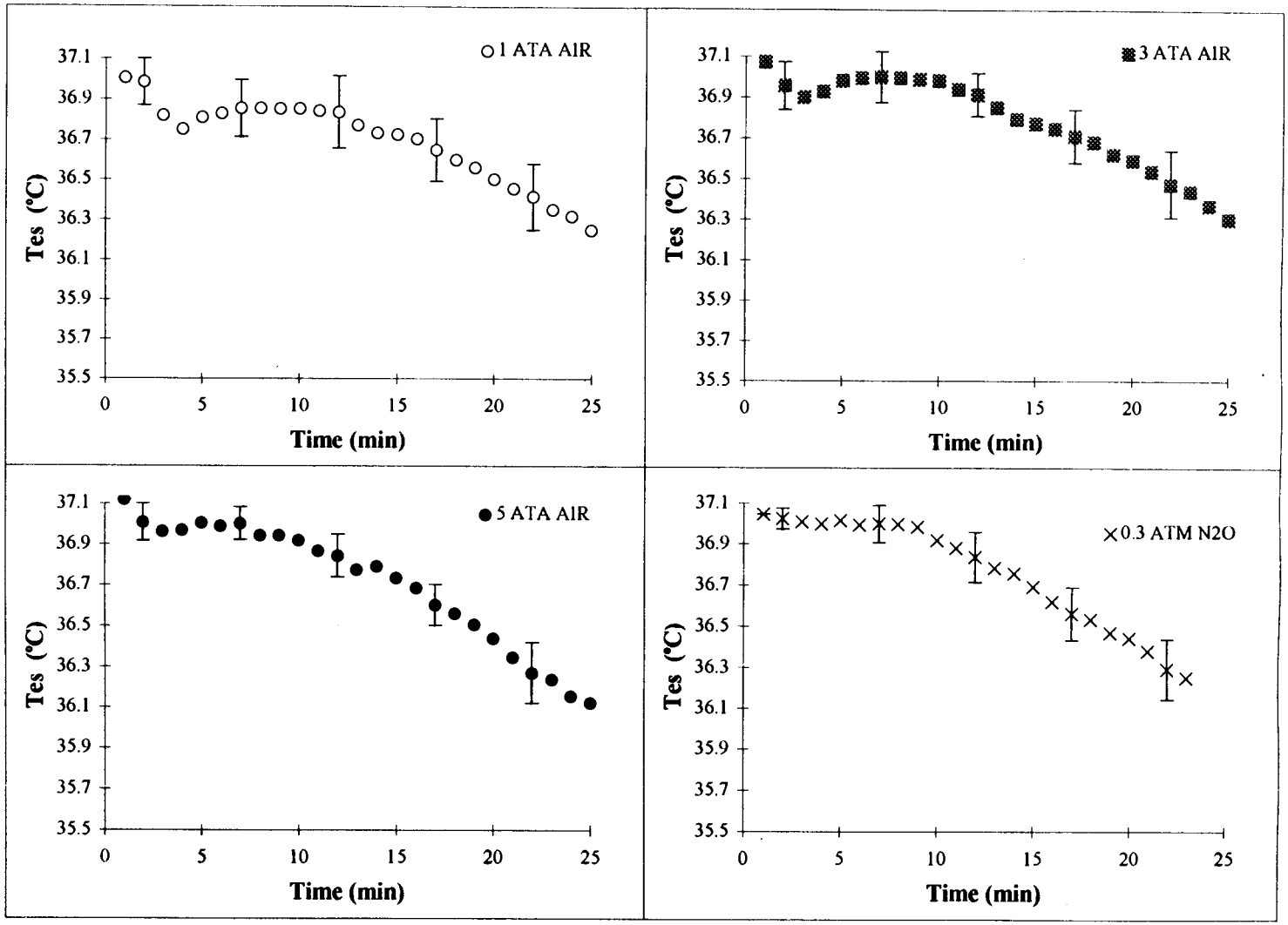

Fig. 3-12: Mean (± SE) T_{es} response of 9 subject during first 25 min of immersion in 4 experimental conditions.

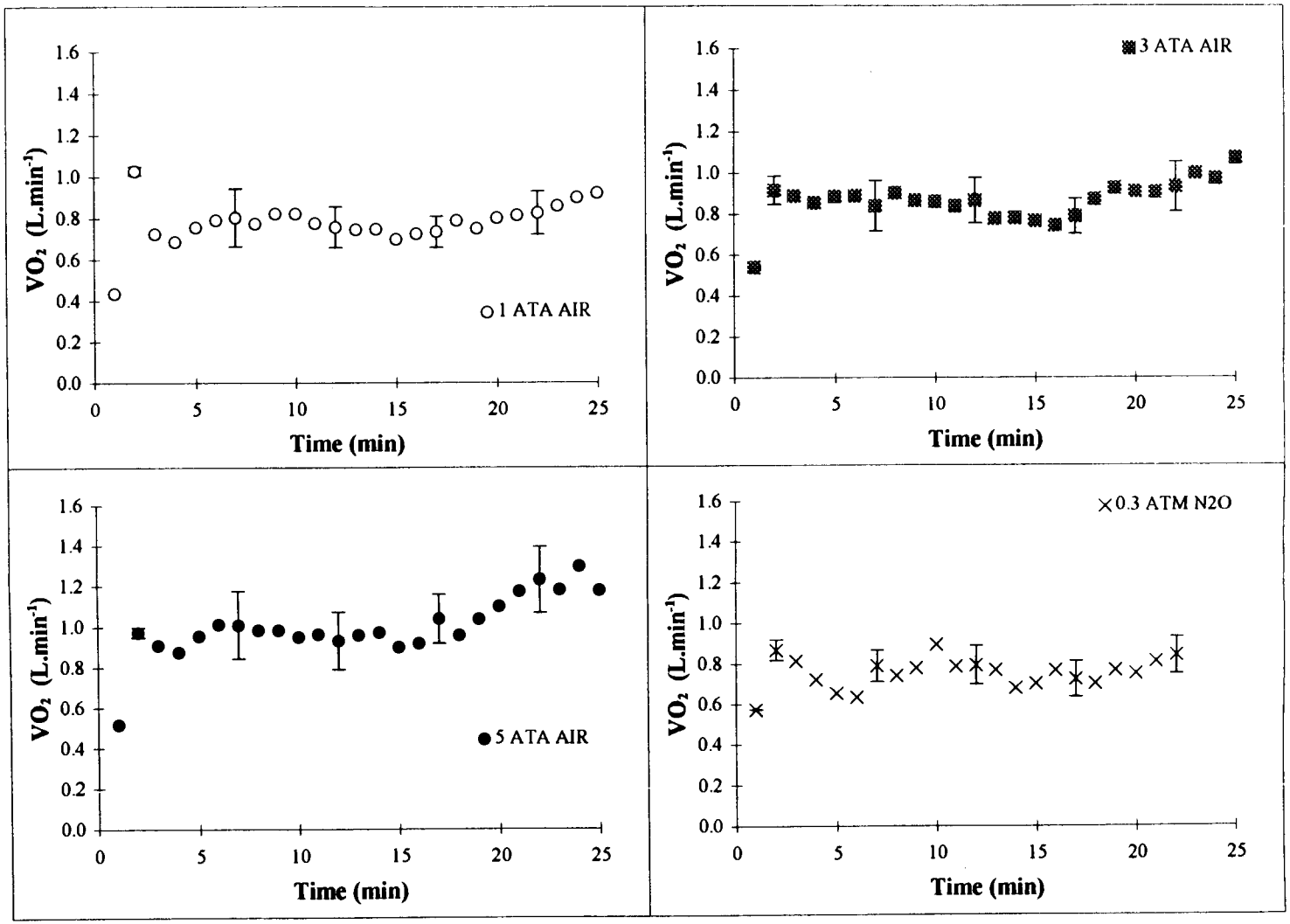

Fig. 3-13: Mean (± SE) $\dot{V}O_2$ response of 9 subject during first 25 min of immersion in 4 experimental conditions.

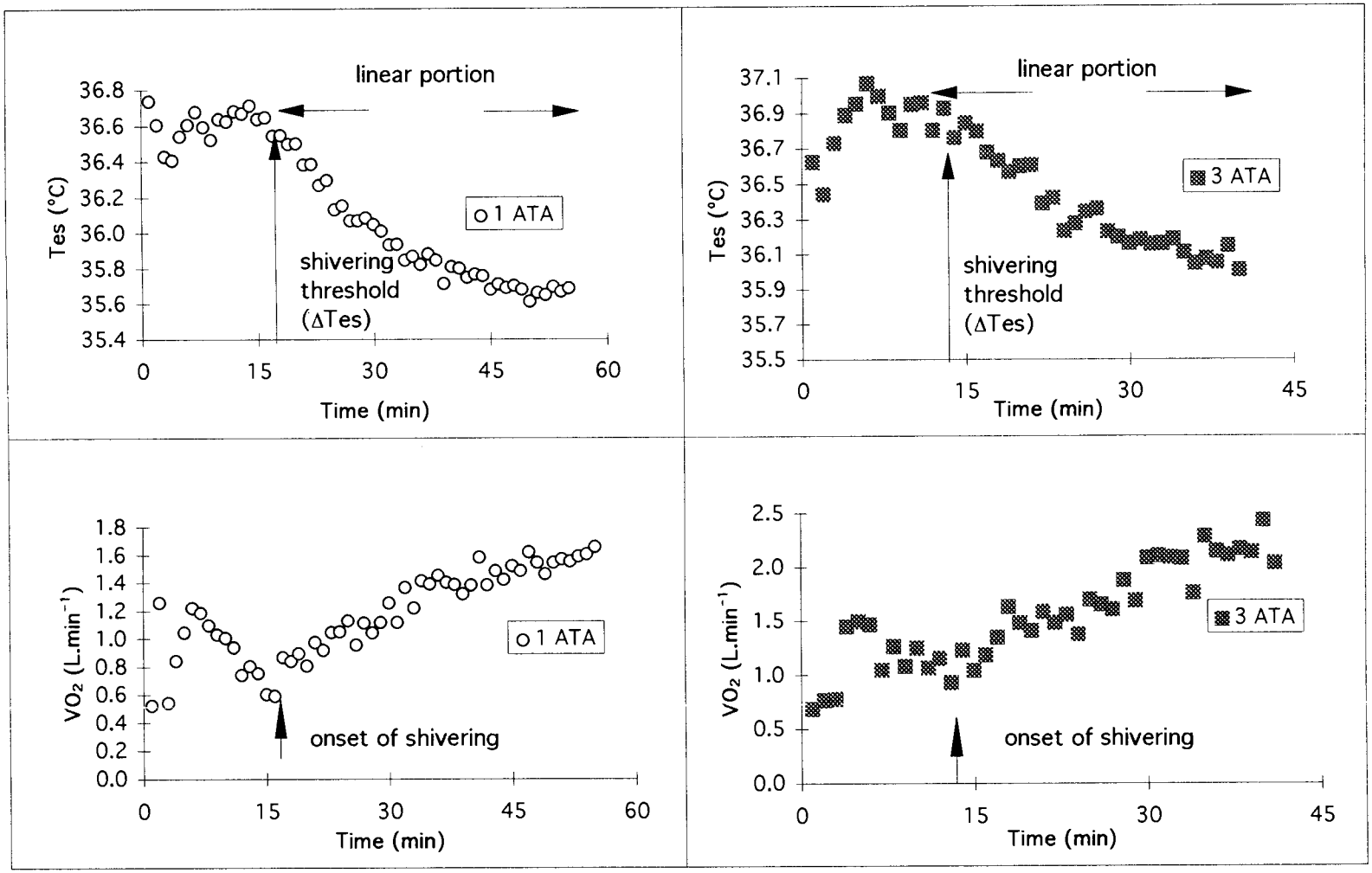

Fig. 3-14: Determination of cooling rate (linear portion of cooling curve, $\dot{T}_{es}$) and shivering threshold (ΔT_{es}) for subject 5 during immersion at 1 ata (left) and 3 ata (right).

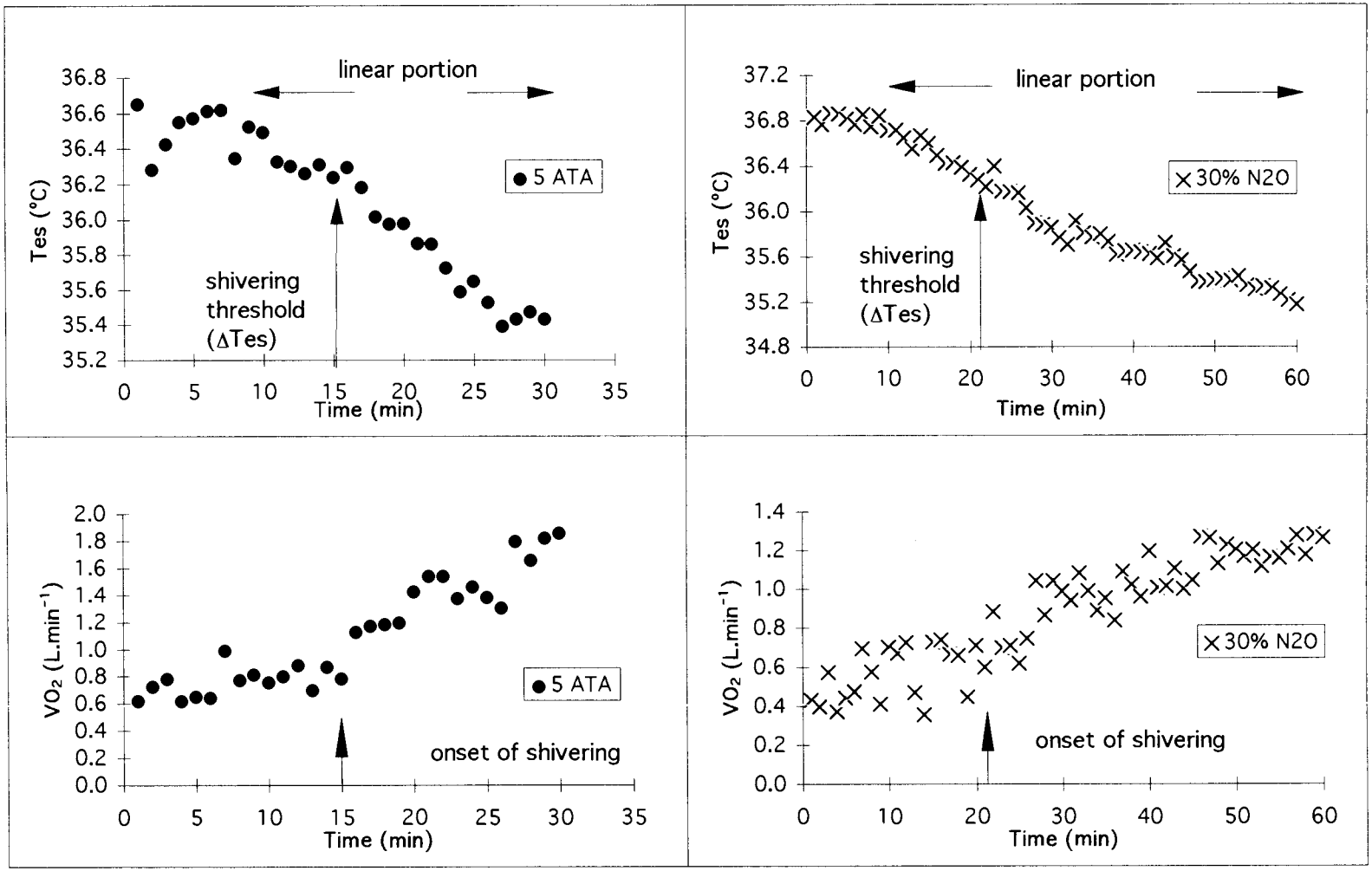

Fig. 3-15: Determination of cooling rate (linear portion of cooling curve, $\dot{T}_{es}$) and shivering threshold (ΔT_{es}) for subject 5 during immersion at 5 ata (left) and at 1 ata breathing 30% N_2O. (right).

STUDY IV

THE PREDICTION OF BODY CORE COOLING RATE AND SURVIVAL TIME OF HUMANS IMMERSED IN COLD WATER

ABSTRACT

This study evaluates the progression into hypothermia of subjects immersed in cold water. A model based on body physique, water temperature (Tw) and narcosis level (NP) was developed for predicting the cooling rate of subjects during compressed air diving. Data were gathered from 4 independent hypothermia studies using the same immersion methodology on 44 subjects. Subjects wearing only a swim suit were immersed up to the neck in cold water until their core temperature decreased to 35°C or for 2°C from the pre-immersion value. Immersions conducted in hyperbaric conditions were limited to the maximum bottom time of the approved decompression schedule. 25 subjects were cooled in water of 11.2°C, 13 subjects in 15°C and 6 in 20°C water. Subjects were of both genders (14 females and 30 males) and included a wide range of physiques. As 19 subjects were cooled at several levels of narcosis, a total of 79 immersions were completed.

To determine the anthropometric measures which would be the best predictors of the rate of core cooling 43 raw and derived anthropometric measures were subjected to regression analysis. The 4 anthropometric measures yielding best prediction were: medial calf skinfold thickness (MCSF), medial calf girth (CG), acromial height (ACHT) and tibial height (TBHT). A linear regression model to predict cooling rate from variables Tw, NP, MCSF, CG, ACHT, TBHT was then developed using all 79 cases. An artificial neural network was used to develop nonlinear models based on the same input variables. The outputs of the models were compared and the linear regression model performed better than the non linear models.

Regression models were also developed to predict cooling rate and survival time during head out immersion based upon water temperature and body composition (MCSF, CG, ACHT, TBHT). The predicted survival times (mean ± SD) of males and females,

based on Canadian population data, were predicted as a function of water temperature and physique. The developed model of survival time was compared to existing predictive models.

INTRODUCTION

Although death in cold water accidents can occur due to burns, drowning or shock, the survivors will often be immersed in cold water supported with a life jacket and the prediction of survival of hypothermic victims is of practical importance. Scarce and inadequate data obtained from accidental hypothermia in shipwreck survivors (Molnar 1946), recreational boaters and fishermen (Harnett et al. 1983) and aircraft accidents (Brooks and Rowe 1984) usually refer to the "tolerance limit" of the victim. The definition of tolerance uses death as an end point which is, of course, unacceptable in the context of human experimentation. Immersion experiments designed to estimate the tolerance limit under laboratory conditions, usually bring core temperature to 35°C, from which the recovery from hypothermia is complete and without complications. Predictive models developed from the above studies have resulted in complex nonlinear computer model solutions using heat loss and heat productive thermoregulatory mechanisms (Wissler 1985, Tikuisis et al. 1988) or simple linear models establishing the relation between the environmental temperature, core temperature and time, as a measure of survival (Hayward et al. 1975). Other models for predicting survival time are based on limits of heat production and heat loss (Timbal et al. 1976, Hall 1972, Smith and Hames 1962).

There is a general agreement in the literature that subcutaneous fat provides an insulative barrier to the loss of body heat during exposure to cold. Clark and Edholm

(1985), Sloan and Keatinge (1973), Burton and Edholm (1969), Wyndham et al. (1968), Keatinge (1960), Pugh and Edholm (1955) have shown that subjects with greater skinfold thickness will cool more slowly than lean subjects resting in cold air or water of the same temperature. Comparative studies of the thermoregulatory response between gender have shown that total body mass and muscle mass contribute significantly to core cooling, while gender and adipose tissue mass do not have an important effect (Park et al. 1984, Veicsteinas et al. 1982, Anderson et al. 1995). According to Park et al. (1984) and Veicsteinas et al. (1982) a skeletal muscle beneath the superficial insulative shell of skin and subcutaneous fat can provide up to 75% of insulation in non-exercising man. This insulation provided by muscle which is poorly perfused due to vasoconstriction is removed by exercising hyperemia. Hayward and co-workers (1975) reported a significantly slower (40%) cooling rate in the male subjects than the female subjects, but only at a water temperature of 10.5°C. The difference was attributed to significantly greater body mass of males compared to females. Also Keatinge (1960) and Kollias et al. (1974) have reported a slower rate of core cooling and metabolic heat production in men. Other studies have found a positive correlation between the surface area to mass ratio and cooling rate in adults (McArdle et al. 1984, Kollias et al. 1974, Pugh and Edholm 1955) and children (Sloan and Keatinge 1960).

The purpose of this study was to develop a reliable and simple quantitative relationship between the rate of core cooling of a diver and, body physique, water temperature and narcosis level. A second objective was to develop a model for prediction of survival time during head out immersion based on body physique and water temperature at 1 ata. The prediction is pertinent for an inactive, unclothed person, in cold water. It was assumed that death occurs at 30°C core temperature. Animal experiments suggest that ventricular fibrillation (Bigelow 1950) or respiratory failure (Popovic and Popovic 1974) is a terminal event occurring between 25 - 30°C rectal temperature. Death due to hypothermia in man is generally attributed to ventricular fibrillation (Hervey 1973,

Swan et al. 1955) although direct evidence such as an ECG recording, is seldom available at the time of death.

METHODS

The decrease in core temperature in response to cold immersion was compared in 4 separate studies. Three studies were conducted by the same experimenter (Study I, II, III by Savic in 1991, 1993 and 1994 respectively) and the fourth study was conducted by another experimenter in the same laboratory (Conn and Morrison 1979), using the same immersion techniques. Core temperature monitoring sites were in the distal esophagus (37 - 42 cm; I, II, III) and 15 cm beyond the rectum (IV). In all studies, subjects were wearing a swim suit and sitting quietly in water up to the neck, until core temperature dropped by 2°C from the pre-immersion value, or to a minimum of 35°C. Water temperature was 15°C in Studies I and II, 20°C in Study III, and 11.2°C in Study IV. In Study IV subjects were of both genders (12 females and 13 males) and selected to provide a wide range of body composition, whereas in Study I, II and III subjects were males (except in Study I where 2 females of average built participated).

The anthropometric assessment was performed by an anthropometrist following the standardized procedure as recommended by Ross and Marfell-Jones (1991).

Anthropometric measurements

Anthropometric measurements included the measures of weight, height, sitting height, anterior-posterior chest depth, head girth and foot length; projected lengths including acromial, radial, stylion, dactylion, spinale and tibial height; biacromial, biiliocristal and transverse chest breadth, widths of humerus and femur; relaxed and flexed arm girth,

forearm, wrist, chest, waist, upper thigh, calf and ankle girth. Compressed adipose tissue thickness was determined using the caliper technique at each of 6 skinfold sites (triceps, subscapular, suprailiac, abdominal, front thigh and medial calf) using the same closing pressure. Each measurement of length, height, girth, breadth and skinfold was taken twice to reduce variations, and the mean score was reported. Anthropometric indexes of ectomorphy (ECTO), mesomorphy (MESO) and endomorphy (ENDO) were calculated using regression equations explained in the Heath Carter Somatotype method (Carter 1980). Body surface area was estimated from body height and weight using the formula of DuBois and DuBois (1916) $\mathbf{A = WT^{0.425} \cdot HT^{0.725} \cdot 71.84}$, where A is surface area (cm^2), WT is body mass (kg) and HT is height (cm). These anthropometric variables were used for the fractionation of skin, adipose, muscle, bone and residual tissue mass as suggested by the model of Kerr (1988).

Narcotic potency

For the purpose of this study it was assumed that the narcotic potency of a gas was directly related to the quantity of gas dissolved in the lipid biomembrane. The narcotic potency (NP) of the breathing mixture in various studies was determined by the Bunsen coefficient (Bennett 1982, Carpenter 1954) multiplied by the pressure of the gas (atm). The Bunsen coefficient (Bc) determines to what extent the gas is soluble in olive oil (representing the lipid biomembrane) at 37°C ($cc \cdot cc^{-1}$) at a pressure of 1 atmosphere (760 mmHg). Bc for N_2 is 0.067 and for N_2O is 1.6 ($cc \cdot cc^{-1}$). Therefore, the calculated NP of N_2 in air at normal atmospheric pressure ($PN_2 = 0.8$ atm) is $NP = 0.067 \cdot 0.8 = 0.0536$ $cc \cdot cc^{-1}$. The NP of 30% N_2O normoxic gas mixture inspired at 1 ata ($PN_2O = 0.3$ atm, $PN_2 = 0.5$ atm) is $NP_{N2+N2O} = NP_{N2} + NP_{N2O} = 0.51$ $cc \cdot cc^{-1}$, which is equivalent to the narcotic potency of nitrogen present in compressed air at 9.57 ata ($PN_2 = 7.66$ atm).

Prediction of cooling rate

To test the dependency of cooling rate on the level of narcosis, as well as body physique and water temperature, data were organized in such a way that when the subject participated in several immersions, where only the narcosis level differed, the data from each immersion of those subjects were included as a separate case. Therefore the total of 44 subjects provided 79 data sets, that were treated in the models as 79 independent cases.

Prediction of survival time

The model in the present study is based on the model of Hayward et al. (1975) developed for prediction of survival time of lightly clothed subjects immersed in the ocean. Subjects were lightly clothed in permeable clothes and wearing a life jacket. The onset of cooling was determined to be 15 min from the onset of immersion and the cooling rate was estimated between minutes 15 and 25 of immersion. Hayward et al. (1975) developed a predictive formula for cooling rate (CR):

$$CR = 0.0785 - 0.0034 \cdot Tw \qquad (^{\circ}C \cdot min^{-1}) \qquad \textbf{Eq. 1}$$

Using the same data and the prediction of cooling rate Hayward et al. (1975) then determined the survival time (ST) to be:

$$ST = t_0 + \frac{\Delta T}{CR} = 15 + \frac{7.2}{0.0785 - 0.0034 \cdot Tw} \qquad (min) \qquad \textbf{Eq. 2}$$

where ΔT is the difference between the starting core temperature and a core temperature of 30°C at which hypothermic death is assumed to occur ($\Delta T = 37.2^{\circ}C - 30^{\circ}C = 7.2^{\circ}C$)

The prediction of survival time in the present study was based on the assumption that death would occur on average at 30°C core temperature, where loss of consciousness in the victim is expected. The starting core temperature is based on the average starting temperature of 44 subjects immersed in 4 different water temperatures and breathing air in the present study. The drop in core temperature to 30°C was assumed to be linear. In the model used in this study the cooling rate (CR) and the time at which the cooling started (t_o) were modeled as a function of both water temperature and anthropometric variables that produced a significant effect. The linear regression was applied on the data from 44 subjects immersed in various water temperatures at 1 ata.

Cross correlation

The relationships among all 46 variables (43 raw and derived anthropometric variables, cooling rate, water temperature, and narcosis level) were examined. A statistical analysis software application (SAS) was used to generate a correlation matrix. The strength of the relationship between two variables is reflected in the Pierson correlation coefficient ($-1 \leq r \leq 1$). To have probability significant at the 0.05 level, a single variable would require a correlation of $r = 0.22$. A correlation above 0.44 indicates a probability of ≤ 0.0001.

Regression analysis

In order to examine the extent to which the cooling rate (CR; $°C \cdot h^{-1}$) could be explained in terms of water temperature (Tw), narcotic potency (NP), 31 raw anthropometric measures and 12 derived anthropometric body measures, the following method was used. The variables included in the model were chosen by inspection of scatter plots and the correlation matrix, based on their high individual correlation with cooling rate and low correlation with other variables. Models of this type included theoretically meaningful

variables. Stepwise regression analysis was performed and backward elimination was used to reduce the number of variables. Backward elimination removed, in each step, the variable with the smallest contribution to the model (smallest F statistics), until only the variables that contributed significantly at the 0.1 level were left in the set.

Artificial neural networks

Using the variables that most strongly affect core cooling rate, according to the multiple regression analysis, a series of artificial feed forward neural networks (FFNN) were designed to predict the cooling rate response for a given series of inputs. A supervised FFNN (NeuralWorks II/PLUS, NeuralWare Inc., Pittsburgh, PA) was trained to predict the rate of core cooling as a nonlinear function of the input variables. All networks consisted of 3 layers and had the following structure: 1 input layer with 5 or 6 input neurons, 1 hidden layer with 4 - 10 neurons and 1 output layer with 1 output neuron. A network with one hidden layer was chosen for modeling the cooling rate, since it has been shown that a single hidden layer is sufficient to approximate any complex continuous nonlinear function by adding more neurons in the hidden layer (Funahashi 1989). All neurons (nodes) in the network were fully interconnected. The output of a neuron was a smooth sigmoidal function of the input with values between 0 and 1 (Hush and Horne 1993, Zornetzer and Davis 1990). The FFNN was trained using sets of sample input and output data. The learning rule chosen for training was back-propagation of error which used the least mean square error algorithm and fed the difference between the output and target array back through the network then readjusted the weights in such a way as to minimize the error. This new set of network weights was then used to produce a new output array, which was compared again with the target array. The weights were readjusted until the error for the entire training set reached the minimum or when a predetermined number of iterations had been performed. The architecture of the FFNN:

decision rule, learning ratio and tolerance of error were tested on the whole set of data by varying the number of neurons in the hidden layer, number of input neurons and number of iterations. For validation purposes the data set was then split into a training set containing 69 cases which were used to train the network and a test set containing the remaining 10 cases on which the performance of the network was tested.

RESULTS

Effect of gender and body composition on cooling rate

Data for these statistics were taken from the study of Conn and Morrison (1979) in which 12 females and 13 males were immersed in water with an average temperature of 11.2 °C (Table 4-1). The males had 38.2% lower mean skinfold thickness (MSF, $p \leq 0.05$), were 18.5% heavier ($p \leq 0.05$), had a 44.5% higher muscle mass (Mmuscle, $p \leq 0.05$) and a 10.7% lower surface area to mass ratio (A/M, $p \leq 0.05$) than the females. While there was no significant gender difference in the upper body skinfold thickness (sum of triceps, suprailiac and abdomen skinfold), or adipose tissue mass (AT), females possessed a significantly higher skinfold thickness in the lower body area (sum of thigh and calf skinfold). The cooling rate was not significantly different between genders ($p > 0.05$).

Correlation matrix

The Pierson correlation coefficient for selected raw and derived anthropometric measures is reported in Table 4-2. In the present study there was a negative correlation between cooling rate (CR) and water temperature (Tw; r = -0.44), MCSF (r = -0.48), CG (r = -0.48), ACirc (r = -0.25), and TLArea (r = -0.22). There was a positive correlation

between CR and NP (r = 0.11). There was a significant positive correlation of CG, ACHT and TBHT with the body mass (WT), which had significant negative correlation with cooling rate (r = -035). CR showed significant positive correlation with surface area to mass ratio (A/M), but significant negative correlation with surface area (A) alone (r = 0.41 and -0.28 respectively). There was a significant positive correlation between ECTO, and CR (r = 0.46). While muscle mass (Mmuscle) did not correlate well with cooling rate (r = -0.14), both the adipose tissue mass (AT) and ENDO, derived from the sum of three upper body skinfold thickness (triceps + subscapular + supraspinal) did (r = - 0.54 and -0.52 respectively).

Modeling the cooling rate based on water temperature, body composition and narcosis level

Linear regression model

The four body measures that were the best predictors of cooling rate were medial calf girth (CG), medial calf skinfold thickness (MCSF), acromial height (ACTH) and tibial height (TBHT). The best fit multiple regression equation was derived from these variables (measured in mm) together with Tw and NP:

$$CR = 16.3 - 0.41 \cdot Tw + 1.7 \cdot NP - 0.16 \cdot MCSF - 0.31 \cdot CG + 0.15 \cdot ACTH - 0.36 \cdot TBHT$$

($^{\circ}C \cdot h^{-1}$) $\qquad r = 0.72$ **Eq. 3**

The regression was not improved substantially by inclusion of additional raw or derived anthropometric variables. Inclusion of any single variable increased r by less than 0.1. Figure 4-1 presents the observed cooling rates during 79 immersions in 11.2°C, 15°C and 20°C in comparison with predicted cooling using the regression model of equation 3.

Results of the non-linear model with FFNN

To choose the learning step, allowed error, and other parameters of the ANN, the network was trained with all 79 cases (Table 4-3 - top). Input variables were Tw, NP, MCSF, CG, ACHT and TBHT. There were either 5 or 6 input variables. When only 5 input variables were used TBHT was omitted. The number of hidden layer neurons used varied from 4 -10. The nonlinear approximation was obtained with a sigmoid function and the learning rule which was used was backpropagation of error. The optimal learning ratio was determined by varying the step size for weight adjustment. It was found that convergence was very slow if the step size was too small, and the system became unstable if the step size was too large. The learning ratio was then set to 0.05. The error tolerance was set to 0.001. The smaller the tolerance, the longer it took to train the network. All the weights were initialized by a random generator.

In total, 29 FFNN were trained. The results of testing several different networks in which the number of hidden layer neurons were altered, and the number of iterations adjusted, are shown in Table 4-3 (top). The training sessions were performed using all 79 cases. It may be seen that the number of iterations had a great impact on the performance of the FFNN. When the number of iterations for a FFNN with 10 hidden layer neurons was decreased from 10^6 to $2 \cdot 10^5$, the mean square error (MSE) more than tripled. However, when the number of iterations was decreased in the same way with only 4 hidden layer neurons, the MSE increased only by 31%. When the number of hidden layer neurons was altered from 10 to 4 with 10^6 iterations, the MSE more than doubled. However, with fewer iterations ($2 \cdot 10^5$) there was almost no change in MSE when the number of hidden layer neurons was decreased from 10 to 4. The number of input variables also had a strong effect. For example, decreasing the number of input variables from 6 to 5 with 10^6 iterations, more than doubled the MSE.

The best performing FFNN, with 6 inputs, 10 hidden layer neurons and 10^6 iterations (Fig. 4-2) gave a MSE of 0.12. For comparison, the linear regression yielded a MSE of 0.82.

To test the predictive power, various FFNNs were trained on 69 samples and then tested on 10 independent samples. Two examples are presented at the bottom of Table 4-3. The first is the FFNN which performed best when trained with 10^6 iterations on all 79 cases (Fig. 4-2). In the validation study, the linear regression method outperformed the FFNN. In the example given in Table 4-3, the prediction improved after lowering the number of iterations from 10^6 to $2 \cdot 10^5$, to provide a MSR of 2.03. This network compared favorably with the linear regression model which gave a MSE of 1.95 as shown in Fig. 4-3. The fact that the first FFNN, trained over 10^6 iterations on all 79 cases, provided a better fit than the regression model, but failed to perform as well when tested on unseen data, indicates that the neural network was probably overtrained.

Modeling survival time in head out immersion at 1 ata

The cooling rate (CR) and the time at which the cooling started (t_o) were modeled as functions of water temperature and anthropometric variables that produced a significant effect. Linear regression was performed on the data (Tw, MCSF, CG, ACHT, TBHT) from 44 subjects immersed in 3 water temperatures at 1 ata. The resulting equations have the following form:

$$CR = 17.3 - 0.36 \cdot Tw - 0.16 \cdot MCSF - 0.41 \cdot CG + 0.14 \cdot ACHT - 0.27 \cdot TBHT \ (^{\circ}C \cdot h^{-1}) \qquad \textbf{Eq. 4}$$

$$t_o = -50.6 + 0.11 \cdot Tw + 0.48 \cdot MCSF + 1.8 \cdot CG \quad (min) \qquad \textbf{Eq. 5}$$

From the 4 anthropometric measurements that significantly influence the cooling rate only MCSF and CG had a marked effect on t_o therefore ACHT and TBHT were not included in the model (Eq. 5).

The cooling rates predicted by the regression model of Eq. 4 were compared with those predicted by the model of Hayward et al. (1975) at different water temperatures (Fig. 4-4). For this purpose the values of anthropometric variables in Eq. 4 were selected from the average values of a Canadian population of 239 male university students. These values are given in Table 4-4.

The prediction of survival time in this study was based on the assumption that hypothermic death will occur on average at 30°C core temperature and the drop in core temperature to 30°C was assumed to be linear. The average starting temperature of 44 subjects immersed in 3 different water temperatures and breathing air in this study was 37.2 ± 0.2 °C.

Using the predictive relationships developed for t_o and CR (Eq. 4 and 5) a predictive model for the survival time (ST) was constructed:

$$ST = -50.60 + 0.11 \cdot Tw + 0.48 \cdot MCSF + 1.7 \cdot CG + (7.2 / (17.27 - 0.36 \cdot Tw - 0.16 \cdot MCSF - 0.41 \cdot CG + 0.14 \cdot ACHT - 0.27 \cdot TBHT)) \quad (h)$$

$$Tw \leq 20°C \qquad \textbf{Eq. 6}$$

Fig. 4-5 compares the survival time predicted by the new model (Eq. 6) with Hayward's model (Eq. 2). In this figure the new model (Eq. 6) used the mean anthropometric data from the Canadian population of 239 male university students summarized in Table 4-4 (right).

Gender differences in tolerance limits to cold water exposure

The new survival model was used to examine the effect of gender difference in tolerance limits to cold water exposure (Fig. 4-6). The anthropometric data used in the model were taken from an average Canadian student population of 206 females and 239 males. In Table 4-4, this average Canadian population (right) is compared with 30 males and 14 females used in the present study (left). In addition, as the assumption of a cold tolerance limit of 30°C is hypothetical, and based on very limited data a range of uncertainty was introduced to the prediction of Fig. 4-6. It was assumed that upper and lower limits of survival are 33°C and 27°C of core temperature for males (vertical stripes) and females (horizontal stripes). This infers that at 30°C core temperature 50% of victims survive and that certain death would occur below 27°C core temperature (although there are cases reported when victims survive with even lower core temperature). The safe zone of Fig. 4-6 is below the shaded areas for each gender where the core temperature is above 33°C.

DISCUSSION

The predictive model for survival time developed in this study, is a simple relationship between survival time and body physique of an inactive, nude person immersed in cold water. It is based on linear regression equations of the time to establish core cooling and the linear cooling rate, starting from a core temperature of 37.2°C down to 30°C, where hypothermic death is assumed to occur. The best prediction was achieved by using water temperature, narcotic potency, medial calf girth, medial calf skinfold thickness, acromial height and tibial height.

When conducting multiple regression analysis it was essential to determine the minimum set of meaningful independent variables to be used in the models. According to

the regression analysis, the cooling rate is mainly dependent on the shape of the lower body (CG and TBHT) and its insulative layer (MCSF). This would imply that most of the body heat is lost through the lower extremities due to its higher surface area to mass ratio (A/M) compared with the trunk area . Three out of four variables (CG, ACHT and TBHT) correlated well with body mass, further indication that the body mass plays an important role in the cooling processes. However, if CG, ACHT and TBHT are replaced by weight alone in the predictive equation, important information on body physique is lost. Cooling rate was also correlated with surface area to mass ratio (A/M), and surface area (A) alone. There is also high correlation between A/M and WT which is due to the way in which A/M is determined. While weight and height (HT) are measured directly, A is derived from a function of WT and HT. Similarly, there was a significant positive correlation between ECTO, which is derived from height and weight ratio ($HT/\sqrt[3]{W\,T}$) and cooling rate. While muscle mass (Mmuscle) did not correlate well with CR both the adipose tissue mass (AT) and ENDO, derived from the sum of three upper body skinfold thickness (triceps + subscapular + supraspinal) did. However, when the derived variables ECTO, ENDO and MESO were combined together in a regression equation, or in a multiplicative model of somatotype elements (ECTO/(MESO·ENDO)), the prediction was poorer than with the present measured variables.

An artificial neural network and a linear regression model were applied to all data to determine the model parameters. 29 different neural networks were designed and tested. When the linear regression and neural network models were then applied to 85% of the data and tested with the remainder of the data, suprisingly, the linear regression equaled or outperformed the neural network in its power of prediction. It would be expected, that in nonlinear problems, such as predicting cooling rate, the neural network approach would be better. However, a weakness of the back-propagation algorithm when applied to small data sets using many iterations is the possibility of overtraining the network, and teaching it to perform well on the training sets only by learning the variance.

When 25 subjects from Conn and Morrison's study (1979) were examined for gender differences in core cooling in 11.2°C water as a part of this study, no significance was found ($p > 0.05$). Females had significantly higher surface area to mass ratio (A/M) and lower mass, therefore, more potential for cooling. However, this might have been counteracted by significantly higher skinfold thickness in the lower body area (thigh + calf skinfold). There were no significant gender difference in the upper body skinfold thickness (triceps + suprailiac + abdomen skinfold) or adipose tissue mass (AT). However, when the survival time was predicted by applying the model separately to the data of average females and males, differences were evident for temperatures above Tw = 10°C (Fig. 4-6 top).

The model developed for prediction of survival time was also compared with a similar linear model of Hayward et al. (1975) derived from lightly clothed and inactive subjects immersed in ocean water of 4.6°C - 18.2°C. The cooling rates predicted with a latter model are considerably lower than the cooling rates predicted with the new model, although subjects were of similar height, weight and mean skinfold thickness. The reasons for the difference might have been the huddle H.E.L.P. position (Heat Escape Lessening Position) of subjects during immersion and clothing worn by Hayward's subjects. Minimizing the heat loss by assuming the H.E.L.P. position by drawing the knees up to the chest and holding with crossed arms is surprisingly effective and can decrease the heat loss up to 30% (Hayward 1996, personal communication). Although permeable clothing is not of great value in water it does provide some insulation and can keep T_{sk} 5°C above the water temperature of 15°C, if the victim is not active (Keatinge 1961). However, if the victim is active and struggling in cold water this insulation is almost completely lost (Keatinge 1961). The advantage of the present model is in its ability to account for individual variations in body physique. For example, it was observed that, after 30 minutes immersion in 15°C water, the core temperature of certain subjects dropped 2°C,

whereas for other subjects core temperature dropped only 0.2°C. These differences can be attributed to morphological factors (Keatinge 1960).

Compared to other linear models (Timbal et al. 1976, Smith and Hames 1962), the advantage of the present model is in its simplicity. When the nomogram of Smith and Hames (1962) is applied to a resting nude subject immersed in 10°C water the prediction of survival time is 1.9 hours which is very close to the prediction of the present model (2 hours for average Canadian male). However, when the nomogram is used for prediction of survival at higher or lower water temperatures the differences are larger. Timbal et al. (1976) developed a linear predictive model by dividing rectal temperature in three 5°C zones, from 35°C down to 20°C. They based their prediction only on water temperature and produced separate graphs for three morphological types. Although they assume a linear decline in rectal temperature within a temperature zone, at successively lower levels the cooling rate becomes less steep. Therefore, the model of Timbal et al. (1976) overestimates the survival time when compared with the prediction of the present model. Similarly, the nonlinear model of Tikuisis et al. (1988) for prediction of survival in waters of 20 and 24°C assumes that rectal temperature stabilizes at 35°C before further drop. The longer survival times according to their prediction are then due to an increase in metabolic rate with decrease in rectal temperature until heat production balances heat loss. This may not be possible in water temperatures colder than 20°C, since metabolic rates can not rise indefinitely.

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TABLES AND FIGURES

		FEMALES		MALES		significance
		Mean	±SD	Mean	±SD	($p \leq 0.05$)
WT	(kg)	63.03	9.28	74.7	12.76	√
HT	(mm)	168.52	7.49	180.93	5.98	√
CR	($^{\circ}C \cdot h^{-1}$)	3.28	2.44	4.05	1.55	
A	(m^2)	1.75	0.14	1.85	0.16	
Mmuscle	(kg)	26.87	6.16	38.82	6.71	√
AT	(kg)	21.67	4.65	18.75	8.38	
MSF	(mm)	16.06	4.93	9.92	6.54	√
A/M	($m^2 \cdot kg^{-1}$)	2.80	0.22	2.50	0.18	√
UPSKF	(mm)	40.31	12.27	28.38	19.58	
LOWSKF	(mm)	40.76	14.53	19.30	10.87	√

Table 4-1: Comparison of anthropometric differences in males (n=12) and females (n=12) from the present study. Statistical significance was determined with a one way ANOVA when $p \leq 0.05$. UPSKF = triceps + suprailiac + abdomen skinfold. LOWSKF = thigh + calf skinfold.

	CR	TW	NP	WT	HT	MCSF	CG	ACHT	TBHT	A	Mmuscle	AT	A/M	MSF	ENDO	ECTO	MESO
CR	1																
TW	-0.44	1															
NP	0.11	0.15	1														
WT	-0.35	0.22	0.22	1													
HT	-0.06	0.25	0.11	0.73	1												
MCSF	-0.48	-0.20	0.04	0.10	-0.34	1											
CG	-0.48	0.20	0.10	0.78	0.48	0.21	1										
ACHT	-0.25	0.17	0.08	0.75	0.97	-0.27	0.52	1									
TBHT	-0.22	-0.19	-0.08	0.48	0.74	-0.17	0.28	0.79	1								
A	-0.28	0.14	0.14	0.96	0.82	0.04	0.73	0.83	0.61	1							
Mmuscle	-0.14	0.24	0.14	0.83	0.67	-0.32	0.69	0.67	0.39	0.78	1						
AT	-0.54	-0.03	0.13	0.61	0.18	0.71	0.50	0.27	0.24	0.55	0.21	1					
A/M	0.41	-0.32	-0.30	-0.93	-0.61	-0.08	-0.79	-0.61	-0.30	-0.82	-0.83	-0.52	1				
MSF	-0.53	-0.12	0.09	0.35	-0.17	0.85	0.34	-0.07	-0.02	0.27	-0.04	0.94	-0.30	1			
ENDO	-0.52	-0.07	0.05	0.25	-0.22	0.78	0.27	-0.14	-0.08	0.18	-0.08	0.87	-0.21	0.95	1		
ECTO	0.46	-0.05	-0.20	-0.60	0.09	-0.51	-0.60	0.04	0.18	-0.44	-0.44	-0.63	0.68	-0.66	-0.58	1	
MESO	0.35	0.05	0.05	0.15	0.20	-0.70	0.16	0.16	0.00	0.10	0.59	-0.53	-0.25	-0.62	-0.66	-0.03	1
ECTO/(MESO*ENDO)	0.13	-0.04	0.01	0.01	0.09	-0.35	-0.02	0.04	0.16	0.00	0.18	-0.21	-0.03	-0.26	-0.24	0.08	0.30

Table 4-2: Correlation matrix

	INPUT VAR	TRAIN DATA	ITERATIONS	NEURONS	TEST DATA	MSE	r
	6	79	1000000	10	79	**0.12**	
	6	79	1000000	4	79	0.27	
	5	79	1000000	10	79	0.27	
	6	79	200000	10	79	0.42	
	6	79	200000	4	79	0.40	
★	6	79			79	**0.82**	0.74
	6	69	1000000	10	10	**2.97**	
	6	69	200000	10	10	2.03	
★	6	69			10	**1.95**	0.76

Table 4-3: Comparison of performance of FFNN with linear regression (★). Last column in the table presents the correlation coefficient for linear regression.

	PRESENT STUDY				AVERAGE CANADIAN			
Anthropo-metric var.	MALES (N=30) Mean	±SD	FEMALES (N=14) Mean	±SD	MALES (N=239) Mean	±SD	FEMALES (N=206) Mean	±SD
MCSF (mm)	7.41	3.43	14.54	5.60	7.98	3.99	14.4	5.28
CG (mm)	38.04	2.16	36.41	2.73	37.3	2.14	35.11	2.14
ACHT (mm)	146.17	5.48	136.57	6.10	144.7	6.57	134.48	6.31
TBHT (mm)	47.99	2.83	45.50	2.77	47.24	2.73	43.22	2.65

Table 4-4: Group mean data for the population of the present study (30 males and 14 females) and an average Canadian population (students from University of Victoria, British Columbia and Simon Fraser) ages between 18 and 35 (Carter 1982).

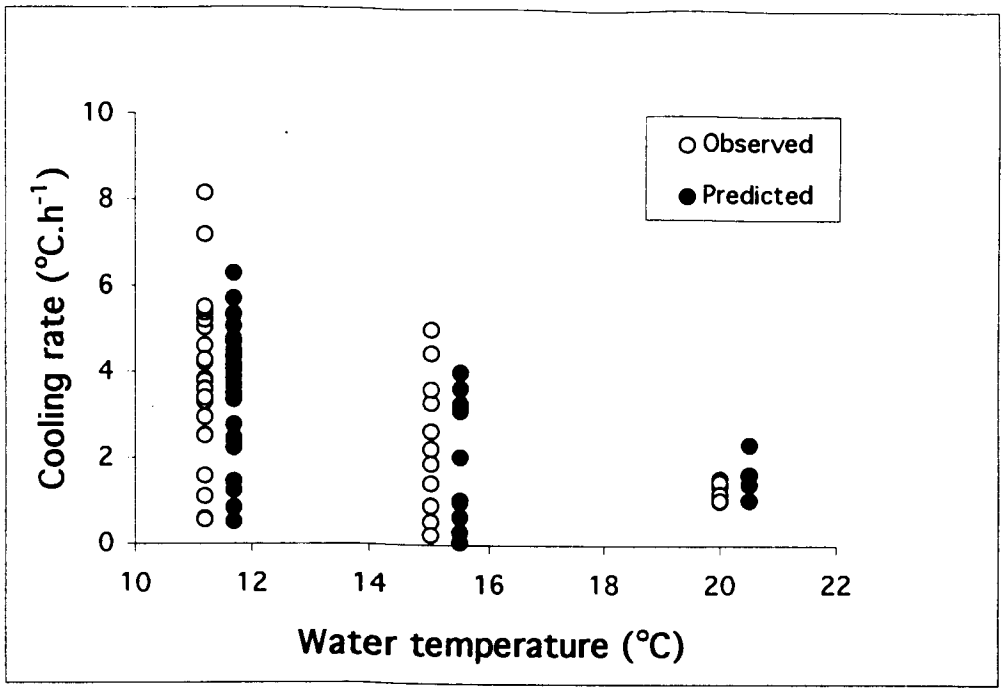


Fig 4-1: Observed cooling rate in 44 subjects (open circles) at 3 water temperatures 11.2°C, 15°C and 20°C compared with predicted (closed circles). The mean square error (MSE) was 1.2, 0.9 and 0.7 for 11.2°C, 15°C and 20°C water temperature respectively. For easier comparison a horizontal shift has been applied to the predicted values in order that the data points are not superimposed.

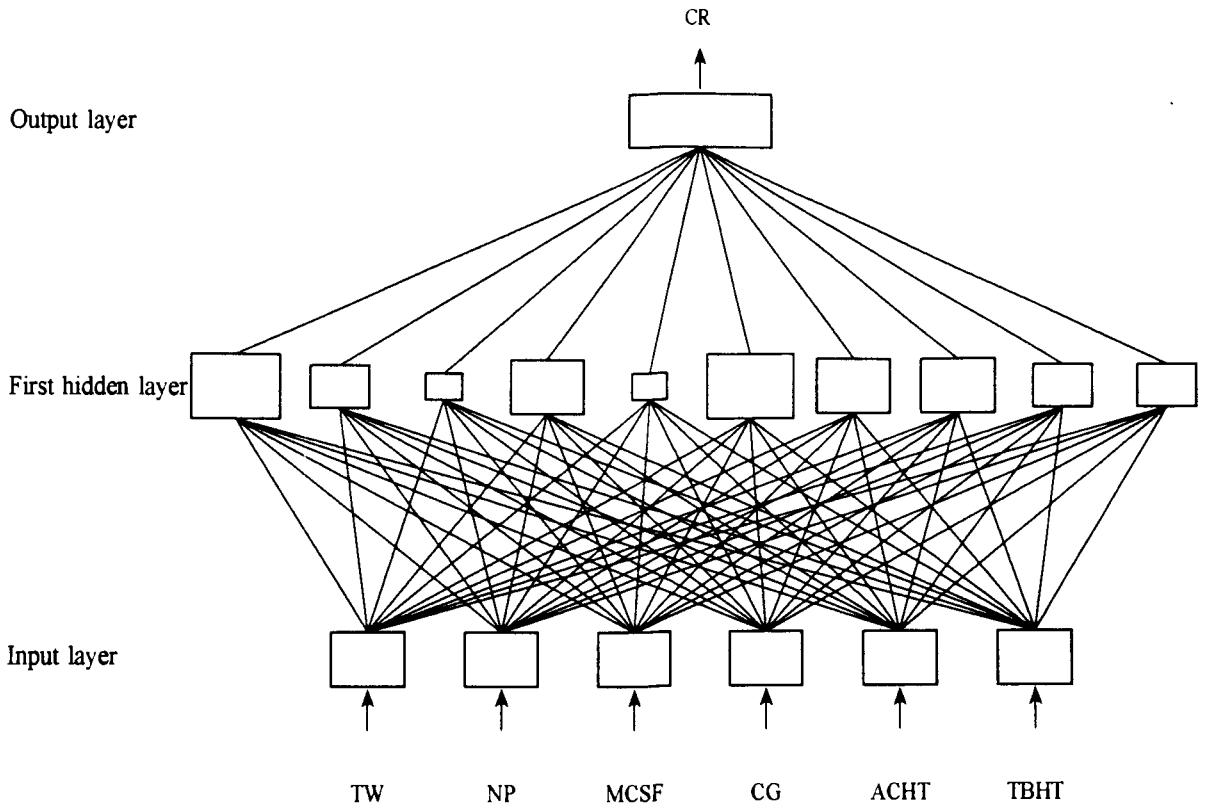


Fig 4-2: The configuration of the best performing FFNN with 6 input layer neurons, 10 hidden layer neurons and one output. The size of the squares (neurons) in the hidden layer represents the individual weights.

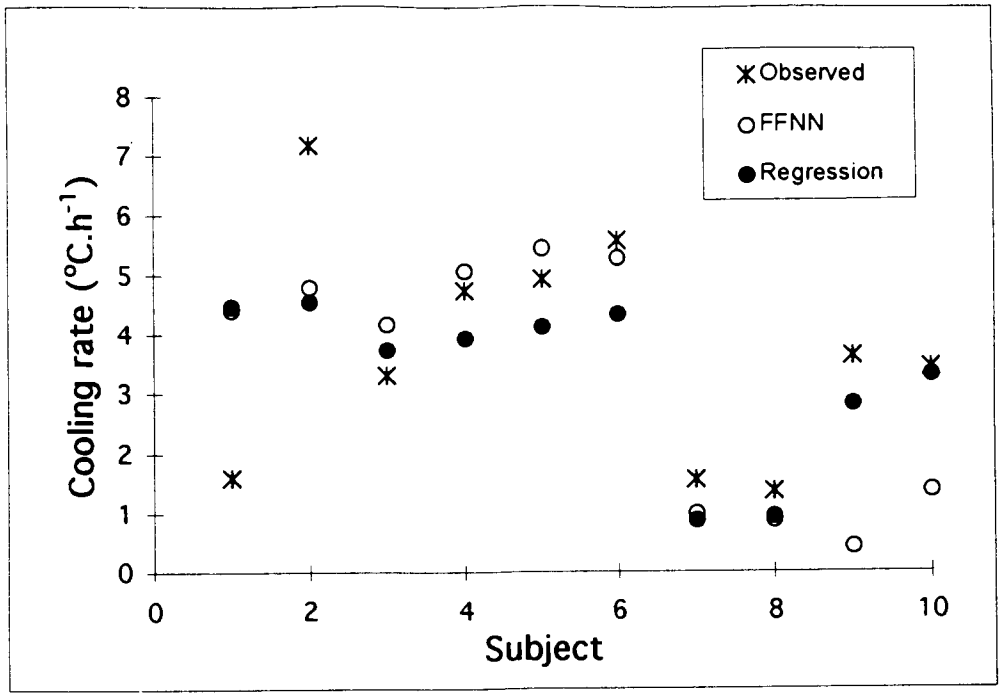


Fig 4-3: Prediction with FFNN (open circles) and linear regression analysis (closed circles) compared to observed cooling rates in 10 subjects.

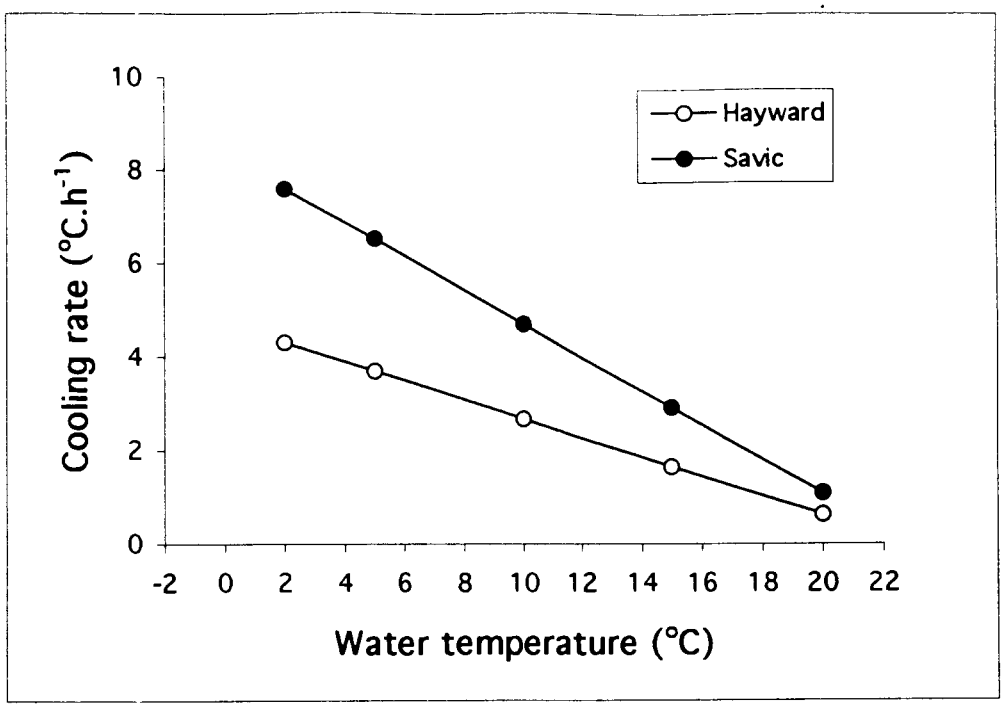


Fig. 4-4: Prediction of cooling rate of inactive, lightly clothed subjects - open circles (Hayward et al. 1975) and for nude, inactive subjects - closed circles (Savic). Data represent group mean values of each study.

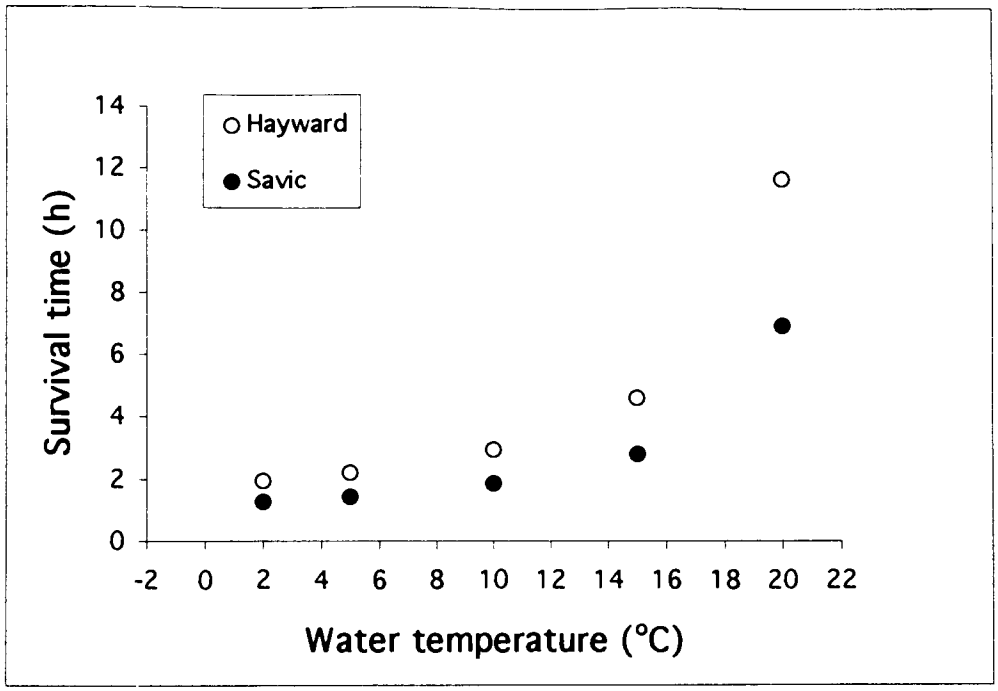
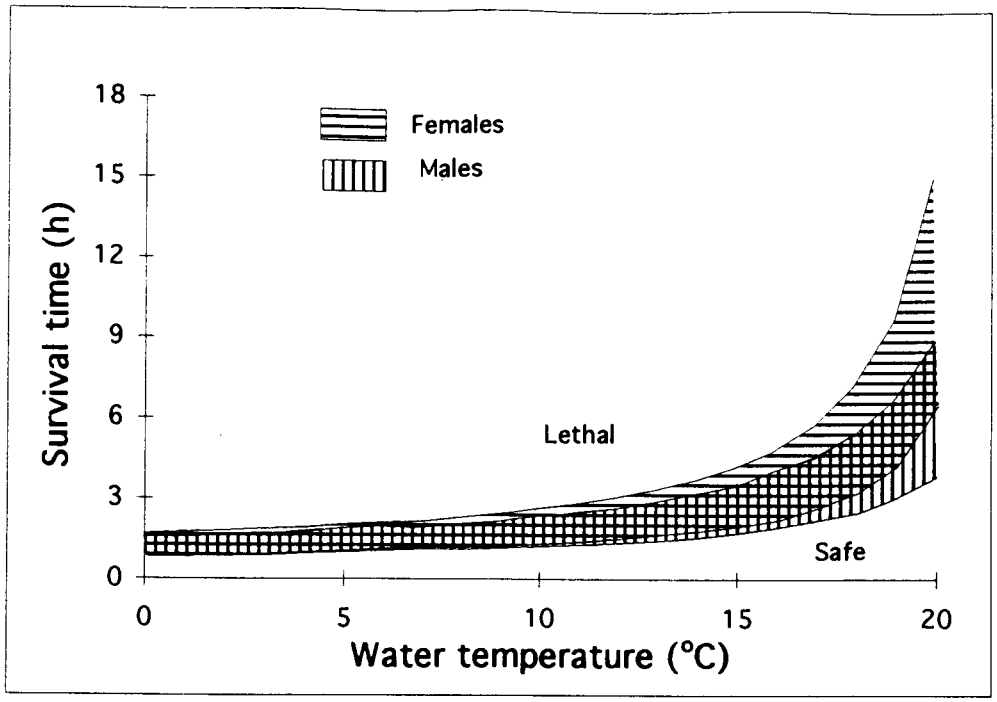


Fig. 4-5: Prediction of mean survival time for inactive, lightly clothed subject according to Hayward et al. (1975) - open circles, and for nude subjects using a new model including anthropometric data (closed circles). The anthropometric measures used represent the mean values of male subjects used in this study.



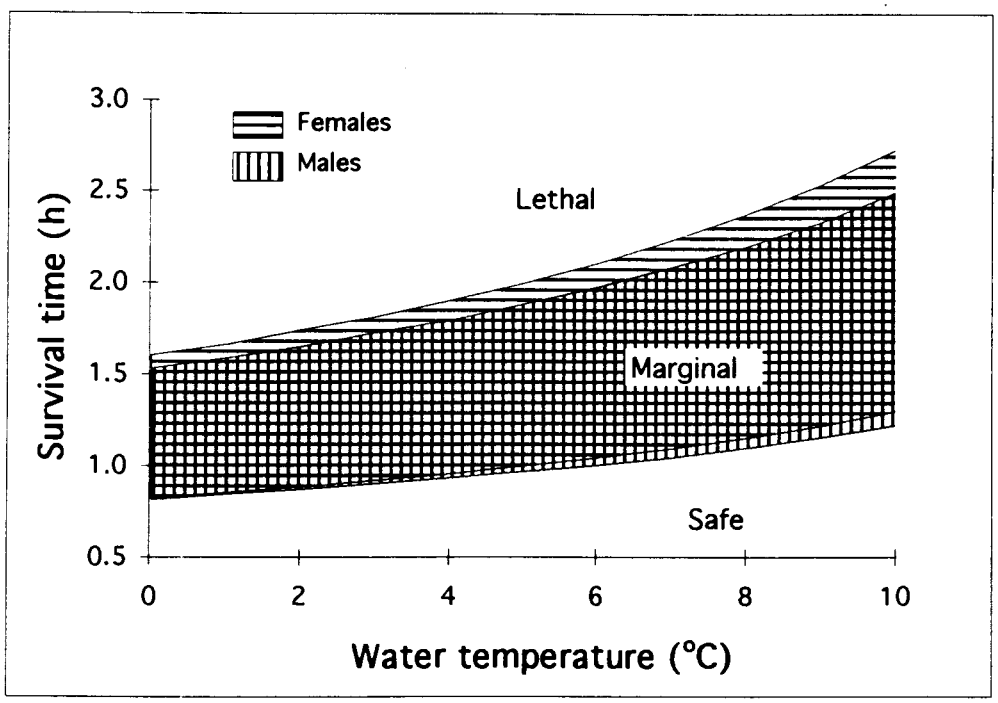


Fig. 4-6: Gender differences in tolerance limits to cold exposure. Prediction is based on average physique determined from Canadian population of university students.

GENERAL DISCUSSION

Despite recent improvements in diver thermal protection (Romet et al. 1991, Webb 1985, Elliott 1981), cold exposure during diving operations continues to be a problem affecting both a diver's performance and safety and is not fully appreciated by either divers or supervisory personnel. With the thermal conductivity of water 26 times greater than air, hypothermia of the body core and extremities is a frequent problem. Divers complain of overheating and fatigue due to having to dress in restrictive thermally protective wet or dry suits and wait prior to cold water exposure. Later during the dive, excessive perspiration during prolonged swimming and heavy underwater work decreases the thermal insulation of divers undergarments exposing the diver to hypothermia. Repetitive dives started before the diver is properly rewarmed, cause the depleted body heat stores to be further eroded. Although hypothermia observed in divers has been attributed primarily to the hostile physical conditions of the underwater environment, which accelerate the heat loss from the skin surface and respiratory tract, the findings of this thesis show that the contribution of inert gas narcosis to the development of hypothermia during diving cannot be neglected.

Study I, undertaken to investigate human thermoregulatory responses to cold water immersion (15°C) during compressed air breathing (6 ata) yielded several important findings. The core cooling rate of immersed subjects was significantly greater and the onset of continuous cooling was significantly faster at 6 ata than at 1 ata. This would imply that either a subject's heat loss or heat production was altered due to compressed air breathing. In addition, immersion at 6 ata was perceived as being significantly less cold, despite a lower core temperature. This confirms the observation of other researchers (Passias et al. 1992, White et al. 1980). It was suggested that faster cooling

and a blunted appreciation of cold are both due to the narcotic effect of N_2 in compressed air.

While N_2 in compressed air has been widely appreciated to exert narcotic effects when breathed at depths greater than 30 meters of sea water (Bennett 1993), and air breathing not recommended for diving beyond 6 ata, the effect of increased PO_2 and pressure *per se* might also account for faster cooling or blunted cold perception. To study the effect of pressure, N_2 in compressed air would have to be replaced by a non narcotic gas such as helium. Helium is commonly used in deep diving but has high thermal conductivity requiring the use of heated diving suits and breathing gas. Oxygen, on the other hand, is almost twice as potent an anesthetic as N_2 according to the lipid solubility theory but is usually recognized for its toxic effects, causing convulsions at a PO_2 greater than 2 atm. In order to eliminate the effects of pressure and N_2 narcosis, the hyperoxia present at 5 ata air breathing was investigated by requiring the subject to breathe pure oxygen at 1 ata (PO_2 = 1 atm; Study II). Hyperoxia did not affect either core cooling or perception of cold in subjects immersed in cold water. This is probably due to respired O_2 being used in metabolism and removed from solution rather than from blood oxyhemoglobin which would tend to lower the actual tension of dissolved O_2 in the brain (Smith and Paton 1976). The lack of an effect of PO_2 strengthened the hypothesis that PN_2 is the principal cause for increased core cooling and altered perception of thermal state. Further experiments were carried out to quantify the effect of PN_2 (Study III).

An increased core cooling rates and an impaired perception of cold has been also observed during 30% N_2O breathing in subjects immersed in 15°C water (Passias et al. 1992). It was, therefore, hypothesized that increased PN_2 would exert a similar effect on thermoregulation as N_2O. Lipid solubility has been found to correlate well with the narcotic effects of an inert gas (Bennett 1993). To quantify the effect of the inert gases, N_2 and N_2O, at various partial pressures. the narcotic potency (atm) of the breathing mixture was calculated as the product of the Bunsen coefficient ($cc \cdot cc^{-1}$) a measure of lipid

solubility, and the partial pressure of the inert gas (Study III, IV). The effect of O_2 was not included in the calculations since PO_2 of 1 atm did not impair the thermoregulatory response in subjects exposed to cold (Study II). Furthermore, the narcotic potency of a gas is usually determined from experimental studies where the abolition of the righting reflex in animals or patients is examined in the presence of 0.6 - 1.2 atm of O_2 (Eger 1985, Smith et al. 1979, Smith and Paton 1976). Results of Study III show that both shivering threshold and perception of thermal comfort are linear functions of the narcotic potency of N_2 and N_2O (Fig. 3-9). The narcotic potency of a 30% N_2O breathing mixture was calculated as the sum of NP for PN_2 = 0.5 atm and N_2O = 0.3 atm. The results of Study I are in agreement with those presented in Fig. 3-9. The average vote of -4 from the thermal comfort scale at ΔT_{es} = -0.5°C in 6 ata trial would lie almost exactly on the linear regression line.

Comparison of results from Studies I, II and III with other studies using hyperbaric N_2 or anesthetic agents is difficult due to the fact that the definition of "anesthesia" and "narcotic potency" varies with investigator and the species used in the study. Winter et al. (1975) demonstrated anesthetic properties of N_2 in air even at normal atmospheric pressure. They showed a 9.3 % decrease in response time to audiovisual stimulus in 20 subjects when N_2 in the air was replaced with He. Fowler et al. (1980) and Biersner (1972) have demonstrated that N_2O and hyperbaric N_2 exert an identical narcotic effect on memory, auditory perception and other functions involved in skilled performance. Comparative behavioral studies by Biersner (1987) have shown that 30% N_2O induces psycho-motor impairment similar to compressed air at 6.7 ata (PN_2 = 5.36 atm).

For comparison of results one of the few accepted definitions of anesthetic potency in clinical practice using general anesthetics was used - MAC. MAC (minimum alveolar concentration of anesthetic) is expressed as the pressure of a gas in atmospheres of, that produces abolition of movement in 50% of the subjects exposed to a noxious

stimulus and is based on lipid solubility (Eger 1974). For humans this relationship is described by: MAC · oil/gas partition coefficient = 1.4 (Hornbein et al. 1982, Eger 1969). The oil/gas partition coefficient for N_2 (0.067) gives a predicted MAC of 21 atmospheres, and MAC of N_2O determined in humans is 1.04 (Eger 1985, Hornbein et al. 1982). The oil/gas partition coefficient describes the relative capacity per unit volume of two solvents such as lipid and gas for particular anesthetic and is equivalent to lipid solubility coefficient. Therefore the PN_2 of 6.5 atm (8.13 ata air) would have similar narcotic potency (0.31 MAC) as 30% N_2O (0.31 MAC). The predicted anesthetic potency of 30% N_2O according to MAC value is approximately 10% lower than the prediction for 30% N_2O alone using the Bunsen coefficient (PN_2 = 7.16 atm). This difference could be due to the different techniques and species in determining MAC and ED_{50}, differences in lipid solubility coefficient (Oswald opposed to Bunsen coefficient) or a pressure reversal of anesthesia. Although Eger et al. (1969) showed an excellent correlation between the anesthetic potency measured in MAC (atm) and lipid solubility, which supports the method used to calculate narcotic potency in this thesis, the authors could not experimentally determine MAC for N_2 at high pressure. Two dogs tested with N_2 in that study continued to respond to a noxious stimulus at PN_2 = 43.5 atm, which was the limit of the pressure chamber. Smith et al. (1979) later demonstrated that anesthesia in mice can be reversed by pressure. Their ED_{50} values for nitrogen and argon, which abolished the righting reflex in animals, were considerably higher (38.3 and 16.7 ata for N_2 and Ar, respectively) than predictions based on olive oil solubility. Although the antagonism of anesthesia as shown in rats (Halsey et al. 1978), newts and mice (Lever et al. 1971) and tadpoles (Johnson and Flagler 1950) required higher hydrostatic pressures, its confounding effect at pressures as low as 5 and 6 ata cannot be excluded. Therefore the anesthetic effect of increased PN_2 on the $\dot{V}O_2$ response in the present studies (I, III) was possibly opposed by the hydrostatic pressure.

The increase in body core cooling observed in Studies I and III, and decrease in core temperature for the initiation of shivering with increased narcosis (Study III) are supported by the results from cold water immersions of subjects breathing 30% N_2O (Passias et al. 1992 and Mekjavic and Sundberg 1992) and other anesthetics (Kurz et al. 1993, Sessler 1991). The ways that inert gas narcosis can affect the thermoregulatory responses is either through an increase in heat loss or decrease in heat production. It is possible that the increased core cooling rates measured in the 5 ata and 30% N_2O conditions are also a result of increased heat loss from the periphery. However, the data from Cheung (1993) and Passias et al. (1992) did not reveal any change in skin heat flux during immersion with N_2O, which indicates that the amount of heat loss is similar during N_2O and air breathing.

From the results of present studies (I and III) it is evident that the relation between $\dot{V}O_2$ and core cooling was different for different levels of narcotic potency. While compressed air at 3 ata did not influence $\dot{V}O_2$, 5 ata caused an increase in $\dot{V}O_2$ in 5 subjects while 30% N_2O attenuated the $\dot{V}O_2$ response in all 9 subjects. The higher $\dot{V}O_2$ during the 5 ata air trial, where only the 5 subjects with the fastest core cooling were analyzed (III), was probably due to the greater cooling rate observed in immersion at 5 ata. The gain of the shivering response $\Delta\dot{V}O_2/\Delta T_{es}$, at 5 ata did not change compared to 1 ata. These findings agree with the results of Cheung (1993), who showed that low doses of N_2O (10% N_2O) significantly increased the rate of core cooling and increased the $\dot{V}O_2$ response over time, but did not affect the gain of the shivering response. This effect of PN_2 up to 4 atm and low doses of N_2O (low NP) is schematically presented in Fig. 5. With an increase in narcotic potency the shivering threshold is shifted to lower core temperatures but the gain of the shivering response is not affected. However, when the narcotic potency of the breathing mixture is higher, such as with 30% N_2O, the $\dot{V}O_2$ response is suppressed (Study III, Cheung 1993). The gain of the shivering response $\Delta\dot{V}O_2/\Delta T_{es}$, is also reduced, while the threshold for the onset of shivering is

progressively shifted to lower T_{es} (Study III). This effect of 30% N_2O on thermoregulatory responses is schematically presented in Fig. 5 with the dashed line marked "high NP".

The amount of heat loss does not depend only on the temperature gradient between the skin and environment and the composition and thickness of the peripheral layers of the tissue, but also on the geometric shape and surface area across which heat is dissipated. It is therefore understandable that the inclusion of morphology in the predictive models would improve the prediction of cooling rates. This agrees with the predictive model developed in this thesis, where cooling rate depends on the shape of the lower body (CG and TBHT) and its insulative layer (MCSF). This would imply that most of the body heat was lost through the lower extremities due to their greater surface area/mass ratio compared to the trunk area. More recent evidence shows that during periods of rest in cold water, unperfused muscle can contribute more than a half of the total insulation, however, during exercise that insulation can be totally lost (Park et al. 1982, Veicsteinas et al. 1982).

Some examples of cooling rates using a predictive model from Study IV are summarized in Table 1. The data are taken from an average Canadian male student population and the alterations made were one standard deviation from the mean. A healthy male of average built and unprotected in 10°C water would cool according to the prediction approximately 12.5% faster at 6 ata compared to 1 ata (Table 1). However, when a male with a higher mean calf skinfold thickness (MCSF) is compared to an average male at the same water temperature (10°C), he would cool 13.3 % slower. If MCSF and calf girth (CG) are both greater, then a person would cool 31.8% slower than an average individual. Also, the cooling rate of a tall person (with greater ACHT and TBHT) is 4.3% greater when compared to a person of average build. When a tall, thin person (smaller MCSF and CG) is compared to an average one, cooling rate is 36% faster.

Although the model developed for prediction of cooling rates accounts for body physique, it is limited to healthy individuals, inactive and unprotected, immersed in cold water. However, even with the use of a wet suit the insulation decreases with depth as the gas trapped in the closed-cell neoprene becomes compressed. Park et al. (1984) have demonstrated that workload also reduces overall insulation during cold water swimming due to an increase in blood flow to working muscle.

Similarly, a limitation of the model for prediction of survival times during head out immersion is that the prediction is based on an average healthy population (Canadian student population). It was also assumed that hypothermia will generally precipitate death in humans at 30°C due to loss of consciousness and drowning. The lower margin for survival was assumed to be 27°C although there are reports of victims surviving with a core temperature below 25°C (Hervey 1973).

In order to test the hypothesis that experimentation carried out with N_2O is applicable to diving applications, experiments were conducted to find the parallels between the narcotic effect of PN_2 and N_2O. Clinical studies have reported that body core temperature decreases during prolonged anesthesia. Though this finding has been attributed primarily to increased heat loss resulting from exposure of body cavities and infusion of cold solutions, low temperature of operating rooms and ventilation with cold gases, it is now generally recognized, that anesthesia interferes with the thermoregulatory system. The finding that N_2O in relatively low concentrations diminishes an individual's ability to maintain thermal balance should be considered in clinical practice, for instance when delivered to women during parturition.

Although the confounding effect of hydrostatic pressure can not be excluded, it seems that in compressed air diving the levels of N_2 are below the narcotic level that would seriously affect the gain of shivering thermogenesis. However, the increased PN_2 seems to have stronger effect on diver's appreciation of cold, which may ultimately lead to hypothermia by influencing behavioral responses (Studies I-IV). The duration of a

dive and safety of the diver is normally determined by the subjective sensations of cold. The blunted appreciation of cold at depths, together with a faster onset of cooling and greater cooling rate as observed at 6 ata (Study I), will speed the progression of hypothermia. Therefore, in deeper and more prolonged dives in cold water, the continued reliance on a purely subjective assessment of thermal status must be considered questionable.

Twater (°C)	Average male ($°C \cdot h^{-1}$)	**MCSF+1SD** ($°C \cdot h^{-1}$)	**MCSF+1SD CG+1SD** ($°C \cdot h^{-1}$)	**TBHT+1SD ACHT+1SD** ($°C \cdot h^{-1}$)	**ACHT,TBHT+1SD MCSF,CG -1SD** ($°C \cdot h^{-1}$)
0	8.3	7.7	6.8	8.5	10
5	6.5	5.9	5	6.7	8.2
10	4.7	4.1	3.2	4.9	6.4
15	2.9	2.3	1.4	3.1	4.6

Table 1: The predicted change in cooling rate (last 4 columns) with change in MCSF, CG, ACHT and TBHT at various water temperatures using new model. The alterations made, were one standard deviation (SD) from the mean of an average Canadian male student population.

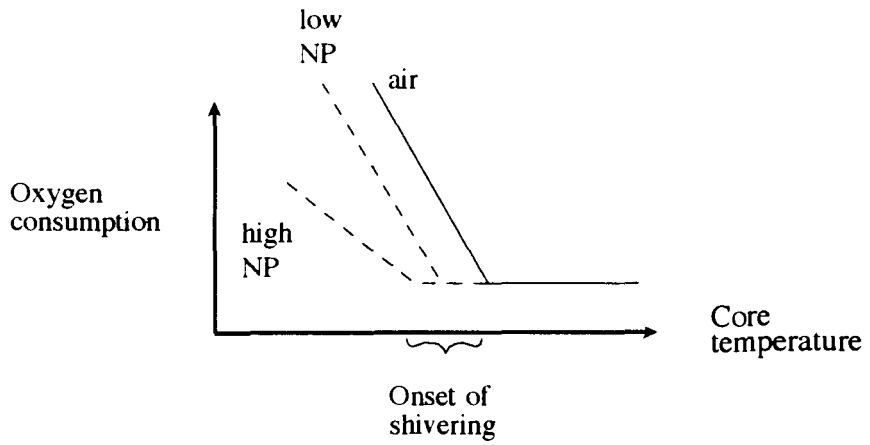


Fig. 5: Schematic representation of the effect of lower and higher levels of narcosis on the thermoregulatory shivering response. With low narcotic potency ("low NP") there is no change in the gain of shivering response, but the parallel shift to the lower threshold for the onset of shivering is observed (PN_2 up to 4 ATM; Study III and 10% N_2O; Cheung 1993). 30% N_2O ("high NP") causes also a suppression of the gain of shivering response.

SUMMARY

To date, the narcotic effects of hyperbaric environments have been based on the observed decrements in psychomotor performance (Hesser et al. 1978) but its effect on autonomic function such as thermoregulation have not been investigated thoroughly. Clinical studies have shown, however, that anesthetic agents inhibit thermoregulatory responses in animals (Hammel 1988) and humans (Sessler et al. 1988a,b, Sessler 1991). It was therefore hypothesized that observed progressive hypothermia in divers could be due to not only increased heat loss but also decreased heat production due to narcosis induced by elevated PO_2 and/or PN_2 associated with compressed air diving. It was further hypothesized that blunted appreciation of cold reported in divers (Winter et al. 1980, Hayward and Keatinge 1979) could be also due to narcotic effect of compressed air and would be similar to observed altered perception of thermal comfort in subjects breathing 30% N_2O while immersed in cold water (Passias et al. 1992, Mekjavic and Sundberg 1992).

In Study I subjects immersed in cold water at 6 ATA showed greater rates of core cooling than at 1 ATA. Despite the greater cooling rates, subjects perceived the immersions at 6 ATA as less cold than at 1 ATA. Due to problem with $\dot{V}O_2$ measurements it is difficult to conclude from Study I whether there is any difference in oxygen consumption between the 1 and 6 ATA immersion, but results from three subjects do not show an effect of N_2 narcosis on shivering thermogenesis at 6 ATA.

Study II demonstrated that 100% O_2 breathing does not significantly affect core cooling rates nor thermoregulatory shivering or perception of thermal comfort in subjects immersed in 20°C water. Therefore increased core cooling at 5 and 6 ATA and altered perception of thermal comfort observed at 6 ATA (I, III), can be attributed to increased

PN_2. The results however do not exclude the possibility of O_2 exerting a significant inhibitory influence on shivering at higher levels of PO_2.

Results from Study III demonstrate that during cold water immersions the gain of the thermoregulatory heat production response does not depend on the PN_2 within the normal range of air diving. However, the core temperature threshold for the onset of shivering is related to the narcotic potency of the inhalate and the relationship is linear. Perception of thermal comfort is progressively improved with increased narcotic potency of the breathing mixture, and the effect is also linear. Lower esophageal temperature threshold for the onset of shivering thermogenesis, greater Tes cooling rate and attenuated perception of cold with an increase in PN_2, suggest that compressed air environments contribute to delayed thermoregulatory and behavioral responses and faster development of hypothermia. Breathing 30% N_2O causes a greater effect on core cooling rates, shivering response and perception of thermal comfort than increased PN_2, which is in accordance with its higher solubility in lipids and calculated narcotic potency. 30% N_2O breathing causes a significant decrease in oxygen uptake despite increased core cooling. When 5 subjects with highest cooling rates were analyzed, there was also evidence of attenuated gain of shivering response.

From complete kinanthropometric assessments of body measures, derived somatotype and other anthropometric variables a linear regression model was developed for prediction of cooling rates in divers in waters up to 20°C. The model is based on four anthropometric measures (mean calf skinfold thickness, mean calf girth, acromial height and tibial height), water temperature and narcosis level. The results show that the rate of core cooling is strongly affected by body shape and composition. The developed model derived from a data base of 79 immersions, breathing gases of 6 different narcotic potencies at 3 water temperatures, provides a good indication of situations that can occur during diving in cold water. A model, based on body physique and water temperature, was developed for prediction of survival time during head out immersion in cold water.

Although both models have the advantage that they are simple and account for individual variations in body physique, they do not account for insulation provided with clothing, activity level or variations in physiological responses such as shivering, vasoconstriction and vasodilation.

CONCLUSIONS

- A compressed air environment increases the core cooling rate and alters thermal perception in humans immersed in 15°C water.

- Thermal balance and perception of thermal comfort are not affected by hyperoxia associated with compressed air breathing. Therefore, the effect of an altered responses in cold may be attributed to hyperbaric N_2.

- The core temperature threshold for the onset of shivering is related to the narcotic potency of the gas breathed and hence to the increase in PN_2 of compressed air. The relationship between the shivering threshold and narcotic potency (N_2 and N_2O gas mixtures) is linear.

- The gain of shivering thermogenesis ($\Delta \dot{V}O_2/\Delta T_{es}$) in humans is not altered during cold water immersion while breathing compressed air up to 5 ATA.

- Perception of thermal comfort during cold water immersion in humans is progressively improved by an increase in narcotic potency of the breathing mixture, and the effect is linear.

- There is no gender difference in the core cooling rate of humans immersed in 11.2°C water.

- The best anthropometric variables for predicting the core cooling rate in humans are medial calf skinfold thickness, medial calf girth, acromial height and tibial height.

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