THE EFFECT OF MILD NARCOSIS INDUCED BY NITROUS OXIDE ON THERMAL BALANCE IN HUMANS

by

Thanasis C. Passias

B.Sc. (Physical Education)

University of Athens, Greece

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (KINESIOLOGY)

in the School

of

Kinesiology

SIMON FRASER UNIVERSITY

August 1990

APPROVAL

APPROVAL : Thanasis Passias

DEGREE : Master of Science (Kinesiology)

TITLE OF THESIS : The effect of mild narcosis induced by nitrous oxide on thermal balance in humans.

EXAMINING COMMITTEE :

Chairman : Prof. J. Dickinson

Dr. I.B. Mekjavic
Senior Supervisor

Dr. O. Eiken

Prof. P. Bawa

Prof. K.E. Cooper
External Examiner
Faculty of Health Sciences
University of Calgary

Date Approved : 8 August 1990

PARTIAL COPYRIGHT LICENSE

I hereby grant to Simon Fraser University the right to lend my thesis or dissertation (the title of which is shown below) to users of the Simon Fraser University Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users. I further agree that permission for multiple copying of this thesis for scholarly purposes may be granted by me or the Dean of Graduate Studies. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Title of Thesis/Dissertation:

THE EFFECT OF MILD NARCOSIS INDUCED BY NITROUS OXIDE ON THERMAL BALANCE IN HUMANS

Author:

(signature)

THANASIS PASSIAS

(name)

Dec / 5 / 1990

(date)

ABSTRACT

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, it is generally recognized that anesthesia possibly interferes with the thermoregulatory system. The aim of the present study was to investigate whether mild narcosis induced by inhaling a gas mixture containing 30%N_2O, would affect the thermoregulatory responses at greater thermal drives for thermogenesis, as would be expected at lower skin and body core temperatures. Nine male subjects were immersed in 15°C water on two separate occasions. In one condition subjects inspired room air (20%O_2, 80%N_2) (control), while in the other condition the inspired gas mixture contained 20%O_2, 30%N_2O, 50%N_2 (N_2O). In both conditions, subjects were immersed to the neck for 60 minutes, or until their core temperature decreased by 2°C from the pre-immersion value. Following the cooling phase subjects rewarmed via endogenous thermogenesis while lying in a well-insulated bed for 48 minutes. Oxygen uptake ($\dot{V}O_2$), esophageal (Tes) and rectal (Tre) temperatures, inspired minute ventilation ($\dot{V}_I$), mean skin temperature ($\bar{T}sk$), mean heat flux (Q_{mean}), forearm-fingertip temperature gradient (Tsk-gr) and heart rate (HR), were recorded at minute intervals. $\bar{T}sk$, Q_{mean} and Tsk-gr, in both conditions stabilized within 10, 25 and 20 minutes of immersion, respectively, and were not significantly different between the two conditions. The cooling rate of Tes was higher under anesthesia than during air breathing. $\dot{V}O_2$, $\dot{V}_I$ and HR increased during the immersion in both conditions and were higher in the control than in the N_2O condition. In both conditions $\dot{V}O_2$ increased linearly with decreasing Tes, but at any given Tes, oxygen uptake was higher in the control than in the N_2O condition. These results indicate that mild narcosis induced with the inhalation of a gas mixture containing 30%N_2O attenuates the thermogenic response in humans during cold water immersion. The substantial attenuation of shivering thermogenesis occured despite a greater cooling rate of Tes. The results obtained during rewarming were similar to the ones obtained

during immersion. Thus, shivering thermogenesis was impaired by N_2O as judged from the Tes-$\dot{V}O_2$ relationship. Assuming that mild narcosis induced by inhalation of a N_2O gas mixture simulates inert gas narcosis experienced by divers breathing air at elevated ambient pressure, then the present results suggest that hypothermia often encountered by divers, might in part be due to a mechanism of narcosis attenuating thermogenesis.

ACKNOWLEDGEMENTS

I would like to express my genuine respect to professor V. Klissouras who offered me the first scientific eucharist and provided me with the strength and courage to pursue graduate studies.

This thesis would not have been completed without the support of many people.

I am deeply grateful to my senior supervisor Dr. I.B. Mekjavić whose enthusiastic personality helped me to look upon the uphill course of my graduate studies as an exciting and joyful experience. I would like also to warmly thank him for his continuous academic support, encouragement and friendship from the onset of my graduate studies.

Dr. O. Eiken occupies a seat alongside Dr. I.B. Mekjavić in my concsiousness. It was a privilege for me to meet and work with him. His methodical and rational way of thinking guided me in my endeavor to complete this thesis. I am sincerely grateful to him.

I am especially indebted to Dr. P. Bawa. Her teacher-mother academic support and guidance, since my first days in Canada, provided much appreciated encouragement to complete this degree.

I wish to express my genuine appreciation to Dr. K.E. Cooper for his willingness to review my thesis and also to evaluate my work.

I am also indebted to my lab mates Nick Geladas, Pat Sullivan, Wendy Burke and Mat White for their willingness to offer their help whenever it was needed.

Many thanks to Vic Stobbs, Gavril Morariu, Mel Frank, George Mah, Cathy Hunchak and John Sun for their assistance in collecting and analysing the data, and to all of my subjects, without whose unselfish commitment, this thesis would not have been possible.

My final thanks go to my family and my friends Maria Koskolou, Kostas Korontinis and Kyriaki Panourgia whose consistent moral support helped me throughout my endeavor.

I am grateful to Simon Fraser University and the State Scholarship Foundation of Greece for providing me with financial support. This study was, in part, supported by a grant

from the Natural Sciences and Research Council of Canada.

DEDICATION

To the memory of a good friend and teacher, Nickolas Xenakis, whose perception of life reached the limits of perfection.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

The present thesis investigates the effect of mild anesthesia on thermoregulatory function in humans. The problem of maintaining thermal balance during narcosis has been observed both during surgery, and during compressed air diving at depths where nitrogen narcosis becomes significant. Despite the many documented accounts of altered thermoregulatory function during narcosis, the manner in which anesthetic agents affect thermoregulatory effector responses has as yet not been elucidated.

The following sections offer a brief review of temperature regulation in mammals, with particular emphasis on the known effects of elevated ambient pressure and anesthesia on the maintenance of thermal balance in humans.

1. Regulation of body temperature in mammals

Since the initial demonstration by Barbour (1912), that hypothalamic structures function as a thermostat to regulate body temperature, numerous investigators have studied the regulatory role of the hypothalamus by examining the activity of the thermoregulatory effectors to a given range of thermosensory inputs (for review see Zotterman, 1963; Bligh, 1973; Boulant, 1981; Simon *et al.*, 1986). Based on their findings, and inspired by the engineering control systems, many investigators have created mathematical, neuronal, pictorial or analog models representing the mammalian thermoregulatory control system as a thermostat (Stolwijk and Hardy, 1966; Nadel *et al.*, 1970; Wissler 1985). The common concept incorporated by many models is that of a "set-point", whereby the core temperature (Tc) is compared to a set value or "set-point". Thus, a difference between the actual and set-temperature is termed the error, and the effector responses of shivering and sweating are proportional to the magnitude of this error.

Whereas most models incorporate a single regulator with appropriate thermal inputs and effector outputs, Satinoff (1983) adds a new dimension to the problem by introducing the idea of a multicontrol system. According to this concept, there is not only one thermostat but many, distributed at different levels of the neuraxis. Although these thermostats are capable of independent action, they normally act in concert because they are arranged in parallel and hierarchically.

Despite present knowledge of the relation between thermoregulatory effector responses and peripheral and core thermal stimuli, the manner in which the afferent nerves conveying temperature information from the thermoreceptors interface in the central nervous system (CNS) with efferent nerves to thermoregulatory effectors, remains speculative. Assuming however, that each neuron, with all its synaptic connections can be considered an integrator, then the concept proposed by Satinoff (1983) is quite similar to the neuronal model of mammalian temperature regulation proposed by Bligh (1984). This model adopts the Sherringtonian concept of reciprocal inhibition, by suggesting that the thermal information emanating from the warm and cold sensors is reciprocally inhibited as it is conveyed to the hypothalamic region. Thus, the observed responses of heat production and heat loss are a result of the cross inhibition which occurs in the afferent pathways. Such a model further demonstrates that cross inhibition of thermal afferent information will establish thresholds for the effector responses, based on the characteristic of the cold and warm sensors, and thus eliminates the need for a comparator or "set-point" in thermoregulatory models.

Considering that the pathways from cold and warm sensors to heat production and heat loss effectors, respectively, involve polysynaptic pathways which convey neurally coded thermal information, then any non-thermal factor which may significantly alter action potential propagation, and synaptic transmission may also modify the effector response for a given thermal stimulus (Mekjavic and Sundberg, 1990).

2. Thermal balance in compressed air environments

a) Heat loss from the skin surface

Altering the physical characteristics of the environment may either enhance or reduce the ability of heat dissipation or heat gain, which may ultimately lead to undesired elevations or decrements in body temperature. Ambient temperature may be varied over a wide range without activating sweating and the thermogenic responses. Within this range, defined as the "thermal comfort zone" or "thermal neutral zone" (Hensel, 1981; Bligh, 1988), body temperature is maintained constant primarily through vasomotor control of skin blood flow, and thus by regulation of heat dissipation. The following discussion will focus on the alteration of heat loss anticipated in divers exposed to either dry or wet high pressure environments.

i) Dry dives

Numerous studies have demonstrated that the increased thermal capacity of gas mixtures, concomitant with increased pressure, results in enhanced heat loss in subjects exposed to such hyperbaric conditions (Raymond *et al.*, 1968; Webb, 1970; Timbal *et al.*, 1974). This necessitates the elevation of ambient temperature at high pressure, in order to maintain thermal comfort.

A theoretical analysis conducted by Flynn (1974), illustrates that in He-O_2 environments, the convective heat transfer coefficient (hc) increases by a factor of 14.68 between 0 and 5000 feet of sea water (fsw), and that the evaporative mass transfer coefficient (h_D) decreases to 7-6% of the surface value, at 5000 fsw. The former is a result of the increased thermal capacity (Cp) and increased thermal conductivity (K) of the He-O_2 mixture with increasing pressure, and the latter is due to the decreased diffusion coefficient for water vapour, for the same conditions (Schwerts and Brown, 1951). Similarly, heat loss by radiation decreases by 50% at 500 fsw and by 15% of the value at 1 ATA at 5000 fsw. It is evident, therefore, that the main avenue for heat loss in compressed air environments is by convection/conduction. This enhancement of

convective/conductive heat loss at depth more than compensates for the reduction in the amount of heat dissipated by evaporation and radiation. In fact, the increase in heat loss requires higher environmental temperatures, to maintain thermal comfort and to prevent excessive cooling in divers. Furthermore, anecdotal observations reported by Bennett (1988), indicate that the thermal comfort zone is not only shifted towards higher temperatures, but is also reduced in magnitude.

ii) Wet dives

Diving in cold water may severely disturb the thermal balance of divers. The initial response to immersion in cold water of unprotected individuals is vasoconstriction of cutaneous blood vessels, thereby reducing the conductance of heat from the body core region. However, peripheral vasoconstriction is not uniform, and has been reported to be the most pronounced in the extremities, and less significant in the trunk and head region (Shvartz, 1970; Nunneley *et al.*, 1971).

Similar to the dry exposures described previously, the main pathways for heat loss remain conduction and convection. The heat loss is further enhanced by the movement of water across the skin surface, as would be experienced during swimming or working in a region with underwater currents. Theoretical studies, simulating such water immersions, have observed that the heat transfer coefficient for conduction is constant at $11 W.m^{-2}.°C^{-1}$ for any given swimming velocity, whereas the convective heat transfer coefficient is approximately $95\ W.m^{-2}.°C^{-1}$ in still water and increases with increasing swimming velocity to $400\ W.m^{-2}.°C^{-1}$ for a velocity of $5\ m.sec.^{-1}$ (Rapp, 1971). These theoretically derived values have been confirmed by Boutelier *et al.* (1971), who quantified the magnitudes of convective and conductive heat loss from nude men, for a range of swimming velocities.

b) Respiratory heat loss

Heat loss from the respiratory tract, at any given diving depth, will be similar, whether the divers are exposed to an aqueous or dry medium. In both conditions the divers will breathe a similar

cold and dry high pressure gas mixture. In wet dives, respiratory heat loss may be greater, due to the cooling of the gas by the surrounding water prior to reaching the diver. In contrast, the air in a dry chamber might be warmer and contain a larger quantity of water vapour. At normobaric conditions the main contributor to the respiratory heat loss, is the evaporation of water vapour from the respiratory tract. However, with increasing ambient pressure, the contribution of the evaporative component diminishes (Goodman *et al.*, 1971), primarily as a result of the decreasing evaporative mass transfer coefficient, whereas conductive heat loss increases. Webb (1970) has postulated, that subjects breathing He-O_2 mixtures at 5°C at ambient pressures equivalent to 600 fsw, will dissipate an amount of heat equal to the total heat produced by the process of metabolism, through the respiratory tract alone.

3. Undetected hypothermia in divers

Ultimately, high heat loss environments in which divers are usually are exposed to, may induce a significant reduction of the body temperature, and result in a variety of pathophysiological responses associated with hypothermia. Normally, the thermoregulatory system responds to such perturbations of body temperature by activating heat production and heat conserving mechanisms.

Padbury et al. (1987) however, observed that a diver conducting 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, an option which was present during the trial, nor did he exhibit any thermogenic responses. Similar observations have also been made during cold water immersion in normobaric environments (Hayward and Keatinge, 1979), which have lead to the hypothesis, that undetected or symptomless hypothermia may be the cause of deaths in divers.

Several explanations have been proposed to address these observations:

i) There is a tremendous subject variability in the thermogenic response, for identical cold exposures (Mekjavic *et al.*, 1986; Mittleman, 1987;). Thus, some individuals allow their core temperature to decrease and activate the shivering response at much lower core temperatures. It is,

therefore, plausible that such individuals may be susceptible to, and potential victims of undetected hypothermia.

ii) Someren *et al.* (1982) hypothesized that undetected hypothermia during diving or cold water immersion may be due to a uniform skin temperature of 29°C. They observed different thermogenic responses in the same individuals immersed in 29°C water, depending on the temperature of the hands and feet. Their results demonstrate that metabolic rate is not pronounced during whole body immersion in a 29°C water, resulting in a slow decrease in core temperature to 35.6°C. However, when the subjects' hands and feet were immersed in a separate bath maintained at 12°C, while the remainder of the body was in 29°C water, a pronounced increase in metabolic rate was observed. Thus, they concluded, that the hands, which are usually exposed to the environment, act as effective external cold sensors.Similar results, of undetected core cooling during immersion in 29°C, have been previously reported by Hayward and Keatinge (1979).

iii) Someren *et al.* (1982), based on the studies of Hensel and Schafer (1974) and Schafer *et al.* (1978), proposed that the concentration of calcium ions in sea water might explain the observations of undetected hypothermia during immersion in sea water. Hensel and Schafer (1974) showed that intravenous infusion of calcium inhibits the activity of the cutaneous cold receptors and enhances the activity of the warm receptors. Subsequently, Schafer *et al.* (1978) complemented these findings, by reporting that calcium infusion in cats not only significantly reduces the static discharge frequency of cold fibers, but also shifts the activity temperature curve towards lower temperatures. Thus, as postulated by Someren *et al.*, a few hours of immersion in sea water may affect the activity of the cutaneous temperature sensors in such a manner, that their normal output may be perceived as a warmer skin temperature by the central regions involved with the regulation of body temperature. This may explain to a degree the undetected progress of hypothermia during prolonged immersion in sea water.

iv) One possible mechanism of the observed undetected hypothermia during dives utilizing compressed air, which has not received much attention, is the potential effect of inert gas narcosis on the thermoregulatory system. Impairment of neural function associated with narcosis, in general,

may contribute to enhanced heat loss and decreased heat production. In order to examine this hypothesis, a more detailed discussion on the effects of anesthesia on body's thermal balance as well as on the mechanisms and causes of anesthesia and inert gas narcosis is necessary.

4. Thermal balance during general anesthesia

One of the problems often encountered in operating rooms, is the maintenance of normal body temperature in anesthetised patients. Hypothermia is a common phenomenon observed in patients during prolonged anesthesia and surgery.

Hypothermia during surgery has been studied by many investigators and to date, has been primarily attributed to the increased heat loss due to infusion of cold fluids (Stjernstrom *et al.*, 1985), exposure of body cavities (Goldberg and Roe, 1966), low environmental temperatures, ventilation with cold gases, as well as to the impairment of the patient's thermoregulatory system by the anesthetic agents (Thomson, 1967; Pauca and Hopkins, 1971).

It is generally assumed that anesthetics have an inhibitory effect on the thermoregulatory system (Roe *et al.*, 1966; Sessler *et al.*, 1988; Hammel, 1988). However, it remains to be proven that the observed altered thermoregulatory function is a result of a direct anesthetic effect on thermoregulatory mechanisms and not an indirect consequence of the effect of anesthesia on other physiological systems, which in turn might affect thermal balance (Flacke, 1983).

The ability of anesthetics to induce body cooling has long been recognized, as is evident by the statement of Pickering in 1958 (referenced by Hall, 1978): "the most effective way of cooling a man is to give an anesthetic". Although a voluminous amount of evidence exists supporting this statement, the extent to which thermal imbalance during anesthesia is caused by increased heat loss as opposed to reduced heat production remains to be investigated.

a) Anesthesia and heat loss

It is a common observation in many studies that cutaneous vasodilation occurs after the induction of anesthesia (Abramson *et al.* 1941; Foregger, 1942; Thomson, 1967; Pauca and Hopkins, 1971; Sessler *et al.*, 1988). Foregger (1942) reported that inhalation of nitrous oxide and other anesthetics produced substantial increases in cutaneous temperature of the plantar surface of the great toe due to full vasodilation of the peripheral vessels. He reported that the increase of skin temperature was obtained at about the same time that the sensibility to pain was lost.

Thomson (1967), using a heat clearance technique, further demonstrated that cutaneous blood flow in the finger pad increased significantly after the induction of anesthesia by halothane and cyclopropane, whereas forearm muscle blood flow was unaltered. Again the increase of skin blood flow occured quickly and was coincident with the loss of consciousness, thus suggesting that the changes in peripheral vasomotor activity are most probably related to the effects of anesthetics on the central nervous system. Thomson proposed that the vasodilation observed was most likely due to the central inhibition of the vasoconstrictor sympathetic tone of the cutaneous blood vessels.

Similarly, Pauca and Hopkins (1971) using a water plethysmograph, observed that anesthesia instigated by 50% nitrous oxide and by halothane, increased hand blood flow, whereas forearm blood flow was unaffected. Hand blood flow remained increased during halothane anesthesia despite reductions of water temperature in the plethysmograph. In contrast, decreasing the water temperature when the drug was withdrawn caused marked decline of hand blood flow. The failure of sympathetic fibers of the hand to instigate vasoconstrictor tone during anesthesia, possibly, indicates that the anesthetic agent affected the thermoregulatory centre responsible for regulating vasomotor tone.

Therefore, it seems clear that the anesthetics used in the studies mentioned above have a vasodilatory effect on the hands, fingers and toes. Whether the same vasodilatory effect occured in nonacral areas of the body cannot be assumed from the above results, since the nervous control of cutaneous vessels in nonacral and acral regions differ (c.f. Rowell, 1986). However, Saumet *et al.*

(1988) showed that cutaneous blood flow of the leg increased under anesthesia induced by flunitrazepam, hence supporting the notion that anesthetic agents may induce cutaneous vasodilation also in nonacral regions. Similarly, Abramson *et al.* (1941), using a venous occlusion plethysmographic method found that the circulation through both, hand and forearm, were increased under cyclopropane anesthesia.

b) Anesthesia and heat production

Heat production of the body under resting and normothermic conditions is equivalent to the basal metabolic rate. Increases in heat production are achieved by shivering and non-shivering thermogenesis, when the body temperature falls below normal levels. Therefore, in order to examine the effects of anesthesia on the heat production mechanisms of the body, all three mechanisms of heat production should be taken into consideration.

(i) Basal metabolic rate

Basal metabolic rate as expressed by the oxygen consumption values, is reduced by 15% after the induction of general anesthesia (Stjernstrom *et al.*, 1985). Similarly, Bartels (1949), reported a 13% decrease in resting metabolic rate under pentothal anesthesia. Whether this decrease of resting oxygen consumption is due either to an effect of anesthetics exerted directly on the cellular metabolic pathways, or to the elimination of muscular tone caused by neuromuscular blockers, or to the general depressive anesthetic effects on the nervous system, remains to be clarified. Nevertheless, the controversy in the literature regarding the effects of anesthetics on the cellular metabolism remains (c.f. Hoech *et al.*, 1966; Theye and Michenfelder, 1968; Sharr and Hammel, 1972), and is probably due to the different types of anesthetics used as well as to the differences in the doses, species and techniques used.

(ii) Non-shivering thermogenesis

During hypothermia heat production increases through shivering and non-shivering thermogenesis. Although the findings by Joy (1963) and Jessen *et al.* (1980) seem to support the existence of non-shivering thermogensis in humans, its importance in the heat production during hypothermia remains scarce and inconclusive.

Johnson *et al.* (1963) measured the oxygen uptake during cold exposure, in subjects who either were unconscious from cerebral damage and were paralysed with d-tubocarine or gallamine, or were paralysed below the neck (including the respiratory muscles) due to poliomyelitis. Although the core temperature of the subjects dropped by approximately 1°C and the skin temperature by 8-10 °C, no measurable increase in oxygen uptake was observed. From these results the authors concluded that non-shivering thermogenesis does not occur in humans. In contrast, Jessen *et al.* (1980) observed an increase in oxygen uptake of 0.04 $L.min.^{-1}$ in curarised subjects (with persistent severe brain damage) in response to a cold exposure, which lowered their core temperature by 0.7°C; the increased metabolism was attributed to non-shivering thermogenesis.

Stjernstrom *et al.* (1985) showed that the level of catecholamines in the blood, substances which according to Joy (1963) and Jessen *et al.* (1980) are related to non-shivering thermogenesis, were lower during anesthesia compared to post-anesthetic levels, for the same core temperature values. The increase of catecholamine concentration during the post-operative stage was concominant with a 40% rise in oxygen uptake which was probably reflecting the thermogenic effect of catecholamines. However, since the authors did not comment on shivering activity during the post-operative stage, conclusions regarding the effects of anesthetics on catecholamine secretion and on the non-shivering thermogenesis mechanisms in humans, cannot be drawn.

(iii) Shivering thermogenesis

In contrast, the attenuative effect of anesthetics on shivering thermogenesis has been observed by many investigators (Jones and Mclaren, 1965; Roe *et al.*, 1966; Vaughan *et al.*, 1981; Guffin *et al.*, 1987). This becomes more apparent at the beginning of the post-operative stage, following the

withdrawal of the anesthetic agent. Despite no substantial changes in either skin or core temperature, removal of the anesthetic may give rise to several fold increases in shivering thermogenesis.

In a recent study by Mekjavic and Sundberg (1990), a 42% reduction in oxygen uptake was induced by mild N_2O anesthesia compared to the control condition, during immersion in 28°C of water. Similarly, Stjernstrom *et al.* (1985) reported a 55% reduction in heat production during general anesthesia. Regardless of whether these reductions of heat production obtained in the above studies are due to the attenuation of either shivering or non-shivering thermogenesis by the anesthetics, it is evident that they are large enough to cause a thermal deficit.

In conclusion, general anesthesia can lead to hypothermia since it increases heat loss by vasodilation and concomitantly attenuates the heat production mechanisms of the body.

5. Mechanisms of inert gas narcosis and anesthesia

The term inert gas has been used in the literature in a metabolic sense, implying that the chemical structure of the gas does not change in the process of metabolism, neither does the chemical structure of the affected biological system (Featherstone and Muehlbaecher, 1963). Such gases, which are generally accepted as metabolically inert, are: nitrous oxide, ethylene, cyclopropane, as well as nitrogen, helium, hydrogen, neon, argon, krypton and xenon. With the exception of helium and neon, all exert known anesthetic effects. Most only at supra-atmospheric pressures, but some of them at normal atmospheric pressure. Thus, the phenomenon of compressed air narcosis, which was described by Junot in 1835 (as referenced by Bennet, 1982), is an example of the anesthetic effect of nitrogen, when air is breathed at high ambient pressures.

To date, much work has concentrated on the effects of anesthetics at the level of cellular membranes (Miller *et al.*, 1972; Halsey *et al.*, 1978) and their effects on neural structures (Bennett, 1967; Hirata *et al.*, 1984). However, despite the numerous studies reporting molecular and electrophysiological changes, the exact mechanism of inert gas narcosis or anesthesia remains unknown.

Several theories have been formulated with this regard, and all agree that the main action of the inert gas occurs in the central nervous system (CNS). The inspired inert gas is circulated to the cells of the CNS, where it subsequently alters their function.

a) Cellular and membrane mechanisms

Featherstone *et al.* (1963) suggested that the mechanism of narcosis is biophysical rather than biochemical, since the primary chemical structures are unaffected during inert gas narcosis. The excellent correlation between lipid solubility and narcotic potency of a gas confirms this biophysical nature of the mechanisms of narcosis (for review see Bennett, 1982). Inert gas therefore, acts on the lipid part of neural membranes.

Meyer and Overton (referenced by Bennett, 1982) were the first to suggest that narcosis is most probably due to the penetration of the cell membranes by volatile or gaseous narcotic substances.

The more recent theories of "critical volume hypothesis" (Miller *et al.*, 1973) and "multi-site expansion hypothesis" (Halsey *et al.*, 1978), propose that anesthesia is due to the expansion of the cell membranes, as a result of the absorption of the anesthetic substances. In contrast, Bennett *et al.*, (1967) and Galey and Van Nice (1980) suggested that it is the decrease in the surface tension of the lipid-water interface, due to the absorption of the anesthetic substance by the lipid bilayer, which results in the alterations of neuronal function. This latter thesis has been termed the "increased permeability hypothesis", as it suggests that it is the increased permeability of the membrane to cations (Na^+, K^+), which is the primary cause of anesthesia. It is now apparent that this change in permeability is dependent upon the concentration of the anesthetic and is perhaps more prominent in the early stages of anesthesia. In particular, Anderson (1972) demonstrated that low concentrations of anesthetics stimulate Na^+ transport, whereas higher concentrations inhibit it.

b) Neuronal function

There is now increasing evidence that compressed air decreases the propagation of action potentials (Carpenter, 1954), decreases the magnitude and increases the duration of action potentials (Rosenberg and Heavner, 1980) and inhibits synaptic transmissions (Bennett, 1982). From the information available in the literature, it can be hypothesized that, not only central but also peripheral neural structures will be affected by inert gas narcosis imposed at high pressures (Carpenter, 1954).

Similarly, inhaled anesthetics at one atmosphere pressure diminish the rate of rise and the amplitude of excitatory post synaptic potentials recorded from ventral and dorsal horn cells in the spinal cord (Somjen, 1967). In addition, Davis *et al.* (1957) have shown that inhaled anesthetics attenuate to a greater extent the afferent signals passing via the polysynaptic reticular formation pathways than the ones transmitted by the oligosynaptic medial lemniscus pathways.

These results suggest that inhaled anesthetics similarly to the inert gases inhaled at high pressures, most likely affect the synaptic transmission of the neural information, within the nervous system. However, in contrast to the findings of Carpenter (1954), Jong and Nace (1967) suggested that inhalation anesthetics have no significant effect on peripheral nerve conduction or on generation of impulses in cutaneous receptors when they were used in clinical anesthetic concentrations. Nevertheless, considering that Carpenter (1954) observed blockades on the rats' sciatic nerves when they were exposed to 10-13 atmospheres of N_2O, it is obvious that the discrepancy in the results between the two studies is most likely based on the difference in the anesthetic dose administered in each of them.

Thus, considering a physiological system, such as the regulation of body temperature, modification of the neuronal function will be reflected in the transduction of thermal energy into neurally coded frequency information, in the transmission and central integration of this information, as well as in the subsequent activation of effector mechanisms, such as shivering tremor.

Based on these findings, the contribution of inert gas narcosis in the enhancement of heat loss via a vasodilatory action and the reduction of shivering thermogenesis, cannot be excluded as insignificant factors in the development of undetected hypothermia in divers.

INTRODUCTION

Clinical studies have reported that body core temperature decreases during prolonged surgery and anesthesia (Goldberg and Roe, 1966; Roe *et al.*, 1966; Stjernstrom, 1985). Although hypothermia observed during anesthesia has been attributed to the inactivation of body temperature regulation (Hammel 1988), or to the abolishment of the thermostatic reflexes (Roe *et al.* ,1966), the extent to which thermoregulatory mechanisms are affected by anesthesia is not known (Sessler *et al.*, 1988). A major problem with the interpretation of clinical data, is the difficulty in isolating the effect of anesthesia from that of any pre-medication given to the patient, and patients' pathologies. Thus it remains unresolved, whether the major contributing factor is the increased heat loss or decreased heat production.

It is noteworthy, that there may be similar etiologies of the hypothermia observed in patients undergoing surgery with the hypothermia observed in compressed air divers. Namely, divers breathing air at high pressures may experience the narcotic effect of elevated N_2 pressures, also referred to as nitrogen narcosis. Although to date, the hypothermia observed in divers has been attributed primarily to the hostile physical conditions of the underwater environment, which enhance the heat loss from the skin surface and the respiratory tract (Piantadosi *et al.*, 1981; Webb, 1982; Kuehn, 1984), the possible contribution of inert gas narcosis to the development of hypothermia during diving cannot be excluded.

As in clinical studies, the effect of N_2 narcosis on thermoregulatory function has not been investigated adequately to draw any conclusions regarding whether the problem of hypothermia arises due to enhanced heat loss or decreased heat production. Direct comparisons between clinical trials and diving studies is difficult, as such comparisons cannot account for the equivalence of narcotic potencies of gases used in surgery with that of elevated N_2 pressures.

Finally, whether the action of anesthetic gases administered at 1 ATA is similar to that of N_2 at elevated pressure is unknown. However, 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 nitrogen (Carpenter, 1954). Nevertheless, conclusions drawn from simulations of nitrogen narcosis by applying one of the above anesthetics should be made with caution, until the exact mechanisms and effects of anesthetic action on the physiological systems are clarified.

The present investigation was designed to examine the effects of mild narcosis on temperature regulation during cold water immersion. Furthermore, the study examined whether the attenuative effect of mild narcosis on heat production, as reported by Mekjavic and Sundberg (1990), persisted in the presence of a greater peripheral cold stimulus.

METHODS

1. Subjects

Nine male volunteers participated in the study. Their participation was subject to physicians' approval. Before giving their informed consent, they were familiarised with the experimental procedures and the possible risks involved. Subjects' physical characteristics were determined prior to the experiments (Table 1).

2. Protocol

Each subject was immersed to the neck in a cold water bath (15 °C) on two different occasions: breathing normal air (20%O_2, 80%N_2; control) and breathing a gas mixture containing 20% O_2, 30% N_2O and 50% N_2 (N_2O). The two trials were spaced at least one week apart, to avoid acclimation to cold and the order in which they were conducted was alternated among subjects. Any effects of circadian rhythm were minimised by conducting the trials at the same time of the day for the individual subject. Each subject was asked to avoid strenuous exercise during the day preceding the experiment, and to have a light meal 2 hours prior to testing. They also agreed to maintain a similar diet as well as physical activity and sleeping schedules during the 2 day period preceding each of the two experimental trials, thus diminishing the effect of the above factors on the physiological responses recorded.

Upon arrival in the laboratory the subject changed into shorts. Following the insertion of a rectal thermistor probe (15 cm beyond the anus), the subject assumed a supine position on a bed while the remaining transducers were positioned.

Mean heat flux from the skin and mean skin temperature were determined from measurements at four sites (arm, chest, thigh and calf). In addition, skin temperature was

measured on the forearm and on the fingertip of the left arm using thermocouple probes. Forearm-fingertip temperature gradient (Tsk-gr), an indication of cutaneous vasomotor tone (Sessler *et al.*, 1988), was then determined by subtracting the temperature value of the forearm from that of the fingertip. The forearm thermocouple was taped on the radial side of the forearm, mid way between the wrist and the elbow, while the fingertip thermocouple was placed on the palmar side of the second digit, as suggested by Sessler *et al.* (1988). The left arm, on which the skin temperature gradient was recorded, was kept in a horizontal position and supported by a wooden board 1-2 cm above the water surface. The room temperature range was 25-27 °C for both experimental conditions.

An esophageal thermistor probe was inserted last, thus diminishing subjects' discomfort time. The esophageal probe insertion length was determined from sitting height as suggested by Mekjavic and Rempel (1990).

During the experiment the subject wore a noseclip and inhaled the prevailing breathing gas mixture from a Douglas bag via a mouthpiece and a respiratory valve. The breathing mixture was delivered from compressed gas cylinders and expanded in the bag. The bag was designed so that the gas passed through a water bath maintained at room temperature before it reached the mouthpiece, thus ensuring humidification of the gas mixture and hence minimising respiratory heat loss through evaporation.

Following the instrumentation procedure, resting values were recorded for five minutes while the subject assumed the supine position. During the N_2O trial, the anesthetic gas mixture was inhaled for a 7 minute period before resting values were monitored, thus ensuring that the recordings were obtained at a steady state level of anesthesia (Kety *et al.*, 1947, Salanitre *et al.*, 1962).

After resting values had been recorded, the subject stepped into the water bath and immersed himself to the neck. The immersion lasted for one hour, or until the subject's esophageal temperature had fallen by two degrees from the pre-immersion value.

During the immersion phase the subject wore a harness which, was suspended by ropes, in this way preventing the subject's face from falling into the water bath in the event of unconsciousness.

At the end of the immersion phase the subject was removed from the tank, placed supine in a sleeping bag, and allowed to rewarm passively (via endogenous heat production). The recovery from hypothermia was monitored for 48 minutes. Thereafter, the subject was disconnected from the recording equipment and transferred to a hot bath for complete re-instatement of body heat.

The experimental protocol used in the present study was approved by the Ethics Review Committee of Simon Fraser University.

3. Instrumentation

The immersion tank was constructed of plywood (196 x 80 x 76 cm.), encased in a steel frame and lined with a polyvinyl sheet. The tank contained 720 lit. of water which was continuously stirred throughout the immersion by a spa support system (Swimquip, Wicor Canada Ltd., Missassauga, Ont.) and maintained at 15 °C. Water temperature was recorded by a YSI 701 thermistor.

a) Heat flux (Q,W.m. $^{-2}$) and skin temperature (Tsk, °C)

Heat flux from the skin surface was measured with heat flux transducers (Thermonetics Corporation, San Diego, California). Thermistors embedded in the transducers' surface placed on the skin, allowed simultaneous measurement of skin temperature. Heat flux and skin temperatures were measured at four sites (arm, chest, thigh, calf). The transducers were attached to the skin wih waterproof tape (Elastoplast, Smith and Nephew, Inc., Lachine, Que.).

Skin temperatures of the forearm and the fingetip were measured by copper-constantan (T-type) thermocouples also positioned on the skin with waterproof tape.

b) Core temperature (Tc, °C)

Esophageal (Tes) and rectal (Tre) temperatures were assessed using a YSI 702 (Yellow Springs Instruments, Ohio, USA) and a YSI 701 thermistor probe, respectively.

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

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

d) Ventilation ($\dot{V}_I$, $L.min^{-1}$)

Flow rate of the inspired gas was measured using a Hewlett Packard 47304A flow transducer in conjunction with a Model 21073B pneumotachometer. Inspired volume ($\dot{V}_I$) was determined by integrating the inspired flow using a precision low-drift integrator. The subject breathed through a low-resistance two way valve. The expiratory side was connected by Collins corrugated tubing to a 9 liter fluted plexiglass mixing box.

e) Oxygen uptake ($\dot{V}O_2$, $L.min.^{-1}$) and carbon dioxide production ($\dot{V}CO_2$, $L.min^{-1}$)

$\dot{V}O_2$ and $\dot{V}CO_2$ were determined from the analyses of mixed expired gases and inspired minute ventilation. A continuous 500 $ml.min.^{-1}$ sample of mixed expired gas was drawn from the mixing box and analysed for oxygen and carbon dioxide contents using an Applied Electrochemistry Oxygen Analyser (S-3A) and a Statham Godart Capnograph, respectively.

f) Data acquisition

All the physiological variables were recorded at minute intervals. With the exception of heart rate, physiological variables were measured on line with an HP 3497A data aquisition system (Hewlett Packard) controlled by an HP 9817 computer (Hewlett Packard).

4. Statistical analyses

The response of all recorded variables were compared between the control and N_2O conditions with a one way analysis of variance (ANOVA) for a mixed model experimental design. In addition, a regression analysis was conducted over the linear portion of the Tre and Tes responses obtained during the immersion, for each subject separately. The cooling rates determined in this manner were compared between control and N_2O conditions for statistical significance using an one-way ANOVA as described earlier. The observed rewarming rates were compared in the same manner. The $\dot{V}O_2$ response to decreasing core temperature ($\dot{V}O_2$ / Tc, L.min.$^{-1}$.^{o}C^{-1}) was also compared between the control and N_2O condition by comparing both the slopes and intercepts of the linear regressions. A similar analysis was conducted for the $\dot{V}O_2$ / Tc relation during the rewarming period. The linear regressions obtained during the immersion were derived over the same Tc range for both control and N_2O conditions. However, during the rewarming phase, $\Delta\dot{T}c$ values were usually lower in the N_2O condition compared to the control, and hence there was no overlap of the ΔTc ranges between the two experimental conditions. Consequently, the slopes and intercepts of the VO_2 vs. Tc relations during the rewarming phase were determined over different ΔTc ranges in the two conditions.

For all analyses, the 5% level was chosen as the level of statistical significance.

RESULTS

All subjects reported a moderate euphoria during the N_2O exposure. The N_2O condition was perceived to be less stressfull, and in general subjects stated that the level of narcosis appeared to fluctuate; nevertheless, thermal comfort was always perceived higher in the N_2O condition.

Results are reported as mean $\pm$ SD for the subject group.

1. Resting phase

Resting values for all the physiological variables were determined by averaging the values recorded during the 5 minutes of the resting phase. Unweighted mean heat flux from the skin (Q_{mean}, $W.m.^{-2}$) during rest was higher ($p \leq 0.001$) in the N_2O than in the control condition. Resting forearm-fingertip temperature gradient values (Tsk-gr, °C) were lower under anesthesia than in the control ($p \leq 0.05$). All other recorded variables were similar in the two experimental conditions during the resting period.

2. Immersion phase

The transition period from supine rest to the cold water bath required less than one minute and hence no data were collected during this period.

In both conditions, unweighted mean skin temperature ($\bar{T}sk$, °C) dropped in a similar manner during the first 10 minutes of immersion, from initial values of 35.3 ± 0.9 °C (N_2O) and 35.2 ± 0.7 °C (control), to end-immersion values of 17.0 ± 0.4 °C and 17.1 ± 0.4 °C in the N_2O and control conditions, respectively (Fig. 1). There was no significant difference in the $\bar{T}sk$ between the two conditions.

In contrast, unweighted mean heat flux (Q_{mean}, W.m.$^{-2}$) showed a transient increase immediately after the onset of immersion from its preimmersion values of 26.6 $\pm$ 4.8 W.m.$^{-2}$ in the control and 35.8 $\pm$ 8.0 W.m.$^{-2}$ in the N_2O condition, to peak values of approximately 800 and 1000 W.m.$^{-2}$ respectively. Thereafter, Q_{mean} exhibited a non-linear decline in both conditions and was relatively stable within 25 minutes of immersion, attaining end-immersion values of 185.1 $\pm$ 58.5 W.m.$^{-2}$ and 205.7 $\pm$ 51.2 W.m.$^{-2}$, in the N_2O and control conditions, respectively (Fig. 2). The majority of the decline of heat flux occured within 10 minutes of immersion, and $\bar{T}sk$ was relatively stable within 10 minutes of immersion. Although Q_{mean} values tended to be higher in the control condition than in the N_2O condition the difference was not statistically significant.

The time course of Tsk-gr, (°C) followed a similar pattern in both experimental conditions by increasing immediately after the onset of immersion from -2.2 $\pm$ 0.6 °C and 1.1 $\pm$ 1.1 °C at the fifth minute of the resting phase to 8.2 $\pm$ 1.9 °C and 8.2 $\pm$ 2.8 °C at the end of the immersion phase, for the N_2O and the control conditions, respectively (Fig. 3). Almost 85% of the increase was completed within the first 20 minutes of immersion. Room temperature values were fluctuating within the range of 25-27 °C throughout each experimental protocol. Statistical analysis showed no significant difference in Tsk-gr values between the two conditions.

Since Tc values (Tes, Tre) during rest were almost identical in the two conditions, the changes in Tes and Tre from the last minute of the resting phase (ΔTes and ΔTre) were utilized for the study and analysis of the core temperature responses.

In both conditions, ΔTes showed a transient increase upon immersion with peak values of 0.2 $\pm$ 0.1 °C and 0.1 $\pm$ 0.2 °C attained by minute 10 of immersion in the N_2O and control conditions, respectively. This was followed by a continuous ΔTes decrease throughout the remaining cold-water exposure period. ΔTes dropped faster ($p < 0.05$) under anesthesia, thus attaining a lower end-immersion value of -1.2 $\pm$ 0.7 °C than the respective value of -0.95$\pm$ 0.5 °C observed in the control condition.

Similarly, rectal temperature decreased during the cold water immersion for all the subjects in both experimental conditions, being similar in the control (-1.8 ± 0.9 °C) than in the N_2O (-1.6 ± 0.5 °C) conditions (Fig. 5) at the end of the immersion . Nevertheless, the cooling rate of Tre was almost identical in both trials, since comparison of the slopes of ΔTre with respect to time revealed no significant difference for the control and N_2O conditions.

$\dot{V}O_2$ increased as a result of cold water immersion in both conditions (Fig. 6). During the first 2 minutes of immersion, $\dot{V}O_2$ was substantially elevated, from resting values of 0.34 ± 0.08 and 0.34 ± 0.06 L.min.$^{-1}$ to 0.91 ± 0.44 and 0.77 ± 0.32 L.min.$^{-1}$ in N_2O and control conditions, respectively. The $\dot{V}O_2$ remained elevated to the same extent for the next 4 minutes in the control condition, and then linearly declined within the next 5 minutes, before commencing to rising again to attain an end-immersion value of 1.22 ± 0.33 L.min.$^{-1}$. In contrast, $\dot{V}O_2$ under anesthesia dropped after a 2 minute period, attaining values which nevertheless were twice as high as the resting ones. In general, mean $\dot{V}O_2$ followed similar patterns in both conditions with the values observed in the control condition consistantly higher ($p \leq 0.01$) than the ones recorded under anesthesia.

The $\dot{V}O_2$ response with respect to ΔTes and ΔTre, can be seen in Fig. 7. The intercepts which were obtained from the linear regression analyses, were higher in the control than in the N_2O condition for the VO_2 vs ΔTes relation ($p \leq 0.01$) and for the VO_2 vs ΔTre relation ($p \leq 0.01$). The slopes were however similar in both experimental trials. The results indicate that N_2O exposure attenuated the $\dot{V}O_2$ response for a given core temperature.

The core temperature of one of the subjects did not drop substantially during the cold water immersion in either of the two conditions. This was probably due to the insulation offered by the subcutaneous fat tissue, which was observed to be higher in this subject in comparison to the rest of the subjects. Therefore, sufficient data points were not

available for the regression of the $\dot{V}O_2$ against Tc. This subject was excluded from the above analysis.

In both conditions the cold exposure induced an increase in $\dot{V}_I$ (Fig. 8); the $\dot{V}_I$ response followed a similar pattern as the $\dot{V}O_2$ response (Fig. 6). $\dot{V}_I$ values were lower ($p \leq 0.01$) under anesthesia than in the control condition, throughout the cooling phase.

HR increased abruptly upon cold water exposure, and attained peak values of 85 $\pm$ 19 and 91 $\pm$ 22 min.$^{-1}$ within the first 2-3 minutes of the N_2O and control immersion, respectively (Fig. 9). This initial increase of HR was followed by a decline which lasted 10-15 minutes. Thereafter HR started increasing, reaching end-immersion values of 73 $\pm$ 15 min.$^{-1}$ in the N_2O condition vs. 83 $\pm$ 15 min.$^{-1}$ in the control condition. As can be seen in Fig. 9, the patterns of HR responses in the two conditions were almost parallel throughout the cooling phase. However, the values recorded under anesthesia were always lower than the ones recorded in the control condition ($p \leq 0.01$).

3. Rewarming phase

The transition from the cold water bath into the insulated bed required 2-3 minutes, therefore the data for the rewarming phase has been adjusted so that time zero corresponds to the onset of the passive rewarming phase.

The physiological responses generated by the cold water immersion were reversed during the rewarming phase in both experimental conditions. Thus, there was a tendency in all the recorded variables to attain preimmersion levels. However, most of the recorded variables did not reach a steady state level during the 48 minute period of rewarming.

$\bar{T}sk$ values increased throughout the 48 minutes of rewarming, although, approximately 80-90% of the increase was completed within the first 30 minutes. However, $\bar{T}sk$ never reached its preimmersion values of 35.3 $\pm$ 0.9 °C for the N_2O and of 35.2 $\pm$ 0.7 °C for the control condition. At the end of the rewarming phase, $\bar{T}sk$ was 30.8

$\pm$ 0.8 °C and 31.2 $\pm$ 1.2 °C for the N_2O and control conditions, respectively. As can be seen in Fig. 10, $\bar{T}sk$ values followed similar patterns in both conditions although they were higher ($p \leq 0.05$) during normal air breathing throughout the rewarming phase.

Tsk-gr, decreased in both conditions (Fig. 11) and reached end-rewarming values of 5.0 $\pm$ 3.0 °C and 6.7 $\pm$ 2.1 °C for the N_2O and control conditions, respectively, which were substantially higher than the resting values (Fig. 3). As during the cooling phase, the Tsk-gr values observed during rewarming were at any given time similar in the two conditions.

As is shown in Fig. 12, the average ΔTes values followed a linear increase in both conditions, from -1.9 $\pm$ 0.5 and -1.4 $\pm$ 0. °C at the begining of the rewarming phase to -1.0 $\pm$ 0.5 and -0.5 $\pm$ 0.3 °C at the end of the experiment, for the N_2O and control conditions, respectively. Comparison of ΔTes values recorded during the two trials indicates that Tes was higher ($p \leq 0.01$) during air breathing than under anesthesia . However, the rate of recovery was similar in both experimental trials as determined by comparison of the slopes of ΔTes with respect to time.

The time course of mean ΔTre did not follow the same pattern in both conditions during the rewarming phase. As can be seen from Fig. 13, in the N_2O condition ΔTre decreased during the first 20-25 minutes of rewarming from -1.9 $\pm$ 0.5 to -2.3 $\pm$ 0.6 °C . After being stable for a 10-15 minute period, ΔTre increased and reached -2.1 $\pm$ 0.6 °C at the end of the rewarming phase. In contrast, during the control condition, ΔTre started increasing after the 20th minute of recovery period, exhibiting a sigmoid increase, and reached end-rewarming value of -1.8 $\pm$ 0.2 °C. Comparison of the average values of ΔTre recorded during the control and N_2O condition showed that there was no significant difference between the two trials. However, the difference in the rate of rewarming of Tre between the N_2O and control condition was not examined, because the data points of the ΔTre with respect to time could not be fitted by a linear equation in neither of the two condition.

There was no difference in the Q_{mean} values observed in the two experimental trials during rewarming. As can be seen from Fig. 14, Q_{mean} rapidly decreased to pre-immersion values and remained at the same level throughout the rewarming phase.

Mean $\dot{V}O_2$, decreased linearly during rewarming in both experimental conditions, from 1.1 $\pm$ 0.3 and 1.3 $\pm$ 0.2 °C at the onset of recovery to 0.3 $\pm$ 0.1 and 0.4 $\pm$ 0.1 °C at the last minute of recovery for the N_2O and control conditions, respectively (Fig. 15). Statistical analysis indicated that there was no difference in the $\dot{V}O_2$ values between the two conditions.

Similar to the $\dot{V}O_2$ response, minute ventilation decreased over the 48 minutes of recovery, attaining values close to the pre-immersion ones at the end of the recovery period. (Fig 16). Thus, $\dot{V}_I$ dropped from 27.7 $\pm$ 7.9 and 28.8 $\pm$ 6.1 L.min.$^{-1}$ at the onset of the rewarming phase to 10.0 $\pm$ 1.9 and 10.5 $\pm$ 2.5 L.min.$^{-1}$ at the 48th minute of rewarming, for the N_2O and control conditions, respectively. $\dot{V}_I$ did not differ between the two experimental trials.

HR decreased from 66 $\pm$ 11 and 69 $\pm$ 16 min.$^{-1}$ at the onset of the rewarming phase to 59 $\pm$ 12 and 56 $\pm$ 15 min.$^{-1}$ by the end of the rewaming for the N_2O and control conditions, respectively (Fig. 17). Although HR values during the rewarming phase appeared to be lower under anesthesia, the difference between the two conditions was not statistically significant. As shown in Fig. 15, HR in both trials, and especially after 15-20 minutes of recovery, attained values lower than the pre-immersion ones.

The $\dot{V}O_2$ response with respect to ΔTes, for both experimental conditions, is plotted in Fig. 18. Comparison of the slopes of the above relation, showed that for a given Tc the $\dot{V}O_2$ response was higher ($p \leq 0.05$) in the control condition than under anesthesia.

DISCUSSION

The results of the present study indicate that the cooling rate of esophageal temperature in response to cold water immersion was greater when subjects were breathing the gas mixture containing 30% N_2O than when they were breathing normal air. An increased cooling rate of Tes may be due to either an increased heat loss and/or to a decreased heat production. Thus, in the following sections the effects of N_2O on heat conservation and heat production mechanisms will be discussed.

1. Heat conservation

Heat dissipation by convection / conduction from the skin is governed mainly by the magnitude of perfusion of the cutaneous vasculature. Thus, the effects of cold and/or N_2O exposure on heat dissipation should be viewed in the context of the mechanisms underlying changes in skin blood flow. The control of cutaneous vasomotor tone has been aptly reviewed by Rowell (1986). Briefly, in nonacral skin regions (i.e. limbs and body trunk) vasomotor tone is controlled by both sympathetic vasoconstrictor and sympathetic vasodilator innervation. At neutral body temperatures, there is a slight tonic vasoconstrictor activity in these cutaneous arterioles. Such vasoconstrictor tone is withdrawn even by modest increases in body temperature (passive vasodilation); the vasodilator innervation accounts for any further vasodilation (active vasodilation). In acral regions of the body (i.e. fingers, toes, nose and ears), skin vessels form a network of arterio-venous anastomoses which mainly serve a thermoregulatory purpose and whose tone are controlled solely by sympathetic vasoconstrictor innervation.

a) Resting phase

The increased resting heat flux observed under anesthesia in the present study, was possibly due to a N_2O-induced withdrawal of the vasoconstrictor tone of skin blood vessels in nonacral regions of the body, thus enhancing skin blood flow and consequently heat dissipation. Results from other studies (Holdcroft and Hall, 1978; Saumet *et al.*, 1988) proposing that skin blood flow in nonacral regions of the body is increased during anesthesia, supports the present findings.

Corroborative evidence that N_2O exerted a vasodilatory effect on cutaneous blood vessels at rest, was the tendency for Tsk-gr to attain higher values in this condition. According to Sessler *et al.* (1988), the forearm-fingertip temperature gradient reflects the vasomotor activity of the skin blood vessels in the hand. Such a vasodilatory effect of anesthetics on cutaneous vessels of the feet and hands has also been demonstrated for N_2O (Pauka and Hopkins, 1971; Foregger, 1942) and other anesthetic agents (Thomson, 1967; Saumet *et al.*, 1986).

The method used in the present study to determine the vasomotor activity on the blood vessels of the hand does not offer a quantitative estimate of skin blood flow, but it seems capable of qualitatively indicating vasomotor activity. The method has been evaluated and correlates well with other methods used for indirect measurement of skin blood flow, such as the laser Doppler technique (Sessler *et al.* 1987b), and the method by which changes in regional skin blood flow are estimated from changes in venous PO_2 (Sessler *et al.*, 1988). It seems then that the dose of N_2O administered in the present study (30%) although less than the dose (50%) induced by Pauca and Hopkins (1971), exhibited a qualitatively similar vasodilatory pattern in the skin blood vessels of the upper limb.

It appears that the present N_2O exposure induced vasodilation not only in nonacral regions but also in acral regions, where vasomotor tone is controlled solely by vasoconstrictor fibers. Therefore, and because inhalation anesthetics have no significant effect on conduction in peripheral nerves (Jong and Nace, 1967), the vasodilatory effect of

N_2O may be ascribed to a withdrawal of sympathetic vasoconstrictor activity. This is in agreement with the notion of Pauca and Hopkins (1971) and Thomson (1967), that vasodilation observed during anesthesia is probably mediated by a central inhibition of sympathetic tone. It is also suggestive that part of this inhibitory effect of the anesthetic acts at the thermoregulatory centres, since the vasomotor tone in the arterio-venous anastomoses of the hand, which predominantly serve a thermoregulatory purpose, seemed to be attenuated in the N_2O condition.

b) Immersion phase

The immersion period may be partitioned into two phases: the initial phase characterised by a rapid decrease in Tsk with no apparent displacement in Tc, and a final phase during which Tsk was at steady state, and Tc commenced to decrease. In the former, thermal afferent activity from the skin cold sensors would dominate, whereas, in the latter the increasing activity of core cold sensors would augment the thermal afferent information.

In both conditions cold water immersion induced severe vasoconstriction in the hand blood vessels, as judged from the increases in the Tsk-gr values. It seems that the vasodilatory effect of the anesthetic abated during the immersion phase, since there was no difference in Q_{mean} and Tsk-gr values between the two trials. In all probability, the attenuative effect of N_2O on the thermoregulatory vasomotor tone of cutaneous blood vessels was overriden by intense vasoconstriction brought about by increased activity of the cutaneous cold receptors consequent to the immersion in 15 °C water. Also, during the latter part of the immersion it is likely that the drop in core temperature contributed as a stimulus to the vasoconstrictor activity of the hand's cutaneous blood vessels.

The above findings suggest that thermoregulatory vasomotor activity seemed to operate as efficiently during N_2O exposure as during normal air breathing but only after either a peripheral or a combination of peripheral and central cold stimuli had been imposed on the anesthetised subjects. These results are in agreement with the findings by Sessler *et*

al. (1987a) and Sessler *et al.* (1988), which showed that significant vasoconstrictor activity existed during general isoflurane and halothane anesthesia, respectively, but only after the core temperature of the patients had dropped by 2.5 °C below normal.

c) Rewarming phase

During rewarming Q_{mean} and Tsk-gr were unaffected by N_2O exposure suggesting that also during this phase the vasoconstrictive stimuli from the lowered core and skin temperatures were large enough to override any N_2O-induced vasodilation.

In conclusion, with regards to the heat conservation mechanisms, the responses were similar in the two conditions both during the cooling and the rewarming phase. Thus, the observed N_2O induced increase in core temperature cooling rate cannot be explained in terms of exaggerated heat loss.

2. Heat production

The heat production response to cold water immersion has been demonstrated to consist of two distinct phases (Cooper *et al.*, 1976; Hayward *et al.* ,1977; Mekjavic and Bligh, 1989). During the initial minutes of immersion $\dot{V}O_2$ increases transiently peaking at values several-fold that of resting, and finally decaying to near resting levels. This transient elevation in oxygen uptake has been attributed to a combination of hydrostatic pressure inducing a redistribution of blood to the thoracic compartment and hence elevating oxygen uptake, as well as to an increase in metabolic rate resulting from skin cold sensor stimulation (Mekjavic and Bligh, 1989). Following this transient response in oxygen uptake, $\dot{V}O_2$ increases steadily with decreasing Tc.

a) Resting phase

Oxygen uptake during the resting phase was similar in both conditions suggesting that N_2O did not affect basal metabolism.

b) Immersion phase

The pattern of the $\dot{V}O_2$ response observed during cold water immersion was similar to that reported by others (Cooper *et al.*, 1976; Hayward *et al.*, 1977; Mekjavic and Bligh, 1989). In general, the elevated $\dot{V}O_2$ paralleled the observed shivering activity in both conditions. However, the magnitude of $\dot{V}O_2$ and intensity of the visually observed shivering were dramatically decreased by N_2O exposure. The results are in agreement with clinical observations of augmentations of post-anesthetic shivering and $\dot{V}O_2$ (Roe *et al.*, 1966; Stjernstrom *et al.*, 1985). Moreover, a similar observation of reduced $\dot{V}O_2$ at a given range of Tc during cooling has been reported by Mekjavic and Sundberg (1990).

The present finding that mild N_2O anesthesia reduced oxygen uptake by 45% compared to control values, over the time course during which Tc dropped by 0.7°C, agrees well with the study by Mekjavic and Sundberg (1990) in which it was noted that a similar drop in Tc induced a 42% attenuation of $\dot{V}O_2$. However, in the present study skin temperature was substantially lower and the rate of core cooling was substantially greater than in the study by Mekjavic and Sundberg. Thus, the present study indicates that the attenuative effect of N_2O is preserved in the face of more intense peripheral and core cold stimuli.

The question arises then of possible mechanisms underlying the N_2O induced attenuation of oxygen uptake. The findings that resting $\dot{V}O_2$ was unaffected by N_2O seems to exclude the possibility that the anesthetic inhibited oxygen utilisation at the cellular level as suggested by Hoech *et al.* (1966). Moreover, regardless of the effect of anesthetics on the activation of non-shivering thermogenesis, the contribution by this mechanism would be of little significance in the observed overall oxygen uptake (c.f. Jessen *et al.*, 1980).

Thus, it appears that the reduced shivering thermogenesis is the only reasonable explanation for the attenuated $\dot{V}O_2$ during N_2O exposure. The high correlation between post-operative shivering and oxygen demand which has been found in several clinical studies (Jones and McLaren, 1965; Roe *et al.*, 1966; Vaughan *et al.*, 1981; Guffin *et al.*, 1987), supports the notion that the decreased heat production observed during N_2O exposure was mainly due to the attenuation of shivering thermogenesis.

Reduction of shivering thermogenesis during cold exposure succeeding the induction of anesthetic agents may occur in many ways: (i) by decreasing the sensitivity of peripheral thermal receptors and/or by blocking the axonal conduction in peripheral nerves of thermal information to the central nervous system (CNS), (ii) by altering the central processing and integration of the thermal information, (iii) by diminishing the neural input to the skeletal muscles contributing to shivering, and/or by impairing the excitation-contraction coupling at these muscles.

With regards to possibilities (i) and (ii) above, it has been suggested, that inhalation anesthetics (halothane, N_2O), in concentrations commonly used in clinical practice, affect neither generation of impulses in cutaneous receptors, nor conduction in the peripheral nerves and long-fiber tracts of the CNS (Jong and Nace, 1967; Somjen, 1967; Jong *et al.*, 1969).

Nevertheless, the possibility of a central effect of N_2O remains. Sensory nerve impulses reach the cortex either by direct quick pathways (medial lemniscus, anterolateral system) or by a more central polysynaptic root via the reticular formation. Davis *et al.* (1957) have shown that by stimulating the radial nerve of adult anesthetised cats, the evoked responses which came through the polysynaptic reticular system were depressed to a greater degree by anesthetics than the ones transmitted through the medial lemniscus pathway. These findings demonstrate the significant effect of anesthesia in synaptic transmission (Halsey, 1974) and supports the notion that the effector responses during hypothermia may be attenuated due to an effect of N_2O on central processing specifically

on synaptic transmission. Though it has not been shown conclusively that anesthetics may significantly affect the integration and processing of thermal information, Boulant and Dean (1986) have pointed out that the percentages of thermosensitive PO/AH neurons which respond to cold stimuli are consistently lower in studies using anesthetized animals in comparison to the ones using unanesthetized animals. The authors suggested that this difference is probably due to an anesthetic suppression of synaptic activity impinging upon the cold sensitive neurons.

The likelihood of depressed muscle function being responsible for the attenuated oxygen uptake also needs to be examined. However data, which would reveal whether the properties of the contractile element in skeletal muscle is affected by anesthesia, are not available. Thesleff (1956) showed on an isolated sartorius muscle preparation of the frog, that pentobarbital sodium anesthesia increased the electric threshold of the muscle membrane and reduced or abolished the action potential. The increased threshold caused by the anesthetic agent was ascribed to a reduction of the sodium current in the active muscle membrane, probably a consequence of a reduction of the available sodium carrying mechanisms. Thesleff also reported that anesthetics reduced the sensitivity of the end-plate to applied acetylcholine. Although the results of Thesleff (1956) suggest that there is an anesthetic depressant effect on the excitability of the active skeletal muscle membrane in the *in vitro* situation, the relevance of such mechanisms on human muscle function remains unclear.

In a recent study by Eiken *et al.* (1987), it was shown that maximal contractile force of the quadriceps muscle in humans was reduced during air breathing at 6 ATA in comparison to air breathing at 1 ATA. The authors suggested that most likely high N_2 and/or hydrostatic pressure reduced the neural input to the working muscle, although they commented that an impairment of neuromuscular activation might also have accounted for the decreased muscle force production at 6 ATA.

Thus, the possibility that N_2O, to a degree, depressed neuromuscular function in the present study, cannot be excluded.

c)Rewarming phase

During rewarming, N_2O seemed to have a similar attenuative effect on heat production as during the cooling phase, since at a given range of Tes oxygen uptake was lower in the N_2O than in the control condition.

In conclusion, N_2O narcosis as compared to normal air breathing decreased heat production during cold exposure, for a given range of Tc values. These results suggest that the diminished heat production observed during anesthesia may be largely responsible for the greater cooling rate of Tes found in this experimental condition.

3. Rectal temperature

Rectal temperature showed similar responses in the two conditions, but the responses were delayed in the N_2O condition, especially during the rewarming phase.

Eger *et al.* (1965), have shown that enclosed gas-filled spaces contained in the intestine of the dog expanded by 75 to 100% within 2 hours, when 70-80% N_2O was breathed by the animals. This is due to the difference in blood solubility between the gases contained within the gas-filled spaces and the gases inspired (i.e. counter diffusion). Thus, when the breathing mixture is changed from air to one containing a high percentage of N_2O, more N_2O will diffuse into the intestinal space due to a high pN_2O gradient. During this transient period the pN_2 of the intestinal gas will be greater than that of the blood. Furthemore, since the solubility of N_2O in blood is 30-fold greater than that of N_2, which is usually contained in these spaces, the diffusion of N_2O into the intestinal space will be greater than the diffusion of N_2 into the blood (Saidman and Eger, 1965).

Thus, the temperature measurements in the rectum might have been affected by either: (i) changes of the thermistor's position, (ii) variations in the hemodynamics of the rectum, or (iii) changes in the thermal inertia of the inside of the rectum caused by volume variations. Possibilities (ii) and (iii), may explain the delayed Tre response in the N_2O condition, during both cooling and rewarming, in comparison to the Tre response in the control condition. The Tre response was however less delayed during cooling compared to the rewarming phase. It is likely that the effect of the hydrostatic pressure exerted by the water during the immersion on the abdominal counteracted any rectum volume increases. In addition, the one hour duration of the cooling phase may not have been sifficient to allow rectum expansion to sizes similar to the ones occured during rewarming.

It seems that Tre values recorded during the N_2O condition reflect roughly the thermal state of the lower abdominal cavity, but probably cannot be used for fine comparisons with the Tre values obtained during the control condition.

4. Heart rate

The HR response to cold water immersion was attenuated by N_2O. It appears that this attenuation of HR largely reflected the N_2O depression of muscular activity (shivering tremor), since HR was unaffected by N_2O during the rewarming phase; judging from the oxygen uptake response, muscular activity was similar in both conditions during rewarming. However, it should be noted that Bristow *et al.* (1969) have shown that anesthesia in humans induced by 70% N_2O reset the baroreceptor reflex, which resulted in bradycardia. In addition, Biscoe and Millar (1964) observed an increased impulse discharge from single baroreceptor units in the carotid sinus nerve in cats, dogs, rabbits and goats under halothane anesthesia for a wide range of carotid transmural pressures. These authors suggested that this sensitising effect of the anesthetic on baroreceptor discharge may be the reason for bradycardia observed under halothane anesthesia.

Thus, decreased muscular activity alone, or in combination with increased baroreceptor discharge may explain the present N_2O induced attenuation of the HR during cold water immersion.

5. Practical considerations

That N_2O in relatively low concentrations impairs shivering thermogenesis and hence diminishes an individuals ability to maintain body core temperature should be considered in clinical practice, especially when N_2O narcosis is induced over extended time periods such as in conjunction with parturition.

Furthermore, the level of narcosis induced in this investigation is comparable to the compressed air narcosis that divers are subjected to. Thus, assuming that N_2O and high N_2 pressures exert similar narcotic effects the present findings may in part explain why divers commonly experience hypothermia.

6. Theoretical considerations

The central neural integration of body temperature is often described as a single integrator model with multiple inputs and outputs. Satinoff (1978), however, has argued that through the process of evolution, some thermoregulatory functions have been delegated to lower levels of the CNS. Thus, a single integrator is an inadequate analogy. She suggests that a more appropriate representation would incorporate integrators working in parallel at different levels of the CNS, and arranged in a hierarchical manner. Thus, according to Satinoff, the hypothalamus is not the only integrating or processing thermal structure but it coordinates the activity of others. Such an arrangement of the thermoregulatory system, as postulated by Satinoff, also proposes that in the event that

higher centers are not functioning properly, regulation of body temperature would become the responsibility of the integrators at lower levels of the CNS (i.e. spinal cord).

The present findings, as well as those from other studies investigating the effects of anesthesia, support the modelling concept of Satinoff. Namely, fine control of body temperature is achieved by areas of the CNS which are represented at higher levels of the thermoregulatory hierarchy, and experimental evidence (Davis *et al.*, 1957) supports that these are the areas most affected by anesthetics, due to their polysynaptic pathways. In such situations, Satinoff's concept would lead to the conclusion that body temperature regulation is transferred to lower levels of the CNS, which are less affected by the anesthetic due to their simple neural connections. However, as a result of their simpler neural arrangement, finer adjustments to the regulation of body temperature are not possible. Thus, during anesthesia, thermoregulation would not necessarily be abolished but be rather coarse, resembling more the temperature regulation observed in animals once the hypothalamus is removed. Such animals exhibit a much wider null-zone or increased Tc threshold for panting and decreased Tc threshold for shivering. Similar observations of increased and decreased Tc's for sweating and shivering, respectively, have been made in humans subjected to mild N_2O anesthesia (Mekjavic and Sundberg, 1990). Furthermore, the findings of the present study seems to suggest that Tc for shivering was reduced in the N_2O condition compared to the control one (see fig. 7, 18). Similarly, Sessler *et al.* (1988), observed that with increasing dosage of halothane, the Tc at which vasoconstriction occurred was reduced. These results would also suggest that with increasing anesthetic dosage, thermoregulatory integrators at lower levels of the hierarchical order will progressively be affected. This would lead to a decrease in Tc threshold for vasoconstriction, and thus a declining quality of body temperature regulation. Within the context of the Satinoff's model the decrease in heat production observed during mild N_2O anesthesia could be considered as a reduction in the role of higher centres in the CNS, in their effector response, and in their delegation of responsibility to lower centres. It could

further be speculated that the observation of no difference in vasomotor activity between control and N_2O conditions, may suggest that in contrast to heat production, heat conservation is regulated to a significant degree at lower levels of the thermoregulatory hierarchy. Thus, the dosage of anesthetic used affected the higher levels and thus heat production, but the dose was not significantly large to affect lower levels and thus did not have an observable effect on vasomotor activity.

REFERENCES

Abramson I., Grollman A., Schwartz A. Influence of cyclopropane upon peripheral blood flow in man. Anesthesiology. 2: 186-190, 1941.

Barbour G. Die Wirkung unmittelbaren Erwarmung und Abkuhlung der Warmezentra auf die Korpertemperatur. Arch. Exptl. Pathol. Pharmakol. 70: 1-26, 1912.

Bartels E. Basal metabolism testing under pentothal anesthesia. J. Clin. Endocrin. 9:1190, 1949.

Behnke R.and Yarbrouth D. Respiratory resistance, oil-water solubility and mental effects of argon compared with helium and nitrogen. Am. J. Physiol. 126: 409-415, 1939.

Bell C. Vasodilator neurons supplying skin and skeletal muscle of the limbs. J. Auton. Nerv. Syst. 7: 257-62, 1983.

Bennett P., Papahadjopoulos D., Bangham A. The effect of raised pressures of inert gases on phospholipid model membranes. Life Sci. 6: 2527-2533, 1967.

Bennett P. Inert gas narcosis. In: The Physiology and Medicine of Diving. Eds.: Bennett P. and Elliott D., California: Best Publishing, 1982.

Bennett P. Physiological limitations of human performance in hyperbaric environments. In: Environmental Ergonomics. Eds.: Mekjavic I., Banister E., Morrison J., Philadelphia: Taylor and Francis, 1988.

Benzinger T. Heat regulation: Homeostasis of central temperature in man. Physiol. Rev. 49: 671-759, 1969.

Bligh J. The receptors concerned in the thermal stimulus to panting in sheep. J. Physiol. (London) 146: 142-151, 1959.

Bligh J. Temperature Regulation in Mammals and other Vertebrates, Amsterdam: North-Holland Publishing Co., 1973.

Bligh J. Regulation of body temperature in man and other mammals. In: Heat Transfer in Medicine and Biology. Eds.: Shitzer A. and Eberhart R., Plenum Publishing Corporation, 1984.

Bligh J. Human cold exposure and the circumstances of hypothermia. In: Environmental Ergonomics. Eds.: Mekjavic I., Banister E., Morrison J. Philadelphia: Taylor and Francis, 1988.

Boulant J. Hypothalamic mechanisms in thermoregulation. Fed. Proc., 40: 2843-2850, 1981.

Boulant J. and Dean J. Temperature receptors in the central nervous system. Ann. Rev. Physiol. 48: 639-54, 1986.

Boutelier C., Colin J., Timbal J. Determination du coéfficient d' echange thermique dans l' eau en 'écoulement turbulent, J. Physiol. (Paris) 63: 207-209. 1971.

Biscoe T.and Millar R. The effects of halothane on carotid sinus baroreceptos activity. J. Physiol. (Lond.) 173: 24-37, 1964.

Bristow D., Prys-Roberts C., Fisher A., Pickering T., Sleigh P. Effects of anesthesia on baroreflex control of heart rate in man. Anesthesiology 31: 422-428, 1969.

Carpenter F. Anaesthetic action of inert and unreactive gases on intact animals and isolated tissue. Am. J. Physiol. 178: 505-509, 1954.

Cooper K.E., Martin S., Riben P. Respiratory and other responses in subjects immersed in cold water. J. Appl. Physiol. 40: 903-910, 1976.

Davis H., Collins W., Randt C., Dillon W. Effects of anesthetic agents on evoked central nervous system responses: gaseous agents. Anesthesiology 18: 634-642, 1957.

Eger E., Saidman L. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26: 61-66, 1965.

Eiken O., Hesser C., Lind F., Thorsson A., Tesch P. Human skeletal muscle function and metabolism during intense exercise at high O_2 and N_2 pressures. J. Appl. Physiol. 63: 571-575, 1987.

Featherstone R. and Muehlbaecher C. The current role of inert gases in the search for anaesthesia mechanisms. Pharmacol. Review 15, 97-121, 1963.

Foregger R. Surface temperature during anesthesia. Anesthesiology 4: 392-402, 1942.

Flacke W. Temperature regulation and anesthesia. Int. Anesthesiol. Clin. 2: 43-54, 1963.

Flynn T., Vorosmarti J.,Modell H. Temperature requirements for the maintenance of thermal balance in high pressure helium oxygen environments. NTIS, U.S. Department of commerce, Springfield, 1974.

Goldberg M. and Roe F. Temperature changes during anesthesia and operations. Arch. Surg. 93: 365-369, 1966.

Goodman M., Smith N., Colston J., Rich E. Hyperbaric respiratory heat loss study. Final report, Contract no. N00014-71-C-0099, ONR, Washington D.C. 1971.

Guffin A., Girrard D., Kaplan J. Shivering following cardiac surgery: Hemodynamic changes and reversal. J. Cardiothoracic Anesthesia. 1: 24-28, 1987.

Hall G. Body temperature and anaesthesia. Br. J. Anaesth. 50: 39-44, 1978.

Hammel H. Anesthetics and body temperature regulation, Anesthesiology 68: 833-835, 1988.

Halsey M. Mechanisms of general anesthesia. In: Anesthetic uptake and action. Ed.: Eger E., Baltimore: Williams and Wilkins, 1974.

Halsey M., Wardley-Smith B., Green C. Pressure reversal of general anaesthesia a multi-site expansion hypothesis. Br. J. Anaesth. 50, 1091-1097, 1978.

Hayward J., Eckherson J., Collis M. Thermoregulatory heat production in man: prediction equation based on skin and core temperatures. J. Appl. Physiol. 42: 337-384, 1977.

Hayward M. and Keatinge W. Progressive symptomless hypothermia in water: possible cause of diving accidents. Brit. Med. J. 1: 1182, 1979.

Hensel H., Schafer K. Effects of calcium on warm and cold receptors. Pflügers Arch. 352: 87-90, 1974.

Hensel H. Thermoreception and temperature regulation. Monogr. Physiol. Soc. Academic Press, 1981.

Hirata H., Poulos D., Molt J. Differences in thermal responses of cat trigeminal ganglion cold receptors under urethane and pentobarbital anesthatization. Brain Res. 292: 387-89, 1984.

Hoech G., Matteo R., Fink R. Effects of halothane on oxygen consumption of rat brain, liver and heart anaerobic glycolysis of rat brain. Anesthesiology. 27: 770-777, 1966.

Holdcroft A. and Hall G. Heat loss during anaesthesia. Br. J. Anaesth. 50: 157-163, 1978.

Holdcroft A., Hall G., and Cooper G. Redistribution of body heat during anesthesia (A comparison of halothane, fenatnyl and epidural anesthesia). Anaesthesia. 34: 758-764, 1979.

Jahns R. Types of neuronal responses in the rat thalamus to peripheral temperature changes. Exp. Brain Res. 23: 157-66, 1975.

Jessen C., Feistkorn G., Nagel A. Temperature sensitivity of skeletal muscle in the conscious cat. J. Appl. Physiol. 54(4), 880-886, 1983.

Jessen K., Rabol A., Winkler K. Total body and splachnic thermogenesis in curarized man during a short exposure to cold. Acta Anaesth. Scand. 24: 239-344, 1980.

Johnson R., Smith A., Spalding J. Oxygen consumption of paralysed men exposed to cold. J. Physiol. (London). 169: 584-591, 1963.

Jones H. and McLaren C. Postoperative shivering and hypoxaemia after halothane, nitrous oxide and oxygen anaesthesia. Brit. J. Anaest. 37: 35-41, 1965.

Jong de R. and Nace R. Nerve impulse conduction and cutaneous receptor responses during general anesthesia. Anesthesiology. 28: 851-855, 1967.

Jong de R., Robles R., Morikawa K. Actions of halothane and nitrous oxide on dorsal horn neurons ("the spinal gate"). Anesthesiology. 31: 205-212, 1969.

Joy R., Responses of cold-acclimatized men to infused norepinephrine. J. Appl. Physiol. 18: 1209-1212, 1963.

Kety S., Harmel M., Broomel H., Rhode C. The solubility of nitrous oxide in blood and brain. J. Biol. Chem. 173: 487-496, 1947.

Kuehn L. Thermal effects of the hyperbaric environment (invited review). Proc. 8th Symp. Underwater Physiol. Eds.: Bachrach J., Matzen M. Bethesda, Maryland: Undersea Medical Society, Inc., 1984.

Mekjavic I., Mittleman K., Burke W. Incorporating inividual variability in the prediction of shivering thermogenesis. In: Proc. 10th Symp. Man-Thermal Environ. Sys. Tokyo, 1986.

Mekjavic I., Bligh J. Core threshold temperatures for sweating and shivering. Can. J. Physiol. Pharm. 67: 1038-1044, 1989.

Mekjavic I. and Rempel M. The determination of esophageal probe insertion length based on sitting and standing height. J. Appl. Physiol. 69: 376-379, 1990.

Mekjavic I. and Sundberg C. Human temperature regulation during mild narcosis induced by inhalation of nitrous oxide (N_2O). J. Appl. Physiol. (submitted).

Miller k., Paton W., Smith R., Smith E. The pressure reversal of general anaesthesia and the critical volume hypothesis. Molec. Pharm. 9: 131-143, 1973.

Mittleman K. Central thermosensitivity of metabolic heat production during cold water immersion. Ph. D. thesis, School of Kinesiology, Simon Fraser University, Burnady, B.C. Canada, 1987.

Nadel E., Horvath S., Dawson C., Tucker A. Sensitivity to central and peripheral thermal stimulation in man. J. Appl. Physiol. 29: 603-609, 1970.

Nunneley S., Troutman S., Webb P. Heat cooling in work and heat stress. Aerospace Med. 42: 64-68, 1971.

Padbury E., Ronnestad I., Hope A., Knudsen G., Myrseth E., Varnes R. Undetected hypothermia: further indications. Proc. 9th Inter. Symp. Underw. and Hyperb. Physiol. Eds.: Bove A., Bachrach J., Greenbaum J. Bethesda, Maryland: Undersea Medical Society, Inc., 1987.

Pauca A. Hopkins A. Acute effects of halothane, nitrous oxide and thiopentone on the upper limb blood flow. Brit. J. Anaesth. 43: 326-333, 1971.

Piantadosi C., Thalmann E., Spaur W. Metabolic response to respiratory heat loss-indused core cooling. J. Appl. Physiol. 50: 829-834, 1981.

Rapp G. Convection coefficients of man in a forensic area of thermal physiology. Heat transfer in underwater exercise. J. Physiol. (Paris). 63: 392-396, 1971.

Raymond L., Bell W., Bondi D., Lindberg C. Body temperature and metabolism in hyperbaric helium atmospheres. J. Appl. Physiol. 24: 687-684, 1968.

Roe F., Goldberg M., Blair C., Kinney J. The influence of body temperature on early postoperative oxygen consumption. Surgery. 1: 85-92, 1966.

Rosenberg P.H., Heavner J.E. Temperature-dependent nerve-blocking action of lidocaine and halothane. Acta anaesth. scand. 24: 314-320, 1980.

Rowell L. Human circulation regulation during physical stress. New York: Oxford University Press, 1986.

Saidman L., Eger E. Change in cerebrospinal fluid pressure during pneumoengephalography under nitrous oxide anesthesia. Anesthesiology. 26: 67-72, 1965.

Salanitre E., Rackow H., Greene L., Klonymus D., Epstein R. Uptake and excretion of subanesthetic concentrations of nitrous oxide in man. Anesthesiology. 23: 814-822, 1962.

Satinoff E. Neural organization and thermal regulation in mammals. Science. 201: 16-22, 1978.

Satinoff E. A re-evaluation of the concept of the homeostatic organization of temperature regulation. In: Handbook of Behavioral Neurobiology. Eds.: Satinoff E., Teitelbaum P. New York: Plenum Press, 1983.

Saumet J., Lefteriotis G., Dittmar A., Delhomme G., Degoute C. Skin blood flow changes in anaesthetized humans: comparison between skin thermal clearance and finger pulse amplitude measurement. Eur. J. Appl. Physiol. 54: 574-577, 1986.

Saumet J., Lefteriotis G., Dubost J., Kalfon F., Bansillon V., Freidel M. Cutaneous and subcutaneous blood flow during general anaesthesia. Eur. J. Appl. Physiol. 57: 601-605, 1988.

Schafer K., Braun H., Hensel H. Dependence of cold fibreresponse from blood calcium in the cat (Abstract). Pflügers Arch. 373: R68, 1978.

Schwerts R., Brown J. Diffusivity of water vapor in some common gases. J. Clin Physics. 19: 640-646. 1951.

Sessler D., Olofsson C., Rubinstein E. Active thermoregulation during isophlurane anesthesia. Anesthesiology. 67: 37, 1987(a).

Sessler D., Rubinstein E., Eger E. Core temperature during N_2O Fentanyl and Halothane/O_2 anesthesia. Anesthesiology. 67: 137-139, 1987(b).

Sessler D., Olofsson C., Rubinstein E., Beebe J. The thermoregulatory threshold in humans during halothane anesthesia. Anesthesiology. 68: 836-842, 1988.

Sharr F. and Hammel H. Effects of chloralose-urethan anesthesia on temperature regulation in dogs. J. Appl. Physiol. 33: 229-233, 1972.

Shvartz E. Effect of a cooling hood on physiological responses to work in a hot environment. J. Appl. Physiol. 29: 36-39, 1970.

Simon E., Pierau F., Taylor D. Central and peripheral thermal control of effectors in homeothermic temperature regulation. Physiological reviews. 66: 235-300, 1986.

Someren R., Coleshman S., Mincer P., Keatinge. Restoration of thermoregulatory response of body cooling by cooling hands and feet. J. Appl. Physiol. 53: 1228-1233, 1982.

Somjen G. Effects of anesthetics on spinal cord of mammals. Anesthesiology. 28: 135-143, 1967.

Spray C. Characteristics, specificity and efferent control of frog cutaneous cold receptors. J. Physiol. 237: 15-38, 1974.

Stjernstrom H., Henneberg S., Eklund A., Tabow F., Arturson G., Wiklund L. Thermal balance during transurethral resection of the prostate. A comparison of general anesthesia and epidural analgesia. Acta Anaesth. Scand. 29: 743-749, 1985.

Stolwijk J., Hardy J. Temperature regulation in man - A theoretical study, Pflügers Arch. ges. Physiol. 291: 129-162, 1966.

Thesleff S. The effect of anesthetic agents on skeletal muscle membrane. Acta Physiol. Scand. 37: 335-349, 1956.

Theye R., Michenfelder J. The effects of nitrous oxide on canine cerebral metabolism. Anesthesiology. 29: 1119-1124, 1968.

Thomson W. The effects of induction of anaesthesia on peripheral haemodynamics. Brit. J. Anaesth. 39: 210-214, 1967.

Timbal J., Viellefond H., Quanard H. Varene P. Metabolism and heat loss of resting man in hyperbaric helium atmosphere. J. Appl. Physiol. 36: 444-448, 1974.

Vaughan S., Vaughan R., Randall C. Postoperative hypothermia in adults: relationship of age, anesthesia and shivering to rewarming. Anesthesia and analgesia. 60: 46-51, 1981.

Webb P. Body heat loss in undersea gaseous environments. Aerospace Med. 41: 1282-1288, 1970.

Webb P. Thermal problems. In the physiology of medicine and diving, pp 297-319. Ed. Bennett P., Elliott D. California: Best publishing, 1982.

Whitteridge D., Bulbring E. Changes in the activity of pulmonary receptors in anaesthesia and their influence on respiratory behaviour. J. Pharm. Exptl. Therap. 81: 340-359, 1944.

Wissler E. Mathematical simulation of human thermal behavior using whole body models. In: Heat Transfer in Medicine and Biology. Eds.: Shitzer A., Eberhart R. New York: Plenum Press, 1985.

Zotterman Y. Special senses: thermal receptors. Annual Review of Physiol. 15: 357-372, 1963

Table 1: Subjects' physical characteristics

Subjects	Wt kg	Ht cm	Age yr
OE	63.0	173	34
IM	68.0	175	33
TP	68.0	173	26
JF	75.3	185	34
DL	80.4	174	27
SR	63.5	168	24
LW	74.2	175	27
RQ	73.0	173	26
KW	82.0	187	24
Mean $\pm$ SD	71.9 $\pm$ 6.8	176 $\pm$ 6	28.33 $\pm$ 4.2

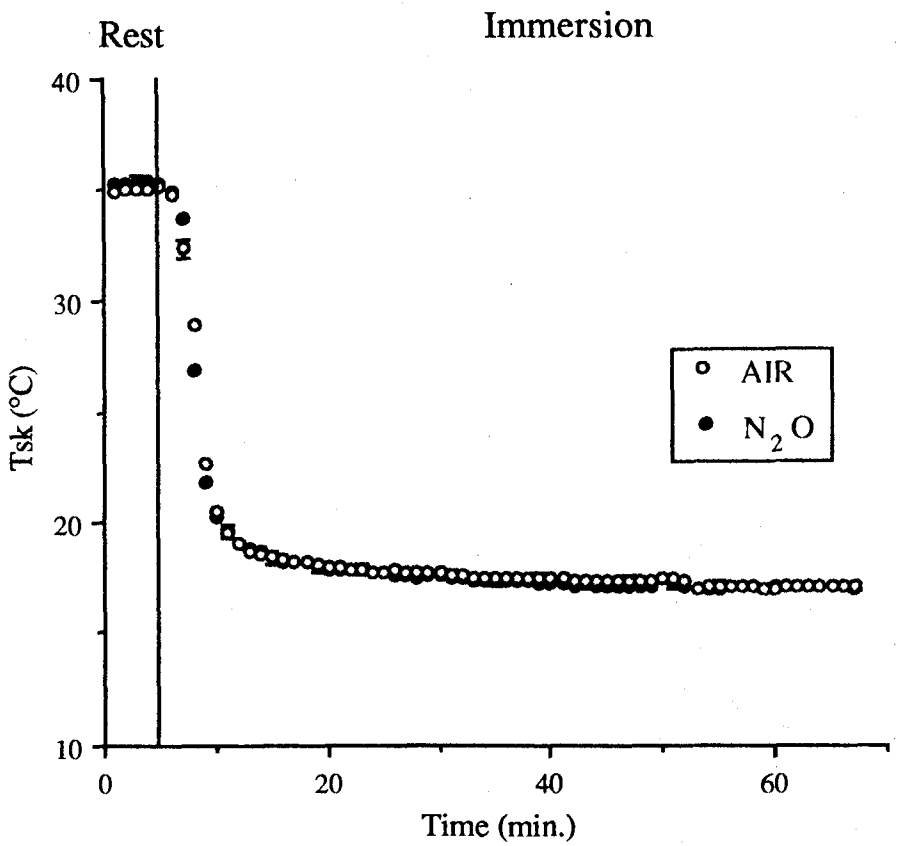

Fig. 1. Skin temperature (Tsk) responses (mean ± SE) during the resting and immersion phases (n=9).

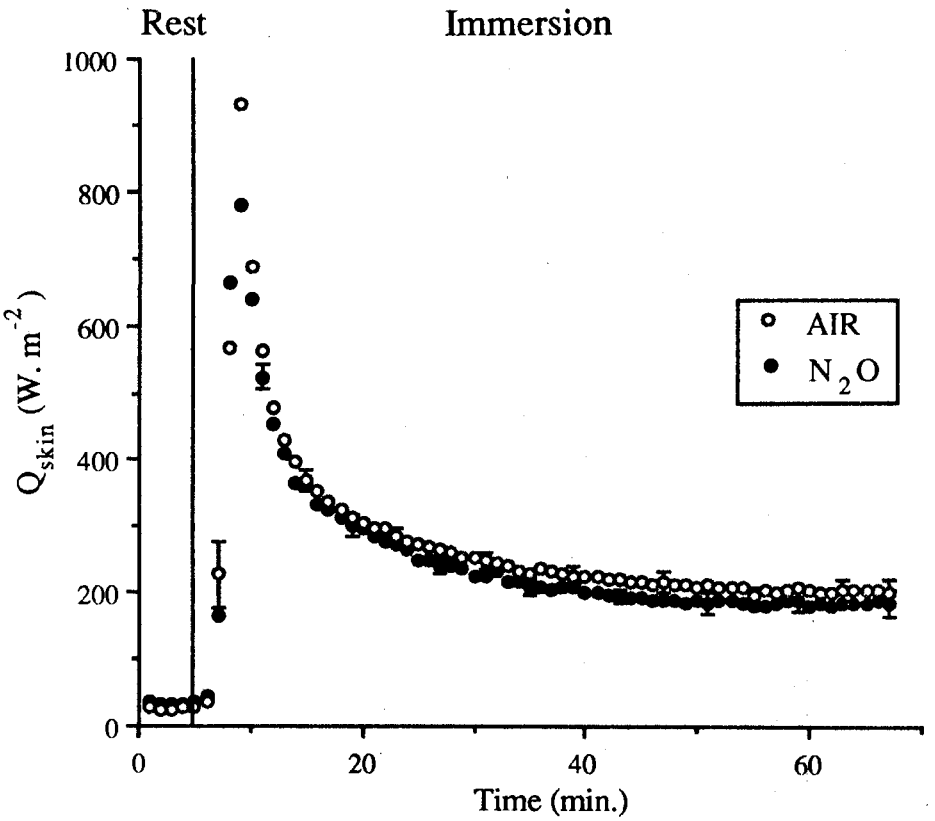

Fig. 2. Heat flux from the skin (Q_{skin}) responses (mean $\pm$ SE) during the resting and immersion phases (n=9).

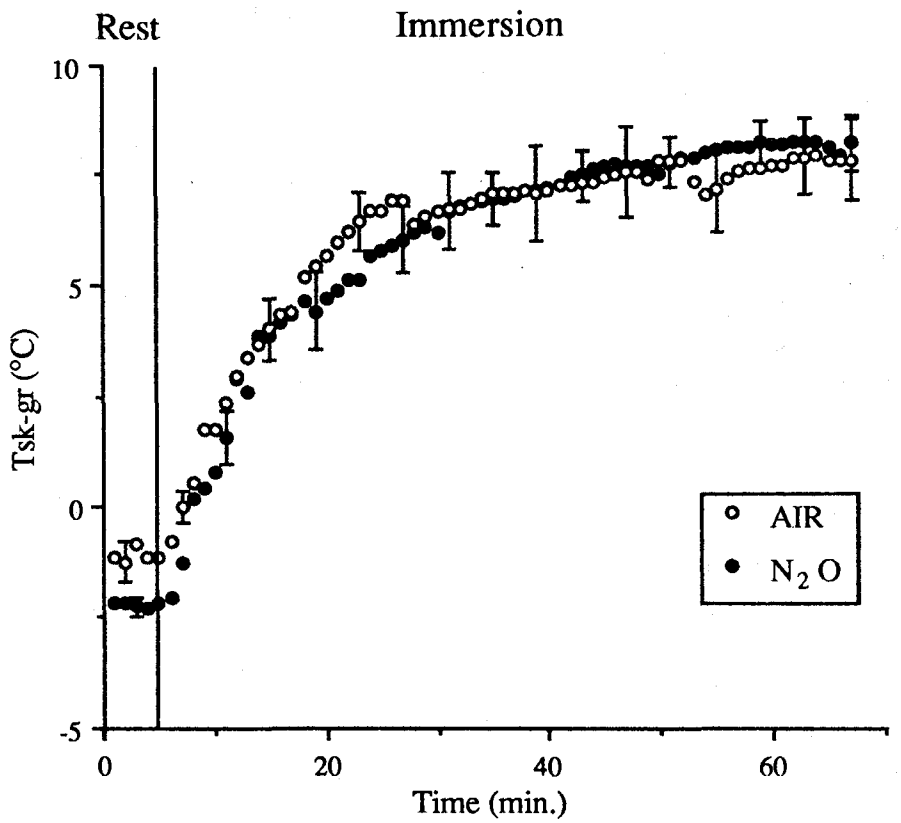

Fig. 3. Forearm-fingertip temperature gradient (Tsk-gr) responses (mean ± SE) during the resting and immersion phases (n=9).

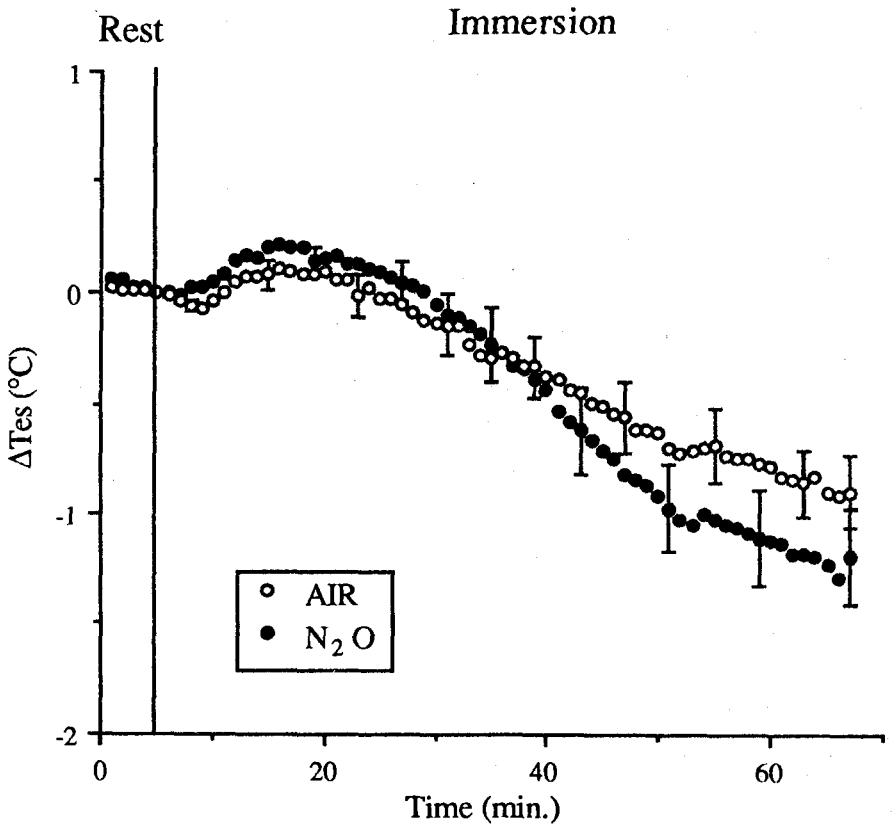

Fig. 4. Esophageal temperature (ΔTes) responses (mean ± SE) during the resting and immersion phases (n=9).

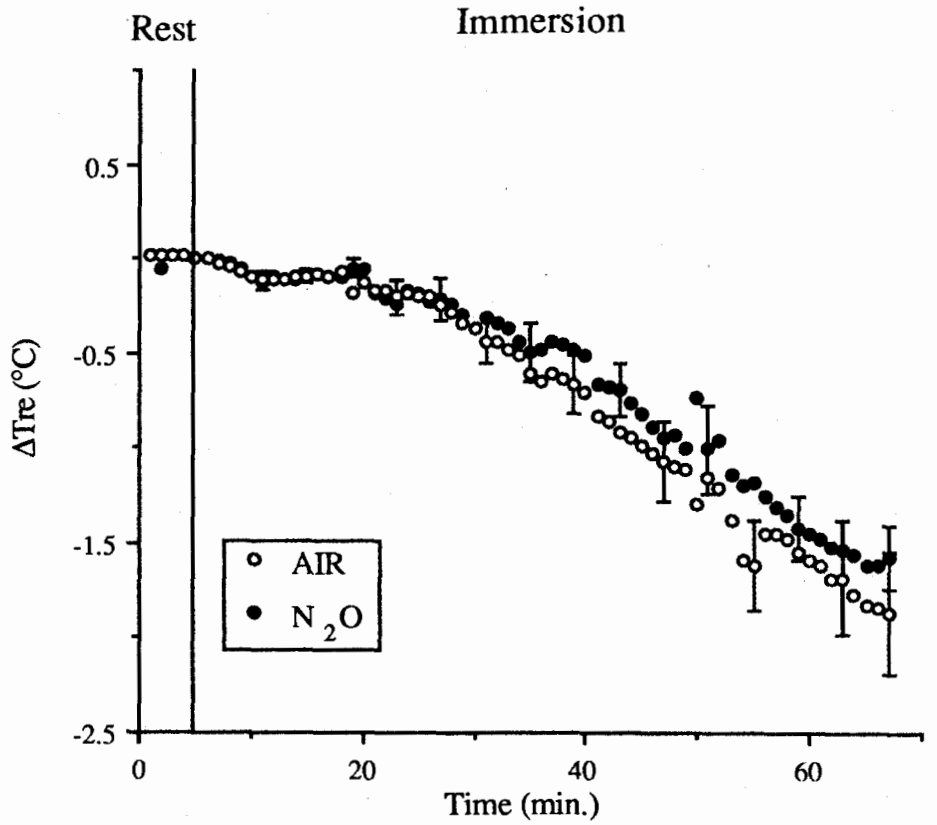

Fig. 5. Rectal temperature (ΔTre) responses (mean ± SE) during the resting and immersion phases (n=9).

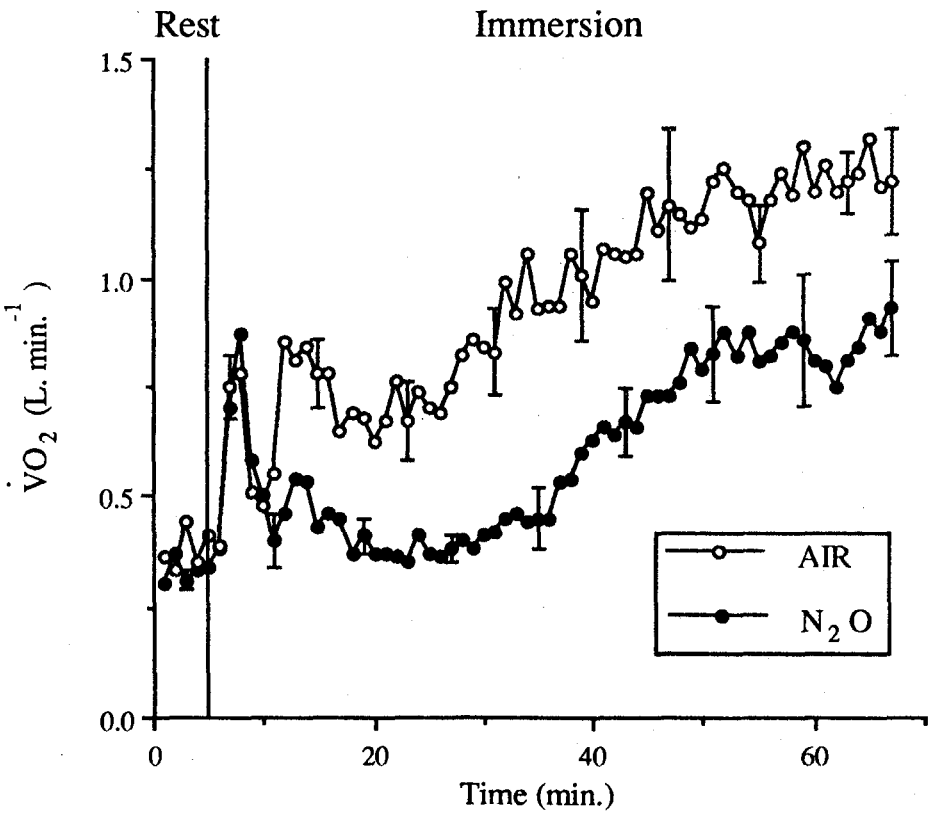

Fig. 6. Mean oxygen uptake ($\dot{V}O_2$) responses (mean $\pm$ SE) during the resting and immersion phases (n=9).

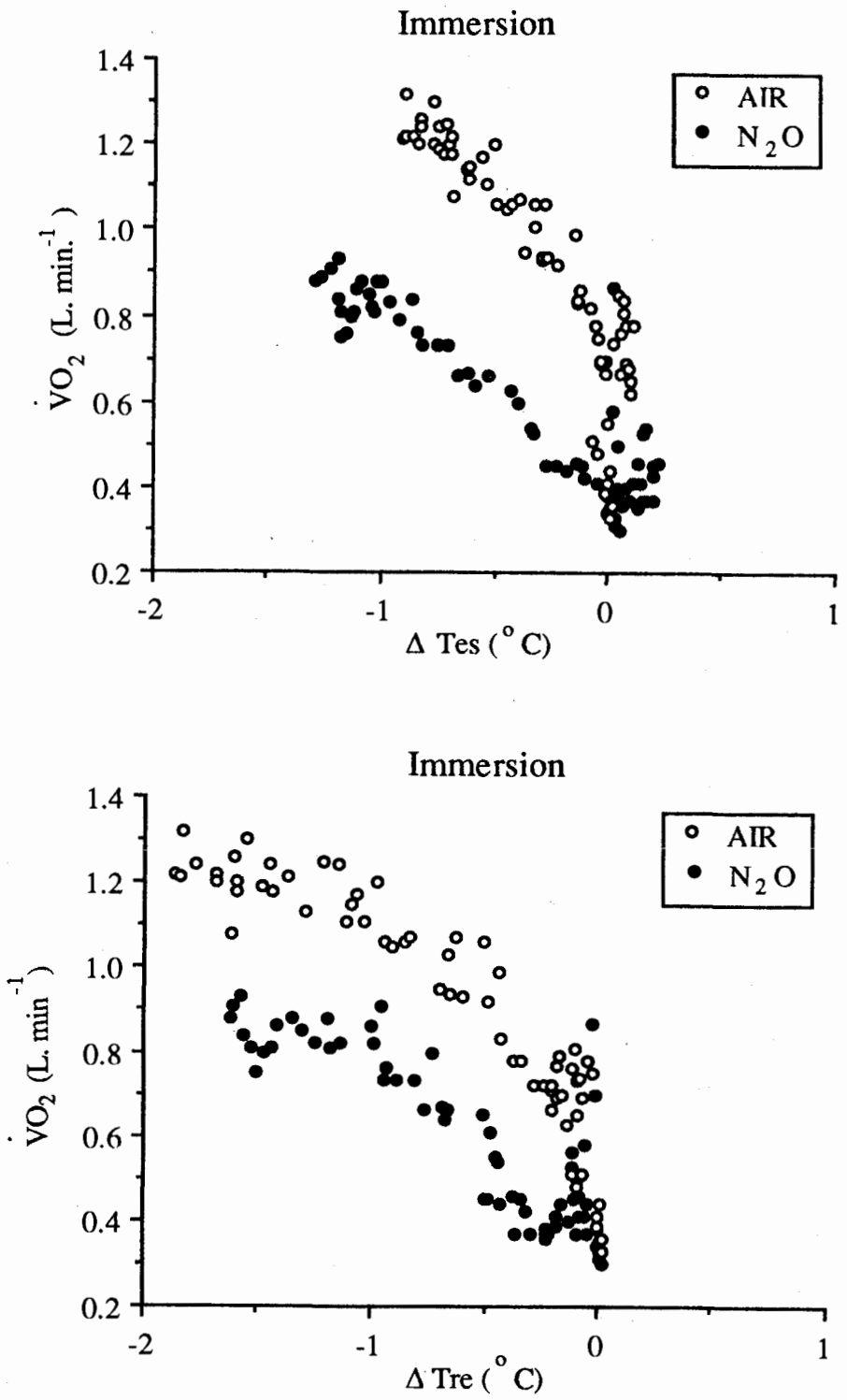

Fig. 7. Oxygen uptake ($\dot{V}O_2$) responses with respect to (top) esophageal (ΔTes) and (bottom) rectal (ΔTre) temperature changes, during the immersion phase.

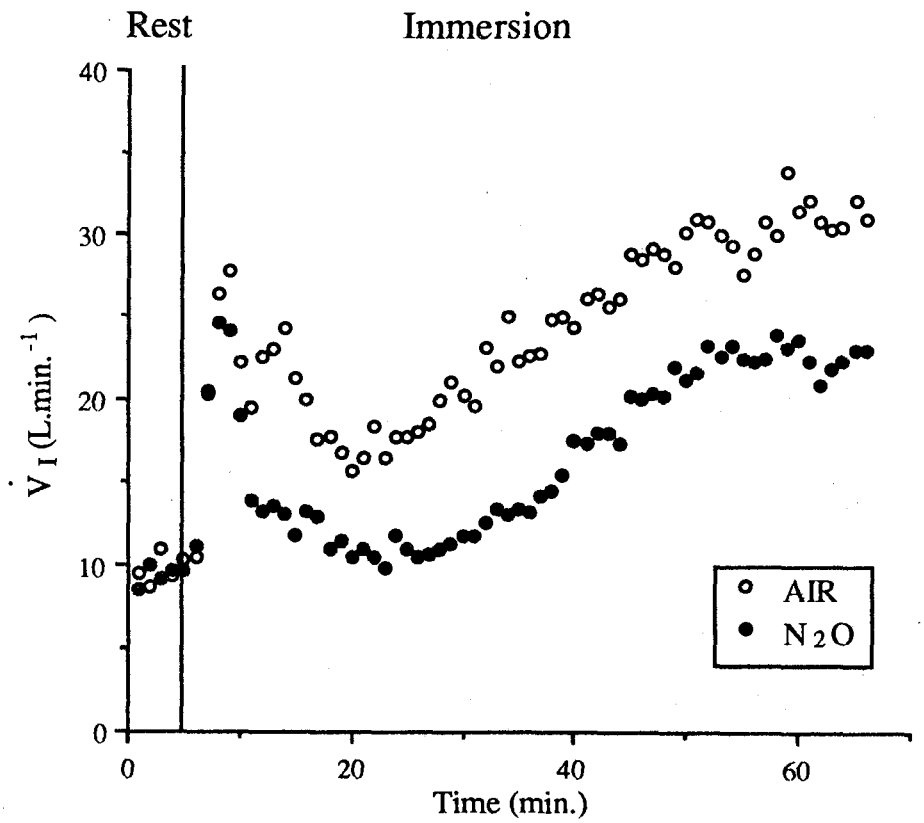

Fig. 8. Inspired minute ventilation ($\dot{V}_I$) responses during the resting and immersion phases (n=9).

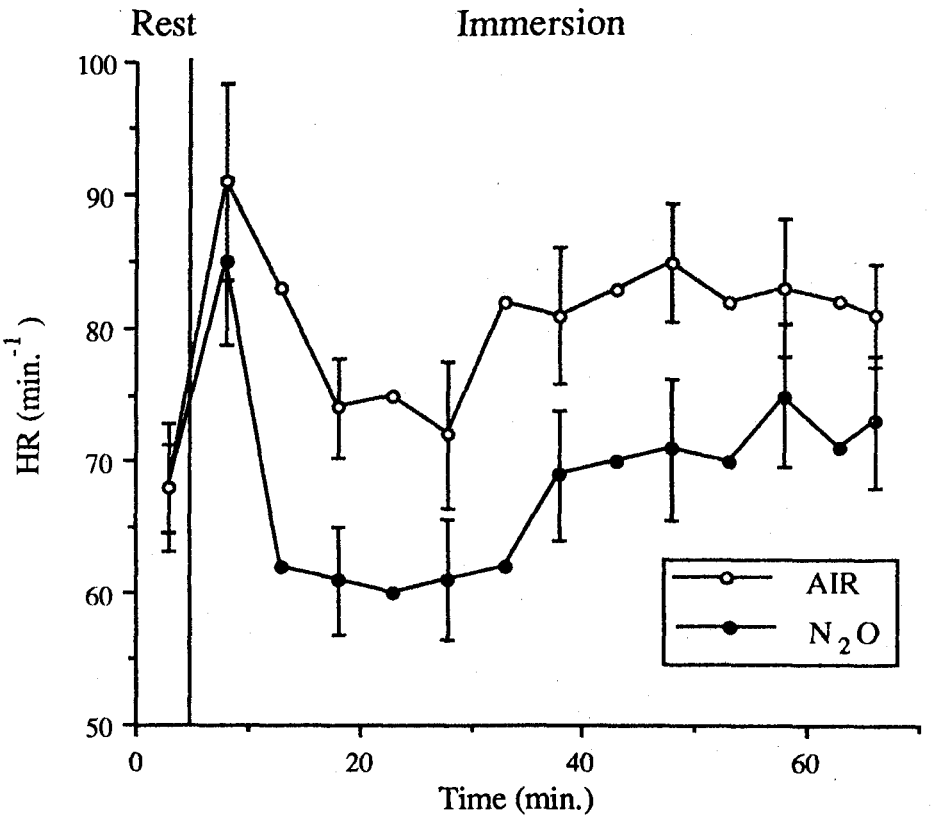

Fig. 9. Heart rate (HR) responses (mean ± SE) during the resting and immersion phases (n=9).

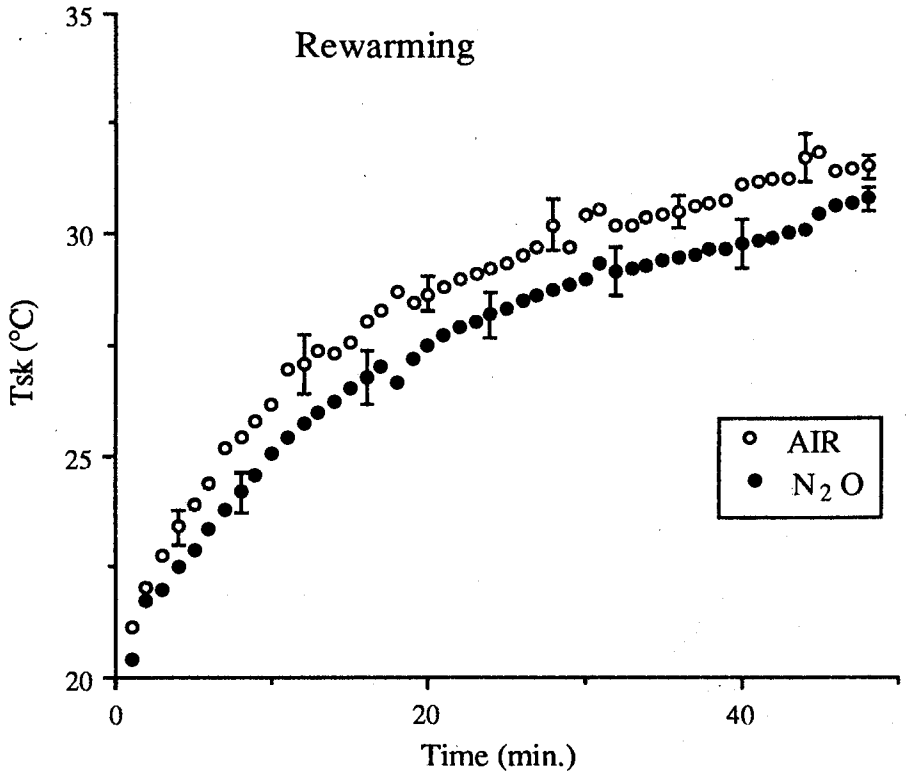

Fig. 10. Skin temperature (Tsk) responses (mean ± SE) during the rewarming phase (n=9).

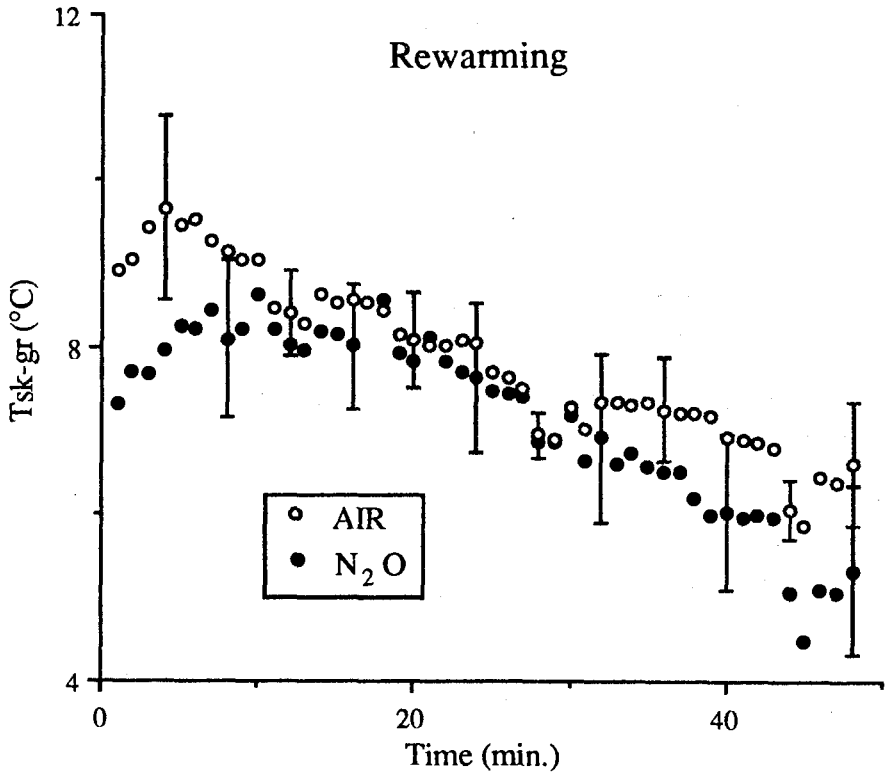

Fig. 11. Forearm-fingertip temperature gradient (Tsk-gr) responses (mean ± SE) during the rewarming phase (n=9).

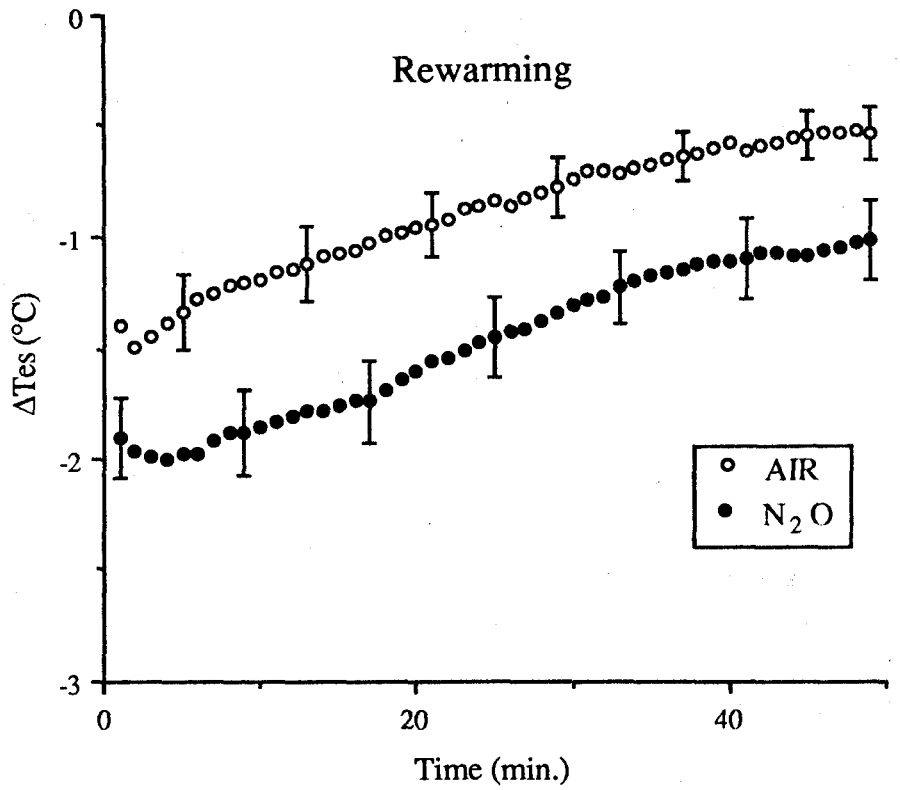

Fig. 12. Esophageal temperature (ΔTes) responses (mean ± SE) during the rewarming phase (n=9).

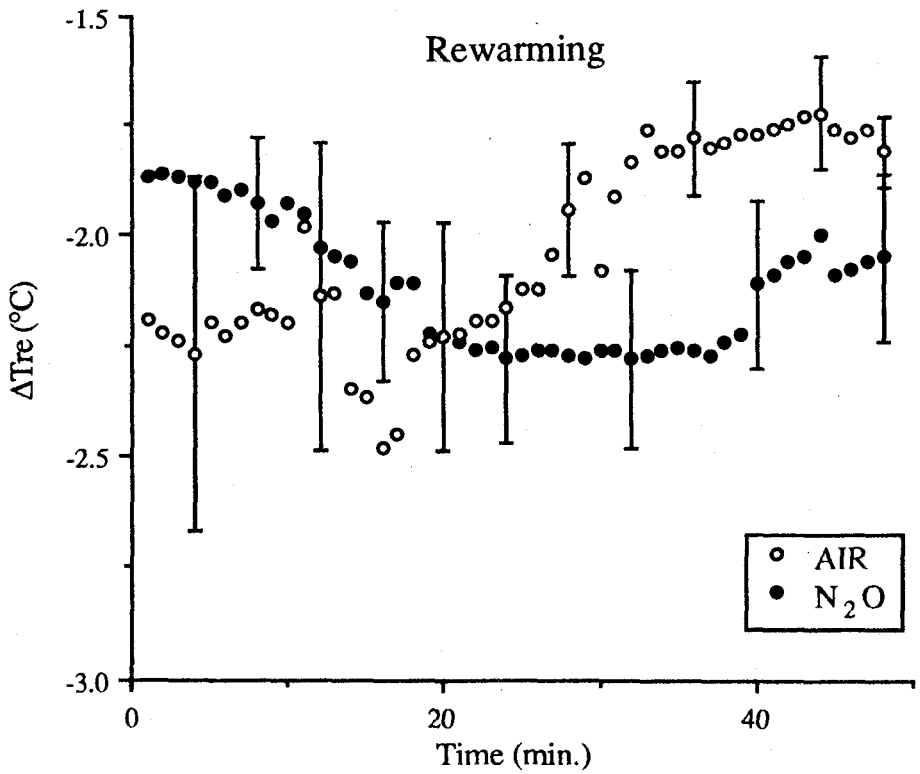

Fig. 13. Rectal temperature (ΔTre) responses (mean ± SE) during the rewarming phase (n=9).

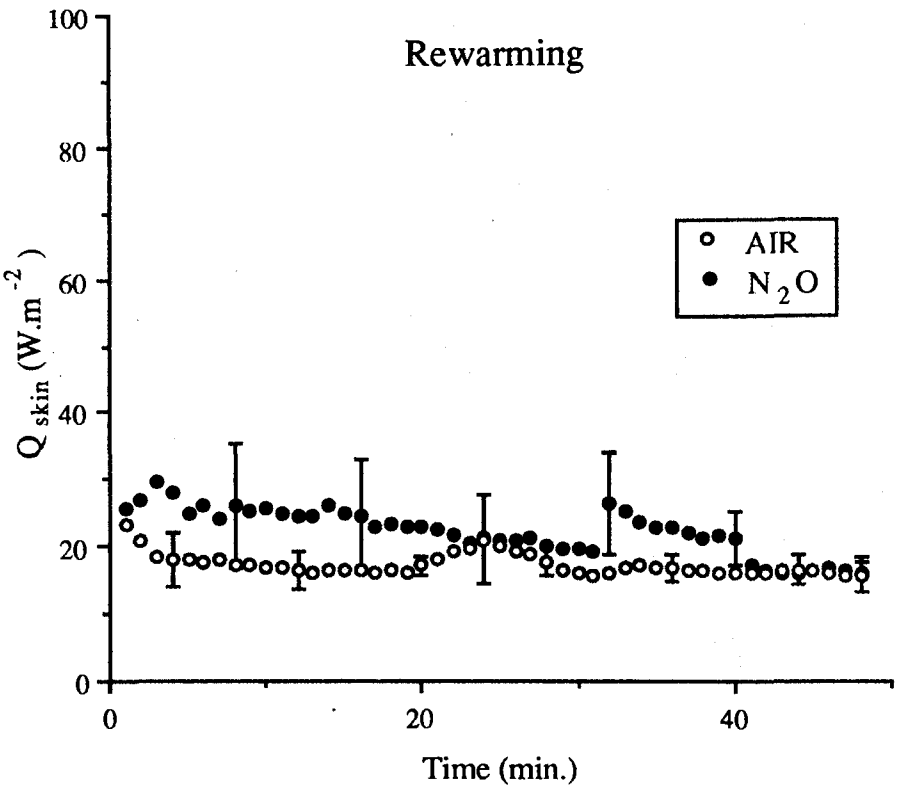

Fig. 14. Heat flux from the skin (Q_{skin}) responses (mean ± SE) during the rewarming phase (n=9).

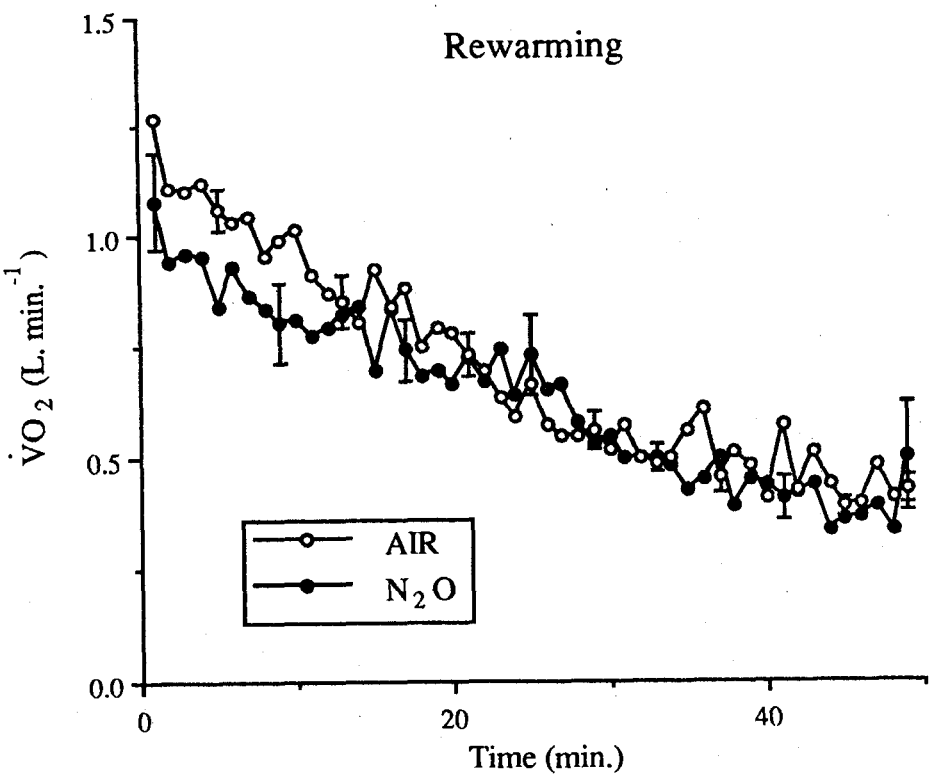

Fig. 15. Mean oxygen uptake ($\dot{V}O_2$) responses (mean ± SE) during the rewarming phase (n=9).

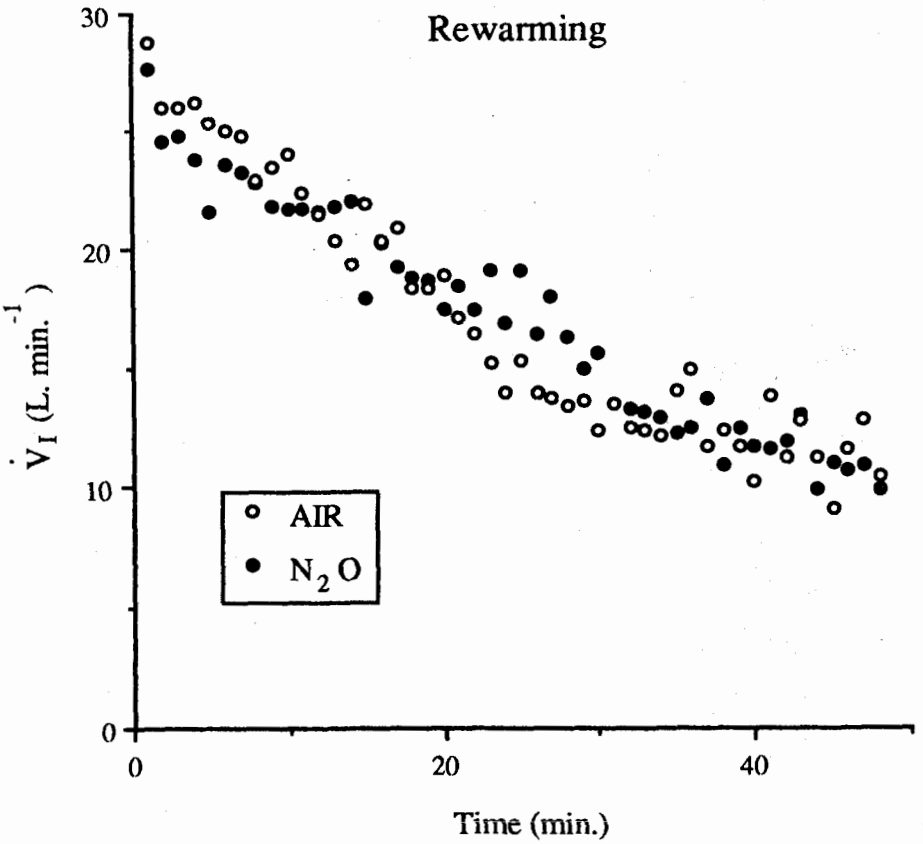

Fig. 16. Inspired minute ventilation ($\dot{V}_I$) responses during the rewarming phase (n=9).

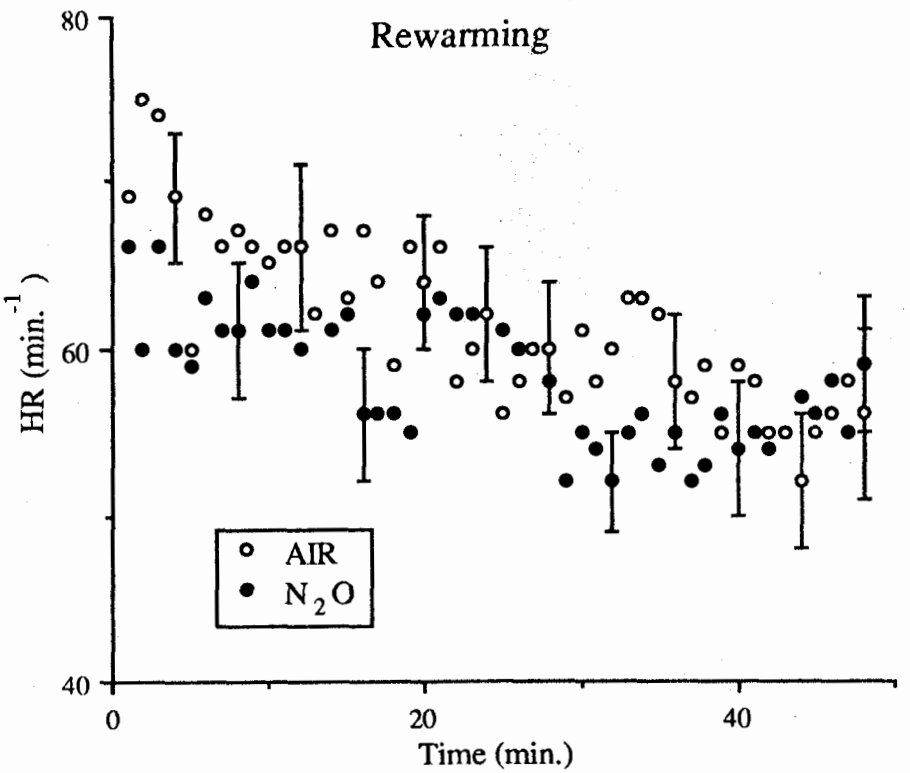

Fig. 17. Heart rate (HR) responses (mean ± SE) during the rewarming phase (n=9).

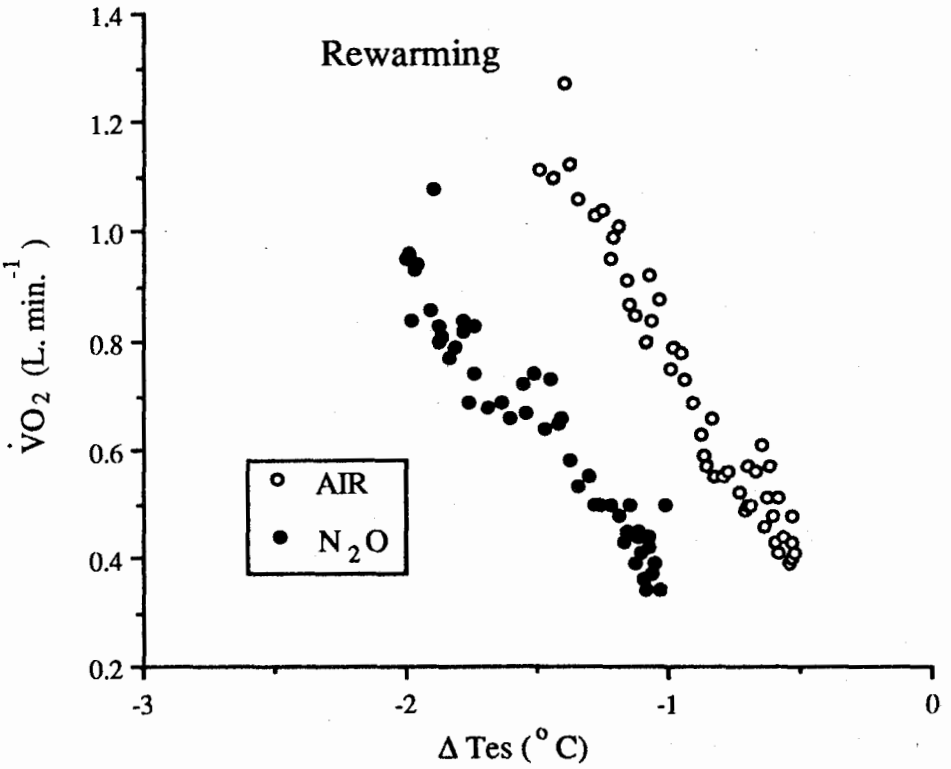

Fig. 18. Oxygen uptake ($\dot{V}O_2$) responses with respect to esophageal temperature changes (ΔTes), during the rewarming phase.