THE INFLUENCE OF HYPOCAPNIC AND NORMOCAPNIC HYPOXIA ON HUMAN THERMOREGULATION

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements for the degree of

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ABSTRACT

ABSTRACT

Hypoxia alters the basic thermoregulatory responses of laboratory animals and humans. In laboratory animals, hypoxia increases core temperature cooling rate, lowers core temperature and inhibits shivering thermogenesis during cold exposure. In humans, the experimental effects of hypoxia on thermoregulation are equivocal. Although Johnston et al. (35) first examined the effect of normocapnic hypoxia on human thermoregulatory response thresholds, no study has compared the effects of hypocapnic hypoxia and normocapnic hypoxia on these responses. To determine the effect of both hypocapnic and normocapnic hypoxia on cold thermoregulatory responses and core cooling during mild cold stress, we examined the esophageal temperature (T_{es}) thresholds for vasoconstriction and shivering as well as the core cooling rates of six subjects immersed in water. On three separate days, subjects sat motionless in a tank of water with an initial water temperature of 37°C. Subjects were warmed until they were peripherally vasodilated. Water temperature was then decreased at a rate of $4°C \cdot h^{-1}$ until they had shivered for 30 min. Subjects inspired humidified room air during the control trial. In the hypocapnic hypoxia trial, they inspired 12% O_2/balance N_2. For the normocapnic hypoxia trial, inspired air was 12% O_2/balance N_2 with CO_2 addition as required to maintain baseline end-tidal CO_2 levels. Arterial blood samples were taken during each trial to determine blood gas and pH values. Hypocapnic hypoxia and normocapnic hypoxia increased core cooling rate by 49% and 54%, respectively, but increased the shivering thresholds by 0.20 and 0.29°C. These results demonstrate that both hypocapnic and normocapnic hypoxia comparably

enhance the core cooling rate in humans during mild cold stress. This may be attributed in part to an increase of respiratory heat loss from hyperventilation during normocapnic hypoxia and an increase in cutaneous heat loss during hypocapnic hypoxia. The small though significant increase in shivering threshold during the two hypoxia conditions was unexpected and may be due to differences in experimental protocol compared to other studies, or due to increased sensitivity to the rate of change in skin temperature.

CHAPTER I. OVERVIEW

A. INTRODUCTION

In the studies of human thermoregulation, core temperature (T_{CO}) (esophageal or rectal temperature) thresholds for shivering, vasoconstriction or sweating are often used to describe thermoregulatory control. Early studies indicated that T_{CO} is kept at a set point by the counteracting processes of heat loss and gain mechanisms (3, 12). This means that the core temperature thresholds for sweating and shivering virtually coincide at a set point. A rise of T_{CO} from the set-point would result in heat loss through peripheral vasodilation and sweating, and a drop in T_{CO} below this point would result in increased heat production by shivering and decreased heat dissipation via vasoconstriction.

Recently, Mekjavic et al. (43) have demonstrated the existence of a thermoregulatory "null zone" between the T_{CO} thresholds for shivering thermogenesis and sweating. Its magnitude is about 0.5°C rather than precisely controlled at a single set point. Generally, many experiments have demonstrated that the null zone model could provide a more accurate description of human thermoregulation than the set point model (8, 11, 35, 39). Even though there are still some debates on these two models, the null zone model has been adopted by many laboratories to analyze the mechanism of human thermoregulation.

Many studies have been conducted on the effect of various perturbations, such as anesthetics (42, 50), alcohol (33), blood glucose status (44), and hypercapnia and hypoxia (34, 35) on the T_{CO} response thresholds for sweating, vasoconstriction and shivering.

It is well known that hypoxia alters the basic thermoregulatory responses of animals and humans. Studies on animals, such as guinea pigs (22), mice, dogs (37), rats (17) and pigeons (24), demonstrate that hypoxia lowers core temperature during cold exposure. Gautier et al. (19) found that the change in body temperature of cats varied directly with inspired O_2 concentration. In cold environments, ambient hypoxia promptly reduces oxygen consumption ($\dot{V}_{O_2}$) and shivering of conscious cats (18). In humans, shivering is inhibited during hypoxia (12% O_2) and $\dot{V}_{O_2}$ does not rise or rises less than during normoxia (37). However, core temperature has been reported to either remain constant (6) or decrease (13, 46) during hypoxic cold exposure. The skin temperature will rise supposedly due to the increased peripheral blood flow during hypoxic conditions (6, 13).

Hypoxia results in hyperventilation which causes a decrease in arterial PCO_2 (hypocapnia). Gautier et al. (19) did a series of experiments in cats to examine the effects of hypocapnic hypoxia and normocapnic hypoxia on thermoregulation. They observed that ambient hypoxia (12% O_2) promptly suppressed shivering activity in a cold environment when hypocapnia was allowed to occur. This suppression of shivering was reversed when end-tidal CO_2 concentration was returned to prehypoxia baseline values (normocapnia) and shivering was again suppressed when CO_2 was withdrawn from the inspired air (hypocapnia). These results indicate that suppression of shivering by 12% O_2 in the cold, reversibly impairs calorigenesis and that this effect of hypoxia requires concomitant hypocapnia. Adding CO_2 to the inspired air might have lessened the degree of cerebral hypoxia by increasing arterial O_2 content through a further increase in ventilation and by increasing

cerebral blood flow (4). In another study, hypocapnic hypoxia shifted the threshold for thermal polypnea to a lower T_{co} in a warm environment. This shift was also reduced when hyperventilatory hypocapnia was prevented (10).

When humans ascend to high altitude (4,300 m), hypoxia does not cause forearm venoconstriction if hypocapnia is prevented by addition of CO_2 to the inspired gas. However, when hypoxia is associated with hypocapnia venoconstriction occurs. Hypoxia of greater severity than that seen at 4,300 m produces venoconstriction in the absence of hypocapnia. Hypocapnia appears to enhance this response (52).

Johnston et al. (35) first isolated the hypoxic stimulus from hypocapnia in humans to examine the effects of normocapnic hypoxia on T_{co} thresholds for warm and cold thermoregulatory responses as well as the rate of core cooling during mild cold stress. Their results showed that normocapnic hypoxia significantly decreased the core temperature thresholds for vasoconstriction and shivering by 0.14 and 0.19°C respectively, and the rate of core cooling increased by 33%.

There are some studies on the effects of hypocapnic hypoxia on thermoregulation in humans and animals. For instance, Weil et al. (52) found that venoconstriction occurred in humans at high altitude (4,300 m) and that this response could be prevented by addition of CO_2 to the inspired gas. Also, the effects of hypocapnic hypoxia in the cold for adult cats can be reversed by increasing F_{ICO2} (19). However, there are no studies on the effects of hypocapnic hypoxia on core temperature thresholds in humans, and there are no comparisons between hypocapnic and normocapnic hypoxia on

these temperature responses. It is necessary to elucidate these factors in human thermoregulation.

STATEMENT OF THE PURPOSE

To determine the effects of hypocapnic and normocapnic hypoxia on T_{co} thresholds for cold (vasoconstriction and shivering) thermoregulatory responses as well as T_{co} cooling rates during mild cold stress. In studies by Johnston et al. (34, 35), exercise was used to increase body temperature above the sweating threshold. There were no effects of either gas mixture on the sweating threshold. One problem with the exercise protocol is that exercise can decrease the T_{co} threshold for sweating by 0.7°C (38), and therefore is a complicating factor. Accordingly, we studied resting subjects in water and only determine T_{co} thresholds for vasoconstriction and shivering and core cooling rate. On three separate days, subjects were immersed in 37°C water after a 15-30 min baseline period. When subjects were peripherally vasodilated, the water temperature was decreased at a rate of $4°C \cdot hr^{-1}$, until subjects fully vasoconstricted and shivered vigorously for 30 min. Subjects inspired humidified room air during the control trial. In the hypocapnic hypoxia trial, they inspired 12% O_2/balance N_2. For the normocapnic hypoxia trial, inspired air was 12% O_2/balance N_2 with CO_2 addition as required to maintain baseline end-tidal CO_2 levels.

IMPORTANCE OF THE STUDY

This study will help to further elucidate the effects of hypoxia and hypocapnia on human thermoregulation. Specifically, the effects of these different inspired gases during mild cold stress have never been compared.

HYPOTHESIS

Compared to normoxia, hypoxia will decrease core temperature thresholds for vasoconstriction and shivering. The effect will be greater for hypocapnic hypoxia than normocapnic hypoxia. The rate of cooling for hypoxia will be greater than normoxia. Because ventilation is expected to be greater during normocapnic hypoxia (CO_2 added), it will increase respiratory heat loss compared to hypocapnic hypoxia. It was hypothesized that the rate of cooling for normocapnic hypoxia would be the same as in hypocapnic hypoxia.

ASSUMPTIONS

It was assumed that changes in fingertip and forearm blood flow accurately reflect the pattern of whole body peripheral blood flow. Second, it was assumed that the subjects would not confound the results by indulging in prohibited behavior (e.g., smoking, drinking alcohol) before their trials or changing their eating or sleeping patterns drastically from one study day to the next.

DELIMITATIONS & LIMITATIONS

1) Only healthy volunteers between the ages of 18 and 40 participated in this study. This may limit the generalizability of the results to this specific group.

2) Arterial hypoxemia was achieved by inhalation of 12% O_2 in N_2. This was chosen as the lowest oxygen fraction that can safely be breathed by human subjects.

3) Esophageal temperature was used as an indicator of T_{co} as this is the best non-invasive indicator of core temperature (14).

DEFINITION OF TERMS

1) **Hypoxia** is the condition in which the oxygen supply to the tissue is below physiological levels. The normal inspired air O_2 content is 20.9%. Under normobaric conditions, mild hypoxia is 16-20%, moderate hypoxia is 11-15% and severe hypoxia is below 11%.

2) **Hypocapnia** is the condition in which the carbon dioxide tension of the blood is below normal (i.e., $PaCO_2 < 40$ mmHg). It often occurs in the condition of hyperventilation.

3) **Normocapnia** is the condition in which the carbon dioxide tension of the blood is normal ($PaCO_2 \sim 40$ mmHg).

4) **Core temperature** is the temperature of the important core organs of the body (i.e. heart + brain), it is often measured by a temperature in the esophagus or rectum.

5) The **core temperature response threshold** is the core temperature at which a given thermoregulatory (i.e., sweating, vasoconstriction or shivering) mechanism is initiated.

6) The **thermoregulatory null zone** (43) is the range between the T_{co} thresholds for sweating and shivering.

7) The **interthreshold range** (48) is the range between the T_{co} thresholds for sweating and vasoconstriction. This represents the range of T_{co} over which no active thermoregulation occurs.

8) **Nonshivering thermogenesis** is the metabolic production of heat via brown fat oxidation without mechanical work (9).

B. REVIEW OF RELATED LITERATURE

THEORIES OF THERMOREGULATION

Human temperature regulation is characterized by the responses of shivering, sweating, and peripheral vasomotor tone (28, 43). Shivering is a defense reaction to cold, found in homeothermic animals (36). The increased activity of musculature in the form of shivering is the main source of heat production in man during exposure to cold (1, 25, 30). On the other hand, sweating often occurs during exercise and under hot environmental conditions. The main function of sweating is to dissipate heat as a consequence of sweat evaporation. Generally, shivering occurs with vasoconstriction during cooling and sweating accompanies vasodilation during warming (2, 26).

Core temperature is often used to describe the thresholds for thermoregulatory responses. The core temperature triggering a thermoregulatory response, at a fixed skin temperature defines the threshold for those responses.

Benzinger (3) indicated that core temperature is kept at a set-point by the counteracting processes of heat loss and gain in human thermoregulation. If T_{co} is higher than the set-point, this would result in heat dissipation through peripheral vasodilatation and sweating, and a drop in T_{co} below this point would result in decreased heat loss through vasoconstriction and shivering. This hypothesis has been supported by experiments on both animals (31) and humans (12).

Cabanac and Massonet (12) warmed human subjects in a 40°C bath and abruptly lowered water temperature to 28°C for cooling. With this protocol, the T_{co} thresholds for sweating and shivering actually overlapped, albeit insignificantly (~0.05°C). One of the fundamental problems with these studies was the large differences in skin temperature between the warming and cooling protocols, since cutaneous vasculature is an effector system in thermoregulation because skin blood flow controls the rate of heat transfer between the body surface and environment (32).

Bligh and Johnson (9) introduced the concept of "thermoneutral zone" that is situated between two critical temperatures and is defined as the range of ambient temperature within which metabolic rate is at a minimum, and within which temperature regulation is achieved by non-evaporative physical processes alone. The "upper critical temperature" is the ambient temperature above which thermoregulatory evaporative heat loss processes, of a resting thermoregulating animal, are recruited. The "lower critical temperature" is the ambient temperature below which the rate of metabolic heat production of a resting thermoregulating animal increases by shivering and/or non-shivering thermogenic processes, to maintain thermal balance, are recruited.

The rates of sweating and shivering thermogenesis are usually determined under separate experimental conditions. It is possible to quantify the T_{co} threshold for these responses at isothermal levels of the skin by combining them on a single core temperature abscissa. It also could assess

whether a single T_{co} (set point) or a range of thresholds (null zone) is defended during the cooling process (43).

Early experiments were always limited to study of responses to either high or low environmental temperatures but not to both (12), some experimental work seemed to indicate the existence of a range of core temperatures devoid of active thermoregulation, or a null zone. When experimental observations of warm and cold thermoregulatory responses, as measured in different protocols, were plotted together versus T_{co}, they often included a dead band which lacks active thermoregulation (7, 27). Such a dead band would be equivalent to a "null zone" of core temperature (12).

More recent studies have convincingly demonstrated a thermoregulatory null zone in human subjects. Mekjavic and Bligh (41) attempted to repeat the experimental protocol of Cabanac and Massonnet (12), by which T_{co} was first raised and then lowered. They did not find any overlap in the sweating and shivering responses. Bruck (11) found a neutral zone of weighted body temperature (T_b) between onset of shivering and sweating. Lopez et al (39) indicated that the range between the sweating and vasoconstriction thresholds (interthreshold range) was 0.2°C in both men and women, but each thermoregulatory response threshold was 0.3°C higher in women. Also, they found all thresholds were virtually identical during slow ($0.7°C \cdot hr^{-1}$) and fast ($1.7°C \cdot hr^{-1}$) core cooling.

Recently, Mekjavic et al. (43) indicated that the core temperatures at which sweating ceases and shivering commences are significantly different ($p<0.01$) regardless of whether core temperature is measured within the

esophagus or rectum. They found there is a "null zone" of about 0.5°C between the T_{co} thresholds for sweating and shivering, rather than precisely controlled at a single, specific point. In their test, subjects were immersed in 28°C water to maintain constant skin temperature. Exercise was used to increase T_{co} above the sweating threshold. Other laboratories have also demonstrated a null zone of similar magnitude using this protocol (34, 35). In 1993, Sessler defined the zone between the T_{co} thresholds for sweating and vasoconstriction as the "interthreshold range" (48). A zone of thermoneutrality is frequently used in defining a range of peripheral temperatures that does not elicit thermoregulatory effector responses (8, 40). Mekjavic et al. (43) suggested the existence not only of a peripheral null zone but also of a core null zone.

Many studies are now emphasizing the effects of various perturbations including anesthetics (42, 50), alcohol (33), blood glucose status (44), hypercapnia (34) and hypoxia (35) on the thresholds for sweating and shivering. Sessler (49) found the interthreshold range without anesthesia is ~0.5°C; isoflurane anesthesia increases this range to ~4°C (29). Other studies showed that the temperature adaptation will change the thresholds of sweating and shivering, but the effects for both sweating and shivering are different, so the null zone or interthreshold range may change (11, 15, 45).

Generally, many experiments have demonstrated that the null zone model could provide a more accurate description of human thermoregulation than the set-point model.

EFFECTS OF HYPOXIA ON THE THERMOREGULATORY RESPONSES

Many studies in this area focused mainly on the effect of hypoxia on the body temperature of men and other animals exposed to cold stress. This is because hypoxia often occurs at high altitude where the ambient temperature is usually low. As early as 1927, Behague [as cited in (22)] showed that the temperature of the body falls with decreasing atmospheric pressure. Later Gellhorn and Janus (22) studied guinea pigs and demonstrated that this fall in core temperature is due to reduced partial pressure of O_2 and not hypobaria itself. Moreover, Mayer et al. (21) have shown that the decrease in body temperature resulting from oxygen deficiency is associated with a decrease in oxygen consumption.

Gellhorn (21) pointed out that the lowering of the body temperature which is associated with oxygen deficiency is an extremely important reaction in the warm blooded animal, since there is a marked relationship between the ability of an animal to lower its body temperature during oxygen deprivation and its resistance to such a condition. If this drop in temperature is prevented, it almost invariably leads to death. It seemed that there is a causal relationship between sensitivity to O_2-deprivation and the temperature lowering capacity in various species. Also, he found that the loss in temperature is greatest in animals with large surface area. In 1948, Kottke et al. (37) reported that hypoxia decreases the ability of mice, dogs and men to control body temperature during exposure to cold. The rectal temperature of mice exposed to hypoxia was on the average less than 1°C above the temperature of the environment within a range of 4 to 24°C. For dogs, body temperature fell on average 2.3°C when exposed 6% O_2 inspired air at environmental temperatures of 12 to 25°C. For men, rectal temperature

dropped about 1°C when exposed to 10% O_2 in environmental temperatures of 11 to 22°C.

Other studies on cats (10, 18, 23, 29), rats (17, 20) and humans (6, 35, 46) have shown similar results. It is likely that the decreased T_{co} results from inhibited thermogenesis (shivering and non-shivering) and enhanced heat loss by altered blood flow distribution (i.e., cutaneous vasodilation). The details will be discussed below.

Shivering thermogensis (ST). Shivering is a defense reaction to cold found in homeothermic animals (36). When animals shiver, oxygen consumption ($\dot{V}_{O2}$) increases ($\dot{V}_{O2}$ is often used to quantify shivering). Since shivering is under control of the central nervous system, it is to be expected that shivering may be inhibited in conditions of severe hypoxia. Kottke (37) observed in humans that shivering was inhibited during hypoxia (F_{IO2}=12%O_2) and the oxygen consumption rose not at all or to a lesser degree than in control conditions. The result was a significant drop in rectal temperature. On return to breathing normal air, vigorous shivering began, oxygen consumption rose, skin temperature fell and rectal temperature rose.

Blatteis and Lutherer (6) examined the thermoregulatory response to cold of sea-level and high altitude natives exposed acutely to various altitudes, and the effect on thermoregulatory responses in sea level natives during 6-wk residence at altitude. The results showed that the extent of the depression of the cold-induced increase in $\dot{V}_{O2}$ caused by altitude exposure was similar for both lowlanders and highlanders (20 and 21%, respectively). The altitude-induced reduction of the $\dot{V}_{O2}$ response to cold of the lowlanders

was not reversed during the course of their 6-wk residence at 4, 360 m. However, the visible shivering intensity of the lowlanders was not diminished at altitude compared to that at sea level. Similar results were confirmed by Robinson and Haymes (46) who extended these observations to exercising human subjects. This study also showed that visible shivering was increased by hypoxia in humans whereas $\dot{V}_{O2}$ tended to be depressed. It was concluded from these studies that hypoxia specifically reduced the nonshivering component of thermogenesis. Non-shivering thermogenesis is not a major factor in adult humans and these unusual results may be due to the fact that shivering was only visually quantified.

A series of studies on cats and rats on the effect of hypoxia on thermoregulation were carried out by Gautier and his colleagues (17, 18). First, they found that when intact and carotid-denervated (CD) conscious cats were exposed to ambient hypoxia (11% to 17%) or carbon monoxide (CO) hypoxia in a cold environment [ambient temperature (T_a) 5-8°C], both groups decrease body temperature and shivering. Exposure to various levels of hypoxia produced graded suppression of shivering, with the result that the change in body temperature varied directly with inspired O_2 concentration. They concluded that hypoxia appears to act on the central nervous system to suppress shivering and that carotid nerve afferents appear to counteract this direct effect of hypoxia. However, they did not agree that the suppression of shivering is by activating peripheral chemoreceptors because carotid denervation did not prevent the depression of shivering by ambient hypoxia, and CO exerted an inhibitory action on thermoregulation in the cold that resembled ambient hypoxia (19).

Later, Gautier and his colleagues (18) reported oxygen consumption and shivering movements of conscious adult cats in a thermoneutral (T_a=24 to 27°C) and in a cold (T_a=3 to 8°C) environment during normoxia, hypoxia, and hyperoxia. The authors pointed out that hypoxia-induced changes in shivering activity are accompanied by parallel modifications in metabolic rate, and they concluded that hypoxia decreases metabolic rate in the cold, in part, by reducing shivering. In a cold environment, ambient hypoxia reduced $\dot{V}_{O_2}$ and shivering. Under thermoneutral conditions, a 20% reduction in $\dot{V}_{O_2}$ with exposure to 12% O_2 was also observed. They also showed that carotid body chemoreceptors do not mediate the suppression of shivering by ambient hypoxia since hypoxia induced by CO also reduced $\dot{V}_{O_2}$ and the shivering index.

In their continued studies, Gautier and his colleagues focused on investigating to what extent the hypoxic hypothermia observed during acute exposure to cold is modified when nonshivering thermogenesis replaces shivering thermogenesis (17, 20). This will be discussed below.

Non-shivering thermogenesis (NST). Non-shivering thermogensis occurs in the brown adipose tissue which is present in many mammals, including humans, particularly in the newborn. On exposure to cold, newborn animals of many species increase their O_2 consumption which is not related to shivering. This increase is reduced or abolished by acute hypoxia in newborn rabbits, kittens and adult guinea-pigs (5).

Gautier and his colleagues (17) showed that the reduction in $\dot{V}_{O_2}$ results from a decrease in both ST and NST in rats. The decrease in shivering

(measured by vibration) is transient, however, because after 40-45 min of hypoxia, shivering has recovered to its control values. However, $\dot{V}_{O2}$ remained depressed indicating a depression of NST. They concluded that NST is markedly sensitive to hypoxia, especially demonstrable in cold-acclimatized rats. These results confirmed the previous reports that with cold acclimation an animal will rely less on shivering and more on a nonshivering metabolic response to cold (28). However, the results differ from their previous study in cats using a similar protocol because in cats, after the abrupt inhibition of $\dot{V}_{O2}$ and shivering at the onset of hypoxia, a partial and parallel recovery occurs in both $\dot{V}_{O2}$ and shivering intensity. This suggests that hypoxia induces a coordinated readjustment of thermoregulatory processes of which the mechanisms may vary in different animal species because the inhibition is of ST in cats and especially of NST in rats (17).

Since the capacity for NST may be inversely related to body size (6) and it mainly exists in brown adipose tissues, its contribution to cold-induced thermogenesis in man, may be insignificant. However, Blatteis and Lutherer (6) observed that at altitude the visible shivering intensity of lowlanders was not diminished compared to that at sea level despite the observed decrease in their $\dot{V}_{O2}$ at altitude. They concluded that the thermogenic response to cold which was depressed by altitude exposure was independent of visible shivering, and that it may have been NST. Finally, they concluded that a small, but significant, hypoxia-sensitive, non shivering thermogenic mechanism, which contributes along with shivering to cold thermogenesis, exists in man as well. Similar results were observed by Robinson and Haymes

who found that hypoxia specifically reduced the nonshivering component of thermogenesis by inhibition of the aerobic catabolism of body fat stores (46).

Blood flow. Human skin is unique in its vascular anatomy, the richness of its vascular supply, its innervation, and its vital role in temperature regulation. Cold is associated with cutaneous vasoconstriction and normal or increased core blood flow to many internal organs. Hot conditions cause high surface blood flow (cutaneous vasodilatation), causing a reduction in thermal insulation and reduced blood flow to the body core so that less heat is stored centrally (47). Rather it is dissipated by radiation from the skin surface.

There are some studies conducted on the variation of cutaneous circulation at altitude. Durand et al. (16) found that at high altitude there is an increase in resistance of the cutaneous circulation at altitude. When acute hypoxia is marked (at altitude above 3750 m), it is accompanied by a cutaneous vasoconstriction and a muscular vasodilatation. Another study by Weil et al. (52) showed that ascent to high altitude (4,300 m) causes a decrease in venous compliance in man and similar results were seen with low fraction of inspired O_2 (12.1%) in the laboratory. Studies on rabbits have shown that the cardiovascular response to brief moderate hypoxia includes not only increased cardiac output but also a major repartitioning of this cardiac output to various tissues. Blood is redirected from the renal and splanchnic vascular beds to the heart, skeletal muscle, and brain. Skin flow showed a smaller nonsignificant increase (51).

Other studies showed that at a T_a of 15.5°C, rectal temperature was 0.3°C lower at 5,000 m and 0.2°C lower at 2,500 m than at sea level in humans. Skin temperature was almost 2°C higher at 5,000 m and 1°C higher at 2,500 m than at sea level. It seems that blood flow to the body surface increased during hypoxia resulting in an increased skin temperature and presumably heat loss (13). Another study showed that when humans at altitude are exposed to 10°C air, skin temperatures were lower than that at sea level (6). Variations in the experimental conditions probably account for differences reported for the direction of change, if any, for either skin or rectal temperature. Such variations involve the degree of hypoxia imposed, ambient temperature, type and amount of apparel worn during the exposure, duration of the exposure, and the activity level of the subjects (13).

The Effect of Hypocapnia. Hypoxia elicits hyperventilation which causes arterial hypocapnia. Weil et al. (52) examined venoconstriction in man upon ascent to high altitude. They found that when subjects voluntarily hyperventilated room air, while CO_2 was added to the inspired gas to maintain $PaCO_2$ at control levels (normocapnia), no change in venous compliance occurred. However, when hyperventilation was performed without CO_2 replacement (i.e. hypocapnia) venoconstriction occurred. They concluded that acute hypoxia of moderate degree does not in itself produce venoconstriction and hyperventilation does not produce venoconstriction if hypocapnia is prevented.

Gautier et al. (18, 19) in their study on cats, assessed the effects of hypocapnia by normalizing end-tidal CO_2 levels during inhalation of 12% O_2. Hypoxia decreased shivering activity and $\dot{V}O_2$ and this suppression was

reversed when end-tidal CO_2 was normalized. Shivering and $\dot{V}_{O2}$ again decreased when CO_2 was withdrawn. Hypocapnia causes cerebral vasoconstriction therefore reducing O_2 delivery. This may explain the smaller effect during normocapnia.

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CHAPTER II. THE EFFECTS OF HYPOCAPNIC AND NORMOCAPNIC HYPOXIA ON HUMAN TEMPERATURE REGULATION

A. INTRODUCTION

Hypoxia is thought to disrupt the thermoregulatory processes of both laboratory animals and humans. In humans, arterial hypoxemia often occurs during exposure to cold environments. Hypoxemia may occur during high-altitude mountaineering (decreased inspired PO_2) or diving (inadequate air supply). During these activities, hypoxia is usually accompanied by cold stress. Hypoxemia also results from primary hypoventilation or interstitial lung disease in patients who are often elderly. Thermoregulatory function is impaired in the elderly (11), and hypoxia may further reduce the ability of these patients to maintain temperature homeostasis. Consequently, it is important to understand the effects of hypoxia on human thermoregulation during thermal stress.

Studies on laboratory animals, such as guinea pigs (16), mice, dogs (26), rats (12) and pigeons (19), demonstrate that hypoxia lowers core temperature (T_{co}) during cold exposure. Gautier et al. (14) found that the change in body temperature of cats varied directly with inspired O_2 concentration. The lowering of T_{co} by hypoxia may be due to impaired thermogenesis, enhanced heat loss, or both. In cold environments, ambient hypoxia promptly reduces $\dot{V}_{O2}$ and shivering of conscious cats (13). Nonshivering thermogenesis is also inhibited during hypoxia, especially in newborn animals and small adult mammals (1, 12).

In humans, shivering in the cold has been reported to be inhibited (26), remain constant (2), or increase (40) during hypoxia. Likewise, T_{co} has been reported to either remain constant (2) or decrease (6, 40) during hypoxic cold

exposure. Studies at altitude have demonstrated elevated skin temperatures supposedly due to the increased peripheral blood flow during hypoxia (2, 6).

Hypocapnia often accompanies hypoxia because hypoxia results in hyperventilation which causes a decrease in arterial PCO_2. Some studies have demonstrated that the inhibitory effect of hypoxia on cold thermoregulatory mechanisms requires concomitant hypocapnia, and these effects of hypocapnic hypoxia can be reversed by increasing $FICO_2$ (14, 54).

Johnston et al. (24) first isolated the hypoxic stimulus from hypocapnia in humans during warm and cold exposure. By maintaining end-tidal CO_2 at baseline levels, they demonstrated that normocapnic hypoxia caused a small but significant decrease in T_{co} thresholds for peripheral vasoconstriction and shivering. Currently, there are no human studies on the effects of hypocapnic hypoxia on thermoregulatory core temperature thresholds or core cooling rates, nor are there any comparisons between hypocapnic and normocapnic hypoxia on these responses. The purpose of this study is to elucidate these factors.

Both skin and core temperatures contribute to control of thermoregulation (30, 35). Cheng et al. (5) showed that skin and core temperatures contribute linearly to control of vasoconstriction and shivering, and that the cutaneous contribution averages ≈ 20%. By using this consistent and linear relationship between skin and core temperature, Matsukawa et al. (30) developed an equation (see Methods) which compensates for the changes in skin temperature to give an equivalent (calculated) core temperature ($T_{co(calc)}$) at a single (common) designated skin temperature. This equation

can be used to compare thresholds for different thermoregulatory responses which occur at different skin temperatures.

We used this method to determine the effects of normocapnic and hypocapnic hypoxia on human thermoregulation. Six healthy male subjects took part in the study. On three separate days, subjects sat motionless in a tank of water with an initial water temperature of 37°C. Subjects were warmed until they experienced peripheral vasodilation. Water temperature was then decreased at a rate of 4°C per hour. Subjects exited the water 30 min after they reported shivering. They inspired humidified room air during the control trial. In the hypocapnic hypoxia trial, they inspired 12% O_2/balance N_2. For the normocapnic hypoxia trial, inspired air was 12% O_2/balance N_2 with CO_2 addition as required to maintain baseline end-tidal CO_2 levels. Arterial blood samples were taken during each trial to determine blood gas and pH values.

B. METHODS

Core temperature thresholds for vasoconstriction, shivering, and T_{co} cooling rates were determined during normoxia, hypocapnic hypoxia and normocapnic hypoxia.

SUBJECTS

With approval from our Faculty Human Ethics Committee, six healthy, physically active male subjects with no history of cardiovascular or respiratory disease were invited to participate in this study. Volunteers were

thoroughly acquainted with the experimental procedures, and gave their written informed consent before participating in any trials.

POWER ANALYSIS

We wanted to be able to detect a medium size difference in core temperature thresholds for vasoconstriction and shivering. The only data available for power calculations are from 2 studies by Johnston et al. (23, 24). In one study, the mean difference in shivering thresholds between hypoxia and normoxia conditions was (±SD) 0.19 ± 0.1°C (24). In the other study, the mean difference in vasoconstriction thresholds between control and alcohol conditions was 0.32 ± 0.2°C. We selected $\alpha = 0.05$ and $\beta = 0.2$ (i.e., power index = 2.8). In order to have a power of 80% in detecting a significant change in vasoconstriction and shivering thresholds, the minimum calculated group sizes were 3.06 and 2.17 respectively. In order to further increase the power of our study, we chose to study 6 subjects.

INSTRUMENTATION

During the experimental trials, subjects had many physiological variables monitored continuously including core temperature, skin temperature and heat flux at 12 sites, heart rate, oxygen consumption ($\dot{V}O_2$), EMG and peripheral finger blood flow. Blood gases (PaO_2, $PaCO_2$, pH and O_2 saturation) were determined from arterial blood samples. During instrumentation (~30 minutes), subjects were dressed in a swimming suit and sat calmly on a chair in the lab. Following completion of instrumentation, subjects were covered by a cotton blanket.

Core temperature was monitored during the experimental trials with a Mon-a-therm® esophageal thermocouple (Mallinckrodt, St. Louis, MO) inserted through a nostril to the level of the heart. Probe insertion depth was determined from sitting height according to the formula where probe length (m) = 0.479 X sitting height (m) -0.044 (31).

Cutaneous heat flux (in $W \cdot m^{-2}$) and skin temperature (in $^{\circ}C$) were measured from twelve sites by thermal flux transducers (Concept Engineering, Old Saybrook, CT). The transducers were calibrated using a Rapid-k instrument (Dynatech, Cambridge, MA) (7). Flux was defined as positive when heat traversed the skin toward the environment (46). Body surface area (BSA) was calculated [area (m^2) = $weight^{0.425}$(kg) • $height^{0.725}$(cm) • 0.007184] and the following regional percentages were assigned based on those of Hardy and DuBois (20): forehead 7%, upper chest 8.7%, abdomen 8.8%, scapula 8.7% and lower back 8.8%, anterior thigh 9.5%, posterior thigh 9.5%, shin 6.5%, calf 6.5%, dorsum of the foot 7%, dorsum of the hand 5%, and upper arm 14%. Flux values from each transducer ($W \cdot m^{-2}$) were then converted into $W \cdot region^{-1}$ [flux at region (Watts) = transducer flux ($W \cdot m^{-2}$) X body surface area (m^2) X regional percentage X 0.01].

Peripheral vessel tone, as indicated by fingertip blood flow, was assessed by using a modified Ohmeda Biox 3700 pulse oximeter (Ohmeda, Louisville, CO) with a clamp-type oximeter probe placed on the middle digit. The oximeter was modified, and a program was developed by Ohmeda to compute a perfusion index. Infrared light of two wavelengths is emitted from one side of the probe, passes through the finger tissues, and is absorbed by the detector. The intensity of transmitted signals is proportional to the

amount of blood between the emitter and detector. Fingertip blood flow is given by the difference between the maximum (systole) and minimum (diastole) signals during each cardiac cycle. This method correlates well with blood flow as measured by volume plethysmography ($r^2 = 0.88$) (36).

Before arterial cannulation, a test of ulnar artery patency was performed. Then, following a local anesthetic injection, a thin plastic tube was placed in the radial artery, at the wrist to permit blood sampling.

Oxygen consumption was determined by analysis of the O_2 and CO_2 content of the expired air. Expired air was collected in a rubber facemask with one-way valves and directed to a 10 L fluted mixing box via corrugated plastic tubing. Mixed expired air was continuously sampled from the mixing box at the rate of 500 $ml \cdot min^{-1}$ and analyzed by a Beckman OM-11 O_2 sensor (Beckman, Anaheim, CA) and at a rate of 200 $ml \cdot min^{-1}$ and analyzed by a DATEX 253 Airway Gas Monitor (Datex Instrumentarium Corp., Helsinki, Finland) for O_2 and CO_2 content, respectively. Ventilatory rate was monitored by a pneumotachometer (Hewlett Packard 47304A Flow Transducer) in the expiratory circuit proximal to the mixing box.

End-tidal CO_2 was monitored with a DATEX 253 Airway Gas Monitor (Datex Instrumentarium Corp. Helsinki Finland). Expired gas was sampled from the mouthpiece at 200 $ml \cdot min^{-1}$ and returned to the breathing circuit proximal to the pnemotachometer. The analog output was monitored on a chart recorder. Gas analyzers were calibrated against gases of known concentration prior to each experiment.

EMG activity of the masseter and trapezius muscles was monitored. This is because these two muscles were out of the water during experiments and shivering has been reported to appear first in the masseter and spreads to the muscles of the trunk and extremities (25). Disposable Pediatric ECG Electrodes (Graphic Controls, Buffalo, NY) were placed 2 cm apart on the belly of each muscle and connected to isolated probes (GRASS Instruments CO. HIP5, Quincy, MA). Signals were amplified by GRASS model P511 pre-amplifiers (band width 30Hz-3KHz), digitized on a Neuro-Corder (Model DR-890, Neuro Data Instruments, Corp., NY), and finally recorded on video cassette (SONY, SVO-140, SONY Corp., Japan) for later analysis.

Heart rate was monitored continuously for the duration of the experiment with a DC battery-operated 43100A Defibrillator/ECG monitor (Hewlett-Packard) with leads in a modified V_5 arrangement. Another Pulse Oximeter (Ohmeda, Louisville, CO) was used to monitor arterial O_2 saturation.

Analog data from the thermocouples and gas analyzers were acquired using an electrically isolated Macintosh IIci computer equipped with a NB-MIO-16L 16-channel analog-digital converter (National Instruments, Austin TX). Data were digitized asynchronously at 2 Hz, averaged over 5 seconds, and scaled using appropriate corrections. The results were averaged, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk at 30 second intervals. The process was controlled by a "virtual instrument" written using LabVIEW 2 graphical signal processing software (National Instruments, Austin TX).

PROTOCOL

3 pilot studies were completed before determination of the final experimental protocol (see Appendix I).

Subjects participated in three trials, control (normoxia), hypocapnic hypoxia and normocapnic hypoxia. In all the trials, subjects sat motionless in 37°C stirred water following a 15-30 min baseline period sitting in room air. When subjects were peripherally vasodilated, the water temperature was decreased at a rate of $4°C \cdot hr^{-1}$, until subjects fully vasoconstricted and shivered vigorously for 30 min (i.e., 2-3 hrs).

Blood samples were taken three times during the baseline period and one more time during hypoxia trials before entering the water. Further samples were then taken at the point of vasodilation and subsequently every 30 minutes during the cooling period.

Experimental Trials

1. Air Trial (Control). Subjects inspired humidified room air during the whole trial.

2. Normocapnic Hypoxia (NH) Trial. Subjects inspired humidified room air for a 15 min baseline period. They then inhaled a humidified gas mixture of 12% O_2/balance N_2. When the subjects' arterial O_2 saturation dropped to ≈ 80%, subjects entered the water. An FIO_2 of 0.12 is equivalent to being at an altitude of ~ 15,000 ft above sea level. Additional O_2 was added to the inspirate, if required, to ensure that arterial O_2 saturation did not drop

below 80%. After immersion, CO_2 was added to the inspirate to bring end-tidal CO_2 to baseline levels.

3. Hypocapnic Hypoxia (HH) Trial. This procedure was identical to the normocapnic hypoxia trial, with the exception that there was no CO_2 added to the inspirate, and end-tidal CO_2 was allowed to decrease. In both hypoxia conditions, N_2 or O_2 was added to the inspirate as required to maintain SaO_2 at 80%.

DATA ANALYSIS

In contrast to other protocols (20, 32), this protocol allows both core and skin temperatures to decrease as the integrated thermal signal to the thermoregulatory centers initiates first peripheral vasoconstriction and then shivering. Based on the study of Cheng et al. (5), vasoconstriction and shivering thresholds are a linear function of skin and core temperatures, with skin contributing 20 ± 6% and 19 ± 8% to vasoconstriction and shivering respectively. Based on these findings, Matsukawa et al. (30) used the following equation to designate a common skin temperature and convert core temperature to an equivalent value for the designated skin temperature: $T_{co(calc)} = T_{co} + (ß/1-ß)\ [T_{skin} - T_{skin(designated)}]$, where T_{co} is the actual T_{co}, T_{skin} is the actual T_{skin}, $T_{skin(designated)}$ is set at 33°C, $T_{co(calc)}$ is the T_{co} equivalent at a T_{skin} of 33°C. ß is the proportional contribution of the skin to the vasoconstriction and shivering responses (ß = 0.2). T_{skin} was designated at 33°C because this was the midrange of skin temperatures observed in the experiments (i.e., 28 ~ 37°C).

The EMG data on the video tape were digitized and captured at 1000 Hz by a Massconp Unix system. The digitized data were then full wave rectified, resampled at 50 Hz (i.e., using every 20th data point), and finally displayed (mV vs time) by "Spinal cord research centre" software. Fig. 1. shows a sample shivering threshold as determined by EMG.

Blood flow and $\dot{V}O_2$ responses were plotted against the $T_{co(calc)}$ values. Response thresholds were determined from these plots by three independent investigators blinded to trial and $T_{co(calc)}$. The threshold for vasoconstriction was defined as the point at which fingertip blood flow reached its minimum (27). The shivering thresholds were determined by the combination of $\dot{V}O_2$, EMG and self-report. Onset of shivering was determined according to the following criteria: 1) For $\dot{V}O_2$ determination, the shivering threshold was indicated by a sustained elevation in $\dot{V}O_2$ above the baseline level (32); 2) The criteria for shivering onset on the EMG plots were one of the following: a) $\geq$ 3 bursts of activity per minute for at least one minute, b) $\geq$ 1 continuous burst for at least 3 minutes, and/or c) a continuous increase in tonic activity above baseline. Synchronization of the signals from the 2 muscles was used to eliminate random activity due to motion artifact; and 3) Subjects were instructed to signal when they perceived that they were either physically shivering or detected a significant increase in overall muscle tension. The final threshold was chosen: 1) If at least two of the three methods provided the same threshold value (n=14); If the threshold determined by $\dot{V}O_2$ was absolutely clear (n=1); or 3) In 3 cases the threshold was difficult to determine by both $\dot{V}O_2$ and EMG analysis. In these cases the shivering threshold was determined by self-report (n=3).

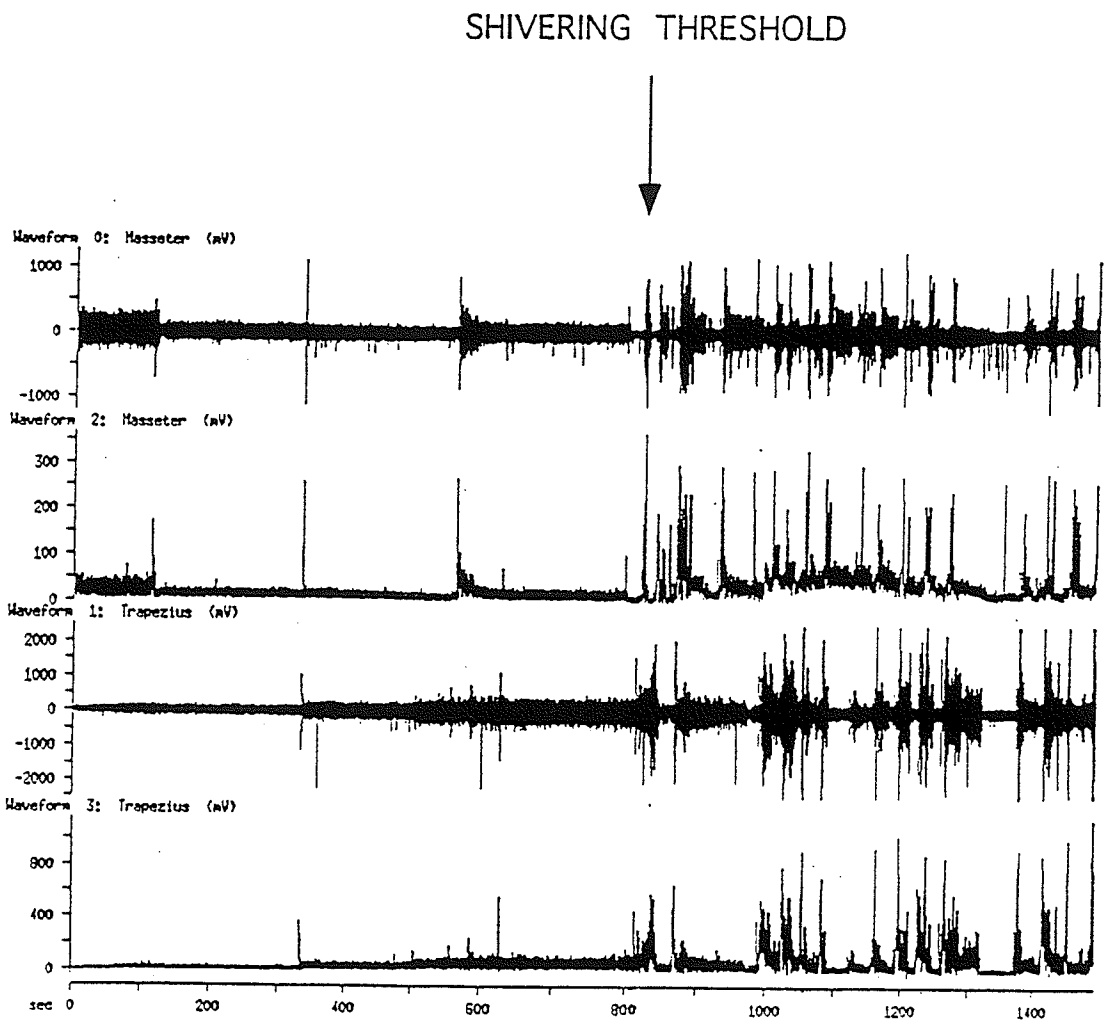

Fig. 1. EMG activities of masseter and trapezius vs time. The arrow indicates the threshold determined by EMG.

Cooling rate was determined by regression analysis of core temperature data from the time of decreasing water temperature to the onset of shivering.

One factor repeated ANOVA was used to test for significant differences in thermoregulatory response thresholds and the T_{es} cooling rates among the 3 conditions ($\alpha = 0.05$). Mean data for $\dot{V}O_2$, blood flow (PI_{avg}), heart rate and minute ventilation ($\dot{V}_E$) were plotted for the three conditions. Each of these variables was analyzed by 2 way ANOVA with a blocked repeated measures design to determine differences between or within conditions ($\alpha = 0.05$). The Fisher LSD test was used for post-hoc analysis of significant differences. Group data was presented as mean ± SD. Correlation analysis was performed between shivering thresholds determined by the three methods (i.e., EMG vs $\dot{V}O_2$, $\dot{V}O_2$ vs self-report, EMG vs self-report). Slopes and intercepts were calculated by linear regression for $\dot{V}O_2$ vs self-report , EMG vs self-report and $\dot{V}O_2$ vs EMG.

C. RESULTS

CORE TEMPERATURE AND SKIN TEMPERATURE RESPONSES

The patterns of T_{co} change in all three trials were the same (Fig. 2). T_{co} decreased about 0.2-0.3°C from baseline (~36.9°C) as soon as subjects entered the 37°C water. The warm water initiated peripheral vasodilation and a redistribution of heat from the core to the periphery. T_{co} subsequently increased because the warm water made subjects vasodilate and warmed peripheral tissues. T_{co} decreased again, when water temperature was lowered, and stopped declining (control) or increased (HH and NH) after peripheral blood flow started to decrease and usually before onset of shivering. T_{co} increased above baseline during the vasodilation period in 37°C water for all subjects except one. The mean elevations of T_{co} were 0.21±0.24, 0.25±0.25 and 0.25±0.27°C in control, HH and NH trials, respectively. When cooling rates were calculated from onset of core cooling to onset of shivering, the mean T_{co} cooling rates during HH and NH trials (0.48±0.16 and 0.51±0.21°C·hr^{-1}) were 181% and 196% greater ($P<0.01$) than during the control trial (0.17±0.12°C·hr^{-1}). However, this method of calculation underestimated the cooling during some of the control trials because, in this condition, T_{co} leveled out for a considerable period (30-50 min) before shivering onset. When T_{co} cooling rate was calculated only over the first 40 min of core cooling (a period in which all subjects were cooling in all trials), the cooling rates during HH and NH trials (0.59±0.15 and 0.61±0.20 °C·hr^{-1}) were only 49% and 54% greater ($P<0.05$) than during control (0.39±0.17°C·hr^{-1}).

Skin temperatures were ≈ 31.6°C during baseline in the three conditions. In the 37°C water, skin temperatures rose to 35.4-36.6°C and

decreased when water temperature was lowered (Fig. 3). The average skin temperature values do not include the foot temperature because the thermocouple on the foot was broken during some of the experiments. The final average skin temperatures before cooling were about 0.2-0.3°C higher during HH and NH trials than during the control trial although the water temperatures (Fig. 4) were the same. Because the experimental protocol required subjects to keep their arms out of the water for measurement purposes, the differences in average skin temperature were mainly seen in the skin which was out of the water (Fig. 5). The temperatures of the skin under the water were clamped at water temperature.

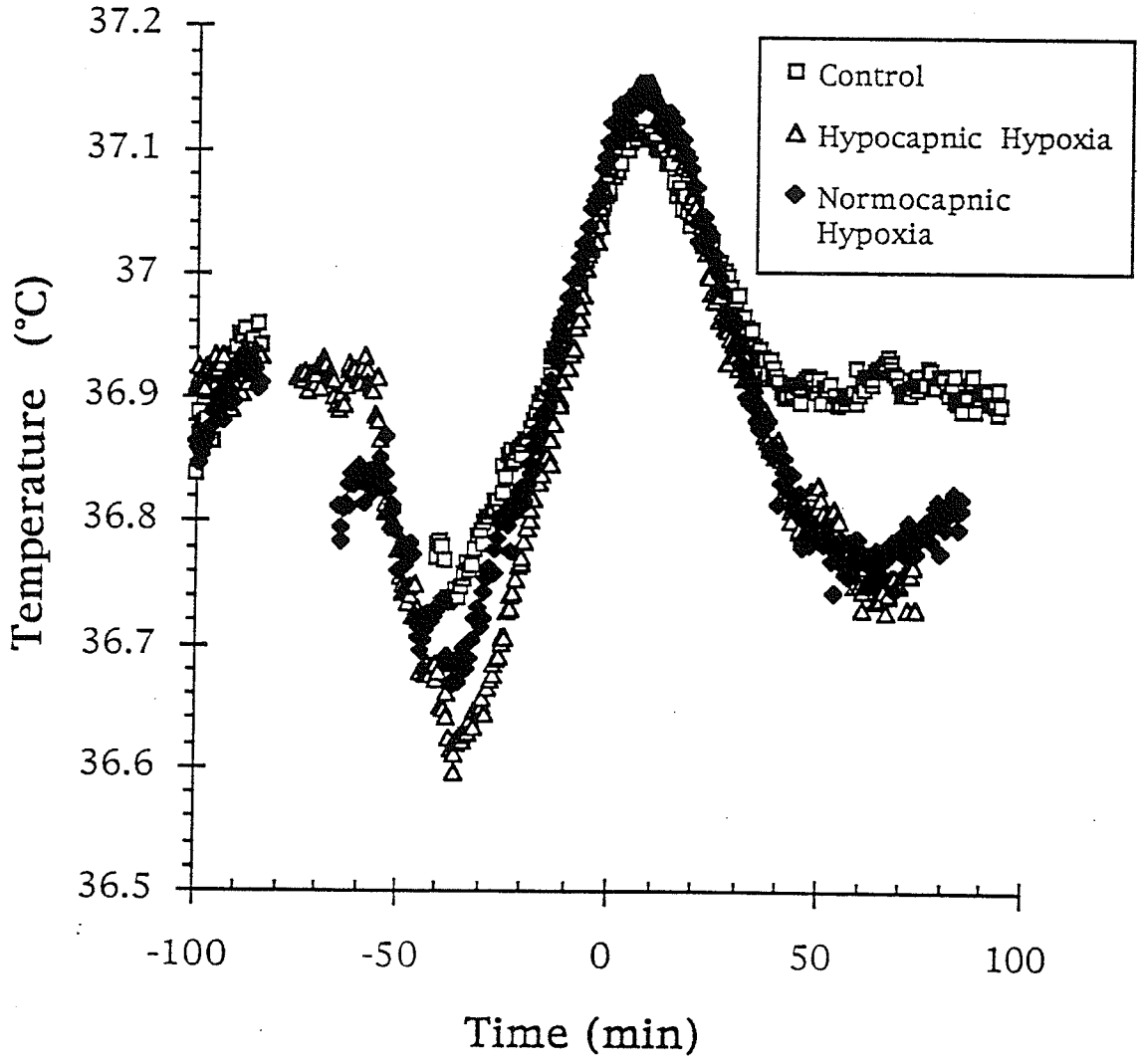

Fig. 2. Average esophageal temperatures for three trials (n=6). Time 0 = the start of water cooling. Minutes -100 to -85 represent baseline (air) periods.

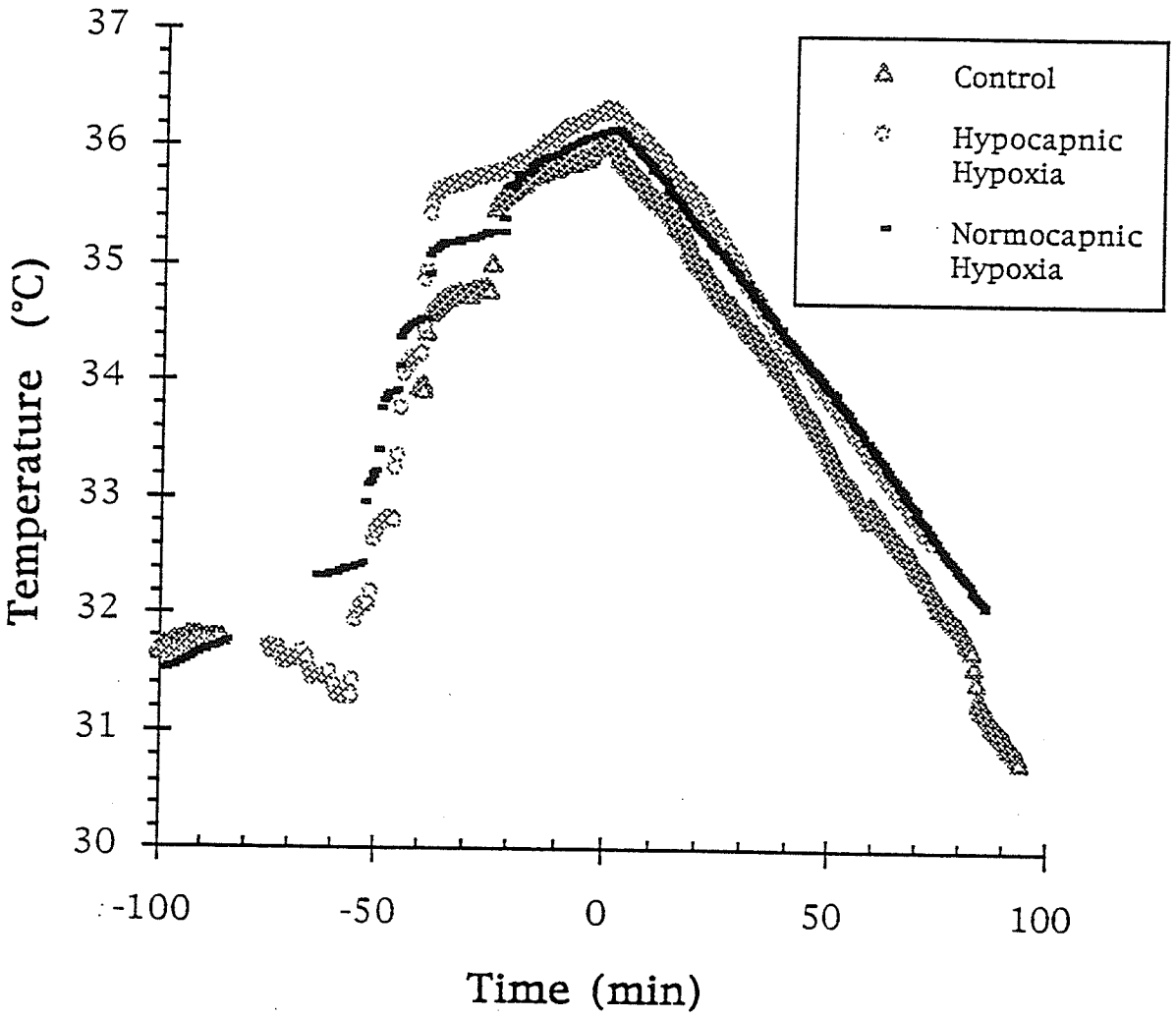

Fig. 3. Average skin temperatures for three trials (n=6). Time 0 = the start of water cooling. Minutes -100 to -85 represent baseline (air) periods.

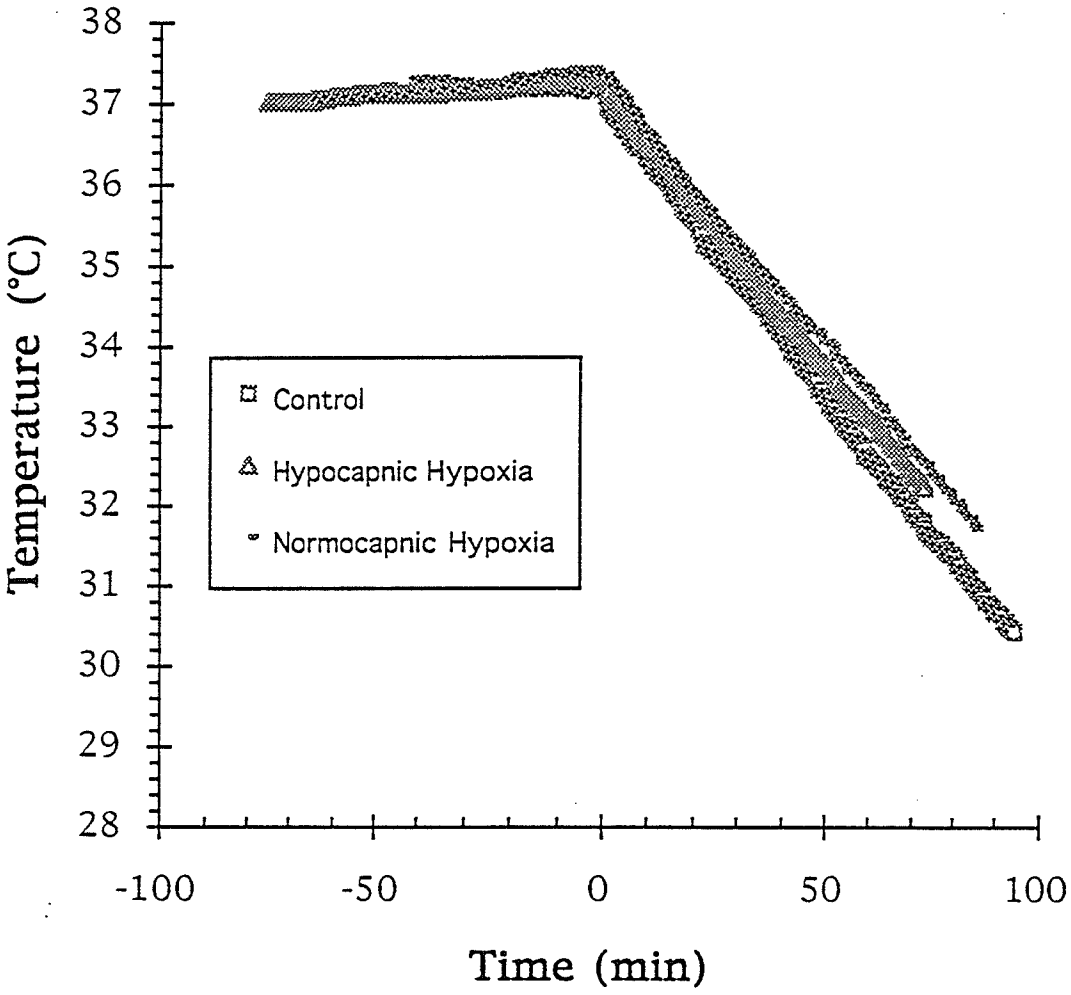

Fig. 4. Average water temperatures for three trials (n=6). Time 0 = the start of water cooling.

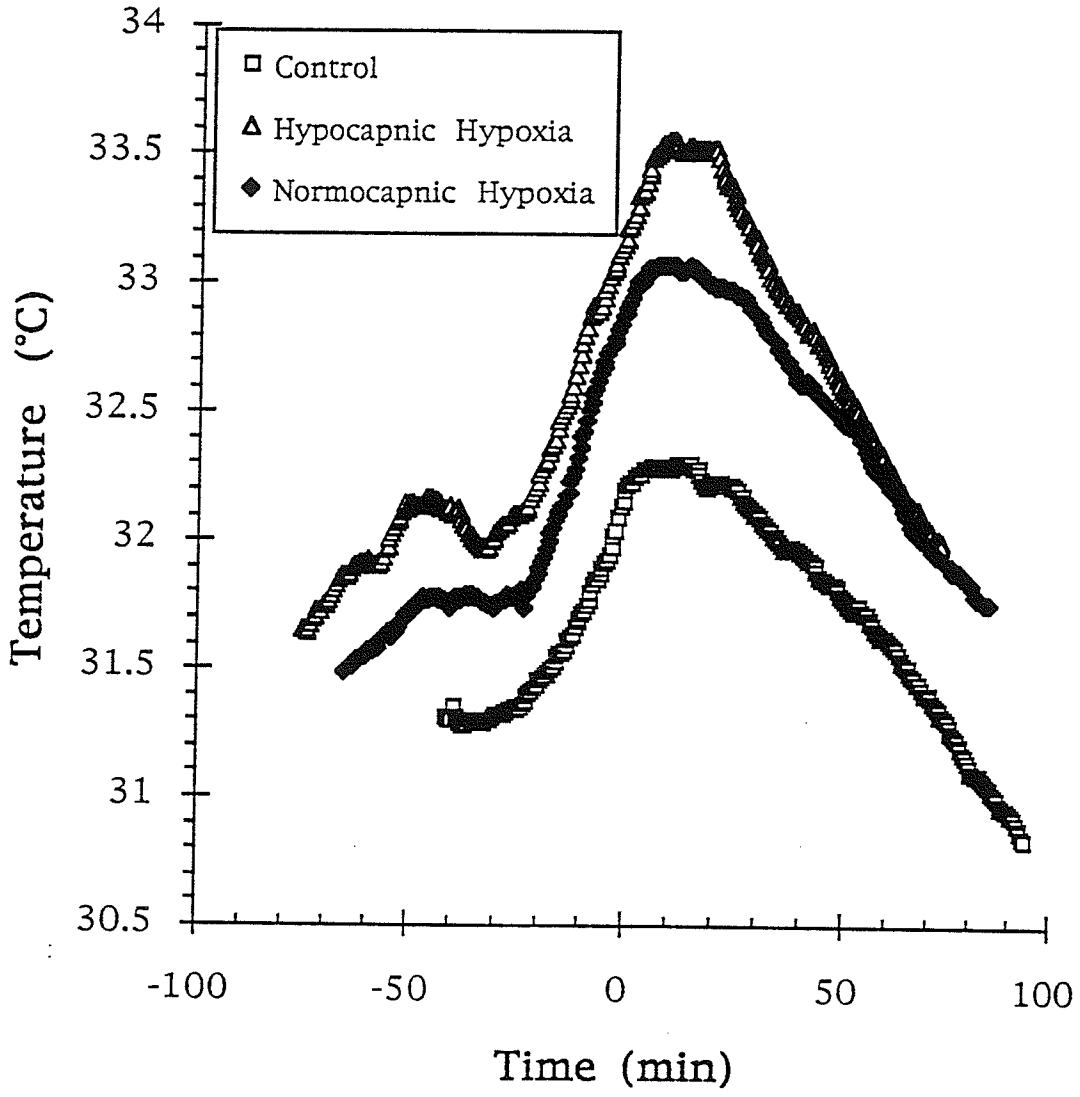

Fig.5. Average skin temperatures for the sites which were out of water (head, arm and hand) for three trials (n=6). Time 0 = the start of water cooling.

$\dot{V}_{O2}$, HEAT FLUX AND BLOOD FLOW

The experimental trials were divided into five periods: baseline (air) (breathing room air in all trials before entering the water); baseline (hypoxia) (breathing hypoxic gas mixtures in HH and NH trials before entering the water); the vasodilation period (when T_{water} remained at 37°C); the vasoconstriction period (from the initiation of water cooling to the onset of shivering); and the shivering period (from the onset of shivering until the end of the experiment). (Average values for each period are presented in Table 1).

$\dot{V}_{O2}$ was similar for all three trials during the baseline (air) period (Table 1). During control and HH trials, $\dot{V}_{O2}$ did not significantly increase until the shivering period. In the NH trial $\dot{V}_{O2}$, during vasodilation and vasoconstriction periods, was significantly greater than baseline (air and/or hypoxia), and further significantly increased in the shivering period. In all periods of immersion, $\dot{V}_{O2}$ in control and NH conditions was significantly greater than HH condition. As well, $\dot{V}_{O2}$ in the shivering period was greater in NH than both control and HH trials. In all trials $\dot{V}_{O2}$ was much higher during shivering than the other periods, increasing by 26.8%, 42.4% and 60.7% compared with the $\dot{V}_{O2}$ in the vasoconstriction period in control, HH and NH trials, respectively ($P<0.05$).

Table 1. Mean Oxygen Consumption in Control, HH, NH trials (Mean±SD)

Trials	Baseline (air) ($ml \cdot min^{-1}$)	Baseline (hypoxia) ($ml \cdot min^{-1}$)	Vasodilation ($ml \cdot min^{-1}$)	Vasoconstriction ($ml \cdot min^{-1}$)	Shivering ($ml \cdot min^{-1}$)
CONT	276±66		306±71†	312±65†	396±93**†
HH	245±54	264±67	242±47	241±52	344±83**
NH	251±15	297±62	321±68*†	328±70*†	527±200**†Δ

** significantly higher than all other periods ($P<0.05$)

* significantly greater than baseline period ($P<0.05$)

Δ significantly higher than control trial ($P<0.05$)

† significantly higher than HH trial ($P<0.05$)

There were no significant differences in heat flux in the baseline (air) periods among the three trials (i.e., 71.2±8.3W in Control, 73.8±5.5W in HH and 68.8±5.7W in NH). During the vasodilation period, heat flux (i.e., heat loss) in HH (-16.0±11.1W) and NH (-21.5±6.6W) trials was significantly less than the control trial (-3.7±7.9W) ($P<0.05$). Heat flux was significantly higher during the shivering period than the vasoconstriction period ($P<0.05$) in all three trials. In the HH trial, there was a trend towards higher whole body heat flux (by 8-10W) in the latter part of the vasoconstriction period (i.e., 20-40 min after the start of water cooling) although this was not significant.

At the initiation of water cooling, finger tip blood flow (as indicated by the perfusion index) was higher in the NH (~3.4 units) and control (~3.2 units) trials than the HH (~2.8 units) trial. Thereafter, there were no significant intertrial differences in blood flow during water cooling (Fig. 6).

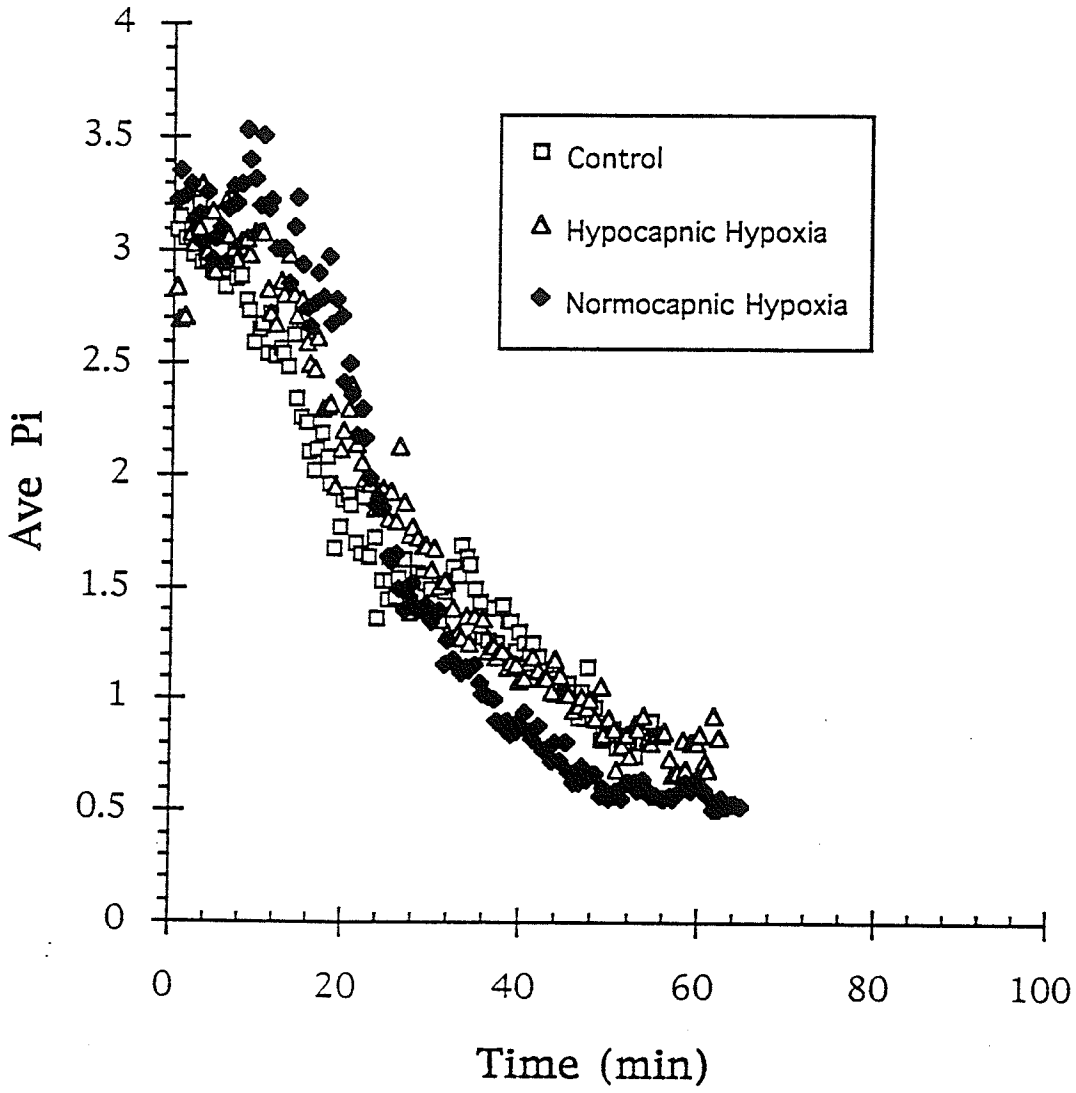

Fig. 6. Fingertip blood flow, as indicated by a pulse oximeter-based perfusion index (Pi), for three trials (n=6). Time 0 = the start of water cooling.

VENTILATION AND HEART RATE

We calculated average $\dot{V}_E$ over the same periods as for $\dot{V}_{O2}$. $\dot{V}_E$ was similar for all three trials during the baseline (air) period (Fig. 7). During the shivering period, $\dot{V}_E$ was significantly higher than all the other periods in HH and NH trials ($P<0.05$). $\dot{V}_E$ during the vasoconstriction (13.5±1.1 $L \cdot min^{-1}$) and shivering (21.7±7.0 $L \cdot min^{-1}$) periods in the NH trial was significantly higher than the $\dot{V}_E$ during comparable periods in control (9.9±2.4 $L \cdot min^{-1}$, and 11.2±2.8 $L \cdot min^{-1}$) and HH (9.3±3.0 $L \cdot min^{-1}$, and 12.6±4.6 $L \cdot min^{-1}$) trials. During the vasoconstriction period, $\dot{V}_E$ (13.5± 1.1 $L \cdot min^{-1}$) in the NH trial was also higher than the baseline (air) period .

Heart rate increased significantly and to the same degree in both baseline hypoxia conditions (Table 2). Following immersion in warm water, heart rate increased above baseline by the end of the warming period (i.e., end vasodilation), decreased back to (HH and NH) or below baseline (Control) at the end of the vasoconstriction period and returned to baseline (Control) or above baseline (HH and NH) by the end of cooling (i.e., end of shivering). Throughout immersion, heart rates in the HH and NH conditions were significantly higher than during Control, but not different from each other.

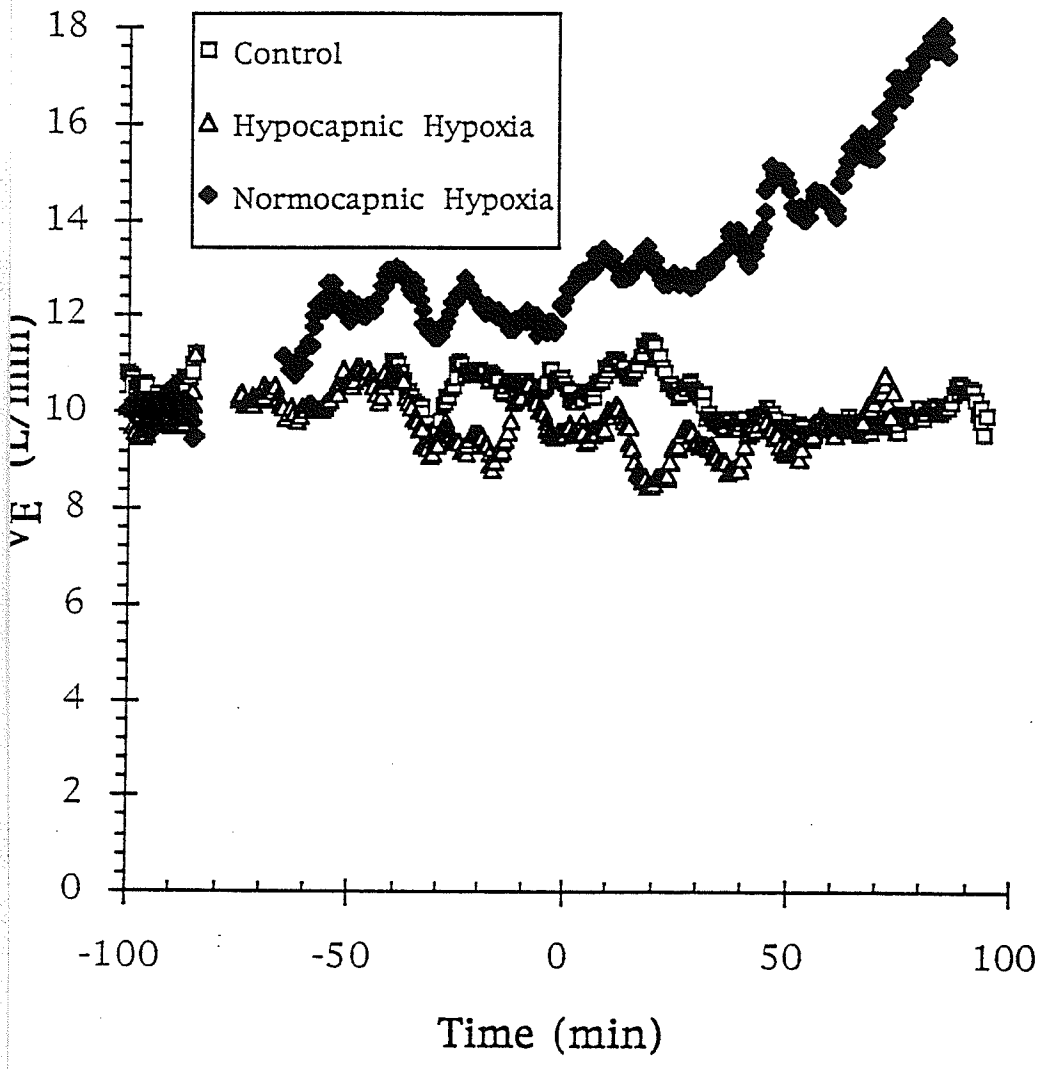

Fig. 7. Mean expired minute ventilation ($\dot{V}_E$) for three trials (n=6). Time 0 = the start of water cooling. Minutes -100 to -85 represent baseline (air) periods. The $\dot{V}_E$ during the normocapnic hypoxia trial increased a lot during the cooling period because of the addition of CO_2.

Table 2. Heart Rate in Control, HH and NH trials (Mean±SD)

Trials	Baseline (air) (beats·min^{-1})	Baseline (hypoxia) (beats·min^{-1})	End of vasodilation period (beats·min^{-1})	End of vasoconstriction period (beats·min^{-1})	End of shivering period (beats·min^{-1})
CONT	69.3±7.6		79.2±9.7*	56.3±9.6*	71.2±7.5
HH	68.7±13.4	78.2±11.3*	92.0±11.7*$^{\Delta}$	67.2±13.2$^{\Delta}$	83.5±10.4*$^{\Delta}$
NH	66.5±10.2	75.3±9.3*	86.8±7.9*$^{\Delta}$	68.8±13.2$^{\Delta}$	81.3±9.5*$^{\Delta}$

* significantly different from baseline air period ($P<0.01$).

Δ significantly different from control trial ($P<0.01$).

BLOOD GAS ANALYSIS AND END-TIDAL CO_2

Although blood samples were taken from all six subjects, values from two of the subjects were not used in the analysis. For each blood sample, the arterial PCO_2 ($PaCO_2$) value was used in the alveolar gas equation (55) to calculate the alveolar PO_2 (P_AO_2). The arterial PO_2 (PaO_2) values were then compared to the P_AO_2 values to determine if the blood gas values were reasonable. For one subject the PaO_2 values for some samples were 15 to 33 mmHg greater than the calculated P_AO_2. This is not possible because of the (alveoli-to-blood) O_2 gradients within the lung. In the second subject, the PaO_2 values were consistently 15 to 25 mmHg less than the calculated P_AO_2. These differences were in excess of the predicted alveolar-arterial gradient for O_2 in young healthy subjects (i.e., 6-10 mmHg) (54). Therefore, the results of only 4 subjects were used.

Table 3 shows the average PaO_2, $PaCO_2$, arterial saturation of oxygen (SaO_2) and pH in the three conditions. The SaO_2 was $\approx$ 98% during the baseline (air) period in all three conditions (Fig. 8), and decreased to 82 and 83% during the baseline (hypoxia) period in the HH and NH conditions, respectively. SaO_2 did not change with time during immersion in any condition and there was no difference between the two hypoxia conditions. PaO_2 values followed the same pattern as SaO_2 (Fig. 9). PaO_2 was between 100-105 mmHg during the baseline (air) period in all three trials, and dropped to between 44 and 48 mmHg from the baseline (hypoxia) period until the end of the experiment in both hypoxia trials.

Table 3. PaO_2, $PaCO_2$, SaO_2 and pH in Control, HH and NH trials (Mean±SD)

		CONT	HH	NH
SaO2	Baseline	98.0±0.0	98.0±0.0	97.8±0.5
	Hypoxia		82.0±0.8*	83.3±3.0*
	Vasodilation	97.5±0.6	84.8±4.3*Δ	84.3±4.3*Δ
	Cooling	97.8±0.5	82.8±2.2*Δ	83.3±4.0*Δ
PaO2	Baseline	104.9±4.3	100.3±5.5	101.1±7.1
	Hypoxia		44.0±2.8*	46.5±4.1*
	Vasodilation	101.8±8.3	45.8±5.4*Δ	48.0±5.5*Δ
	Cooling	100.9±4.3	44.0±1.6*Δ	46.2±5.5*Δ
PaCO2	Baseline	39.7±2.3	38.8±4.3	40.4±3.7
	Hypoxia		34.3±1.5*	33.3±3.4*
	Vasodilation	40.3±4.6	31.0±7.7*Δ	34.5±5.1*Δ†
	Cooling	37.1±2.7	30.7±3.3*Δ	34.1±4.1*Δ†
pH	Baseline	7.39±0.02	7.39±0.03	7.38±0.01
	Hypoxia		7.43±0.03*Δ	7.43±0.03*Δ
	Vasodilation	7.40±0.02	7.48±0.05*Δ	7.43±0.02*Δ†
	Cooling	7.42±0.01*	7.49±0.02*Δ	7.44±0.02*†

* significantly different from the baseline period ($P<0.01$)
Δ significantly different from the control trial ($P<0.01$)
† significantly different from the HH trial ($P<0.01$)

Fig. 10 shows mean end-tidal CO_2 values in the three trials. In the third experiment of this study, the CO_2 analyzer broken down completely and was not used. Upon reviewing the end-tidal CO_2 data from the first two experiments, it was decided that this data was likely inaccurate. Therefore end-tidal CO_2 data from these 3 trials (one from each condition) were not used in the analysis. The CO_2 analyzer was replaced for the remainder of the trials. Subjects breathed hypoxic air during the HH and NH trials following 15 min of baseline (air) measurements. After immersion CO_2 was added to the inspirate to bring end-tidal CO_2 to the baseline level in the NH trial.

End-tidal CO_2 was averaged for baseline (air), baseline (hypoxia), the vasoconstriction period (from the initiation of water cooling to the onset of shivering) and the shivering period (from the onset of shivering until the end of experiment).

End-tidal CO_2 was similar for all three trials during the baseline (air) period (Table 4). During the HH trial, end-tidal CO_2 was significantly decreased from baseline (hypoxia) until the end of the experiment compared with baseline (air) ($p<0.05$). In the NH trial, although end-tidal CO_2 decreased during the baseline (hypoxia) period, it returned to the baseline (air) level in the vasoconstriction and shivering periods. There were significant differences between the HH and NH trials in the periods of vasoconstriction and shivering.

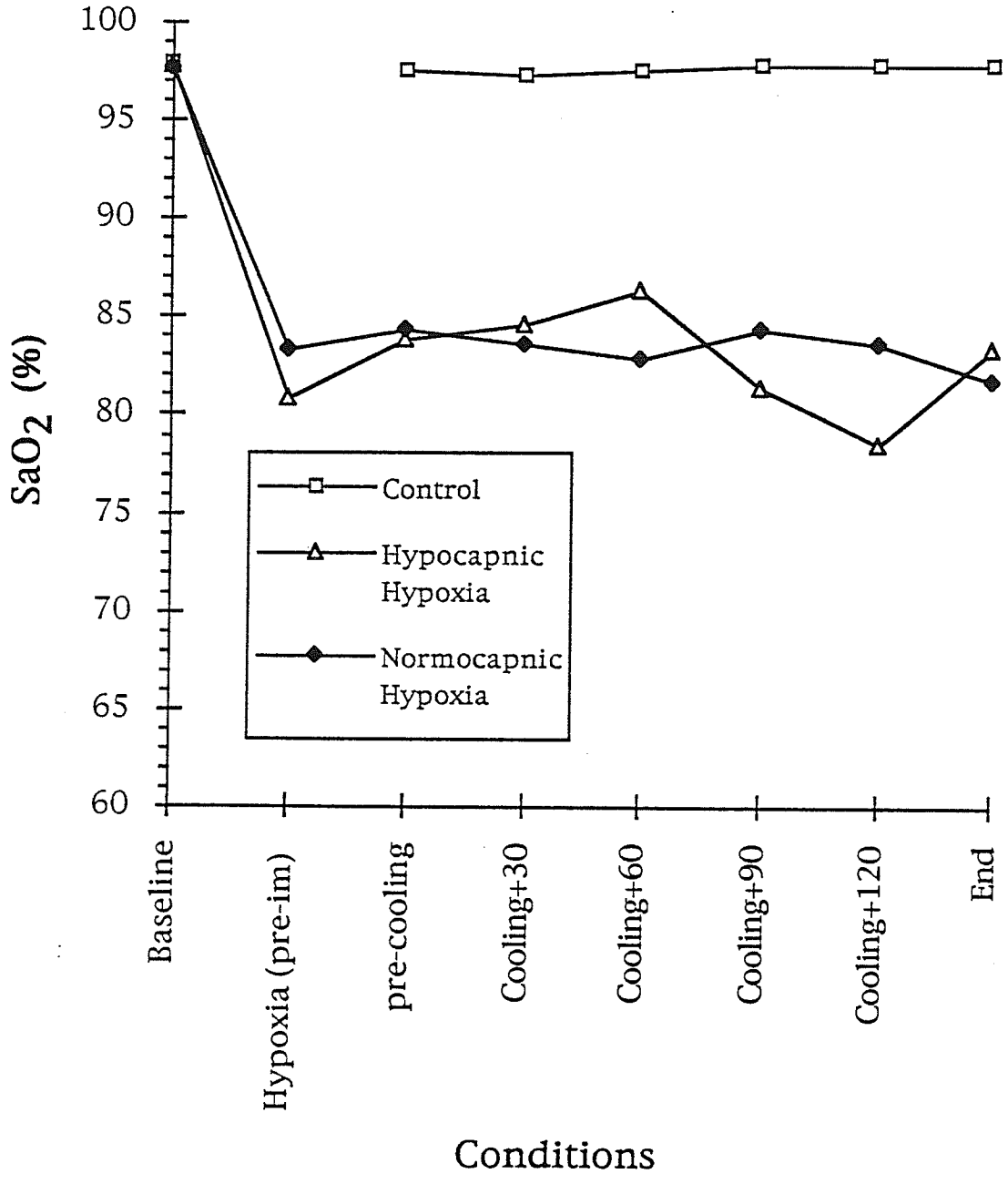

Fig. 8. Average arterial oxygen saturation (SaO_2) for three trials (n=4).

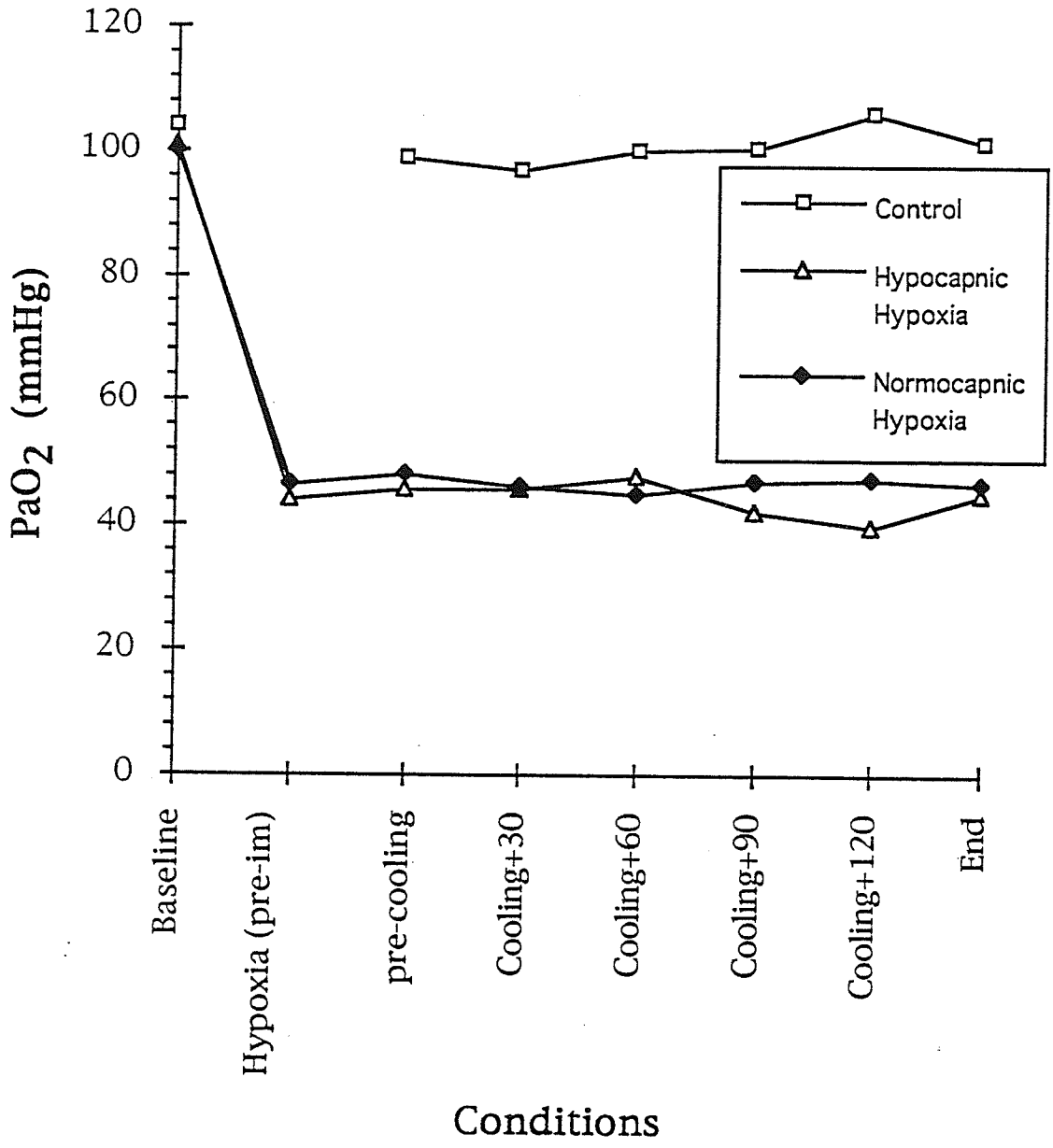

Fig. 9. Average arterial oxygen tension (PaO_2) for three trials (n=4).

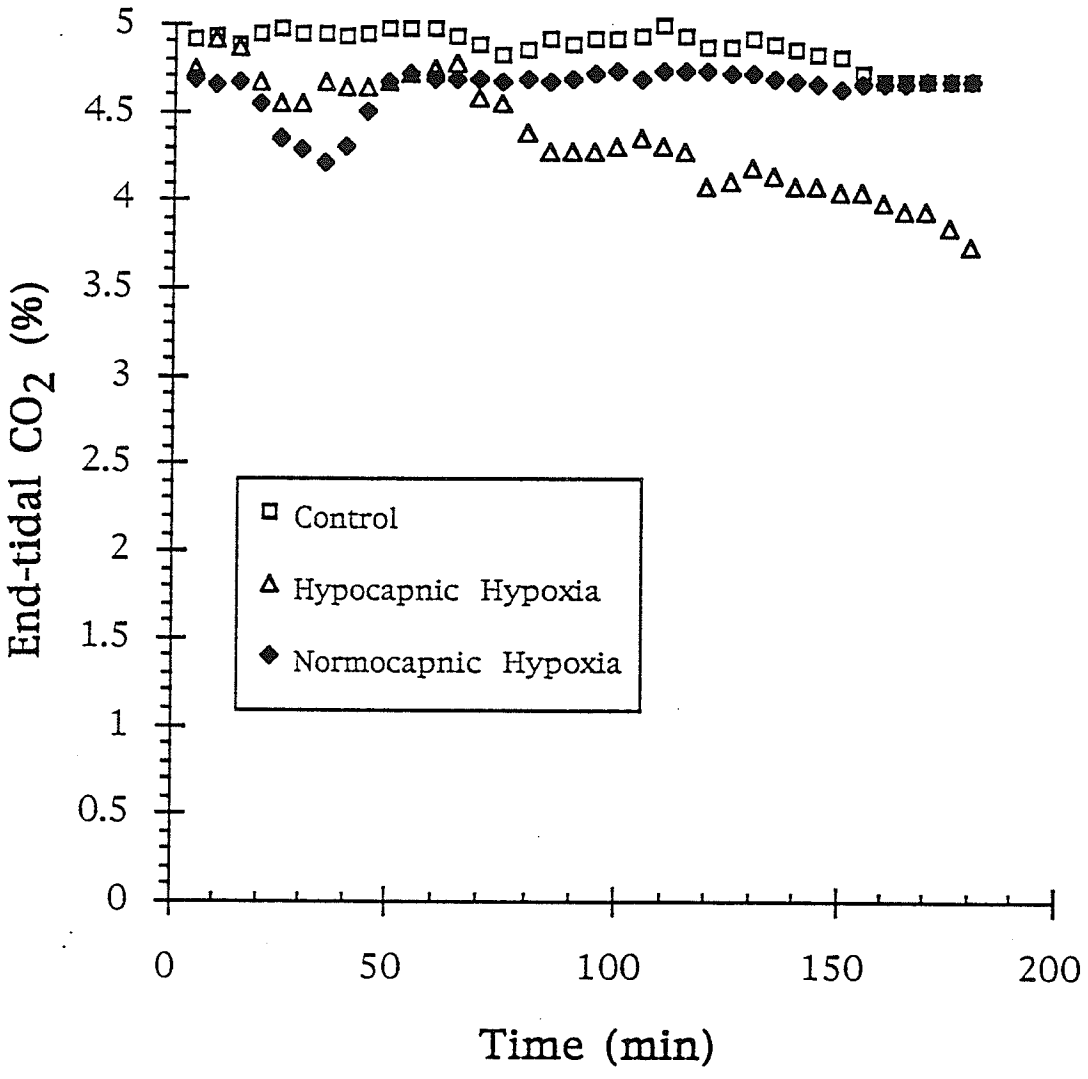

Fig. 10. Average End-tidal CO_2 for three trials (n=5).

Table 4. Mean End-Tidal CO2 in Control, HH, NH trials (Mean±SD)

Trials	Baseline (air) (%)	Baseline (hypoxia) (%)	Vasoconstriction (%)	Shivering (%)
Control	4.9±0.4		4.9±0.6$^{\Delta}$	4.7±0.2$^{\Delta}$
HH	4.7±0.5	4.2±0.7*	4.2±0.7*	3.9±0.4*
NH	4.8±0.6	4.4±0.7*	4.9±0.5$^{\Delta}$	4.8±0.5$^{\Delta}$

* significantly different from baseline (air) ($p<0.05$)

$^{\Delta}$ significantly different from HH trial ($p<0.05$)

During baseline (air), $PaCO_2$ was 39.7±2.3, 38.8±4.3 and 40.4±3.7 mmHg in Control, HH and NH trials, respectively (Fig. 11, Table 3). During Control, $PaCO_2$ remained at baseline levels until 120 min of cooling had elapsed. In the HH trial, $PaCO_2$ significantly decreased to ≈ 31 mmHg following the inspiration of hypoxia gas mixture ($p<0.05$). During hypoxia in the NH trial, $PaCO_2$ significantly fell to a stable level (≈ 34 mmHg) intermediate between Control and HH values. During immersion in the NH trial, end-tidal CO_2 was maintained at baseline values. As stated in the Methods, CO_2 was added to the inspirate during the NH trial in an effort to maintain normocapnic levels of $PaCO_2$. CO_2 was initially added at an average rate of ≈ 100 ml·min^{-1}. The added respiratory stimulus increased $\dot{V}_E$, therefore resulting in a hyperventilatory decrease in end-tidal CO_2. This set up a cycle requiring gradual but continual increase in the rate of CO_2 addition to an average rate of 420 ml·min^{-1}. The resulting hyperventilation (i.e., 21.7±7.0 l·min^{-1} in NH compared to 12.6±4.6 l·min^{-1} in HH) is likely responsible for the $PaCO_2$ values in NH being lower during hypoxia (≈ 34 mmHg) than baseline (40 mmHg).

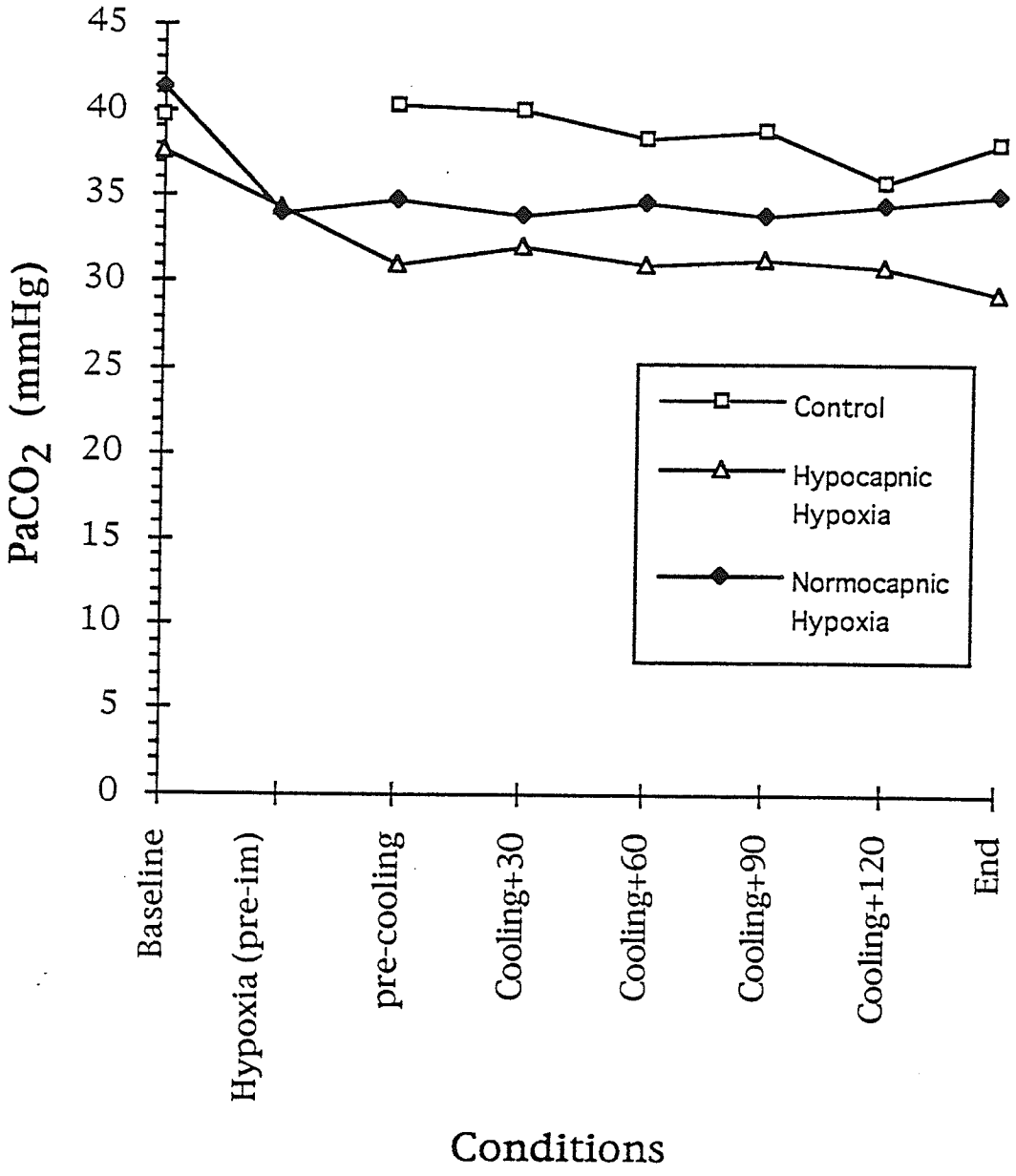

Fig. 11. Average arterial carbon dioxide tension ($PaCO_2$) for three trials (n=4).

THERMOREGULATORY RESPONSE THRESHOLDS

Fig. 12. shows the shivering thresholds (determined by $\dot{V}O_2$ and EMG analysis) plotted against the shivering threshold determined by self report. Thresholds determined by three methods were significantly ($p<0.05$) correlated to each other: self report vs $\dot{V}O_2$, $r^2=0.93$; self report vs EMG, $r^2=0.97$; and $\dot{V}O_2$ vs EMG, $r^2=0.94$. The equation for the regression line for $\dot{V}O_2$ (y) vs self-report (x) was $y=0.89x+4.0$, for EMG (y) vs self-report (x) was $y=0.93x+2.8$ and for $\dot{V}O_2$ (y) vs EMG (x) was $y=0.95x+1.8$.

There were no significant differences in calculated vasoconstriction thresholds for the three conditions. Although the actual core temperatures at the shivering threshold were lower in the hypoxia conditions, the corrected values were significantly higher ($p<0.05$) than control, but not different from each other (Table 5).

Table 5. Mean skin and core temperatures, and calculated thresholds (with a designated skin temperature of 33°C) (Mean±SD)

		Control	HH	NH
Vasoconstriction	Mean Skin (°C)	32.75 ± 1.57	33.01 ± 0.99	33.26 ± 1.41
	Core (°C)	36.85 ± 0.12	36.73 ± 0.17*	36.70± 0.20*
	Calculated Threshold (°C)	36.79 ± 0.41	36.73 ± 0.36	36.76 ± 0.45
Shivering	Mean Skin (°C)	31.09 ± 1.27	32.49 ± 0.90*	32.93 ± 0.82*
	Core (°C)	36.84 ± 0.11	36.68 ± 0.19*	36.67 ± 0.18*
	Calculated Threshold (°C)	36.36 ± 0.39	36.56 ± 0.36*	36.65 ± 0.32*

* significantly different from control. P<0.05

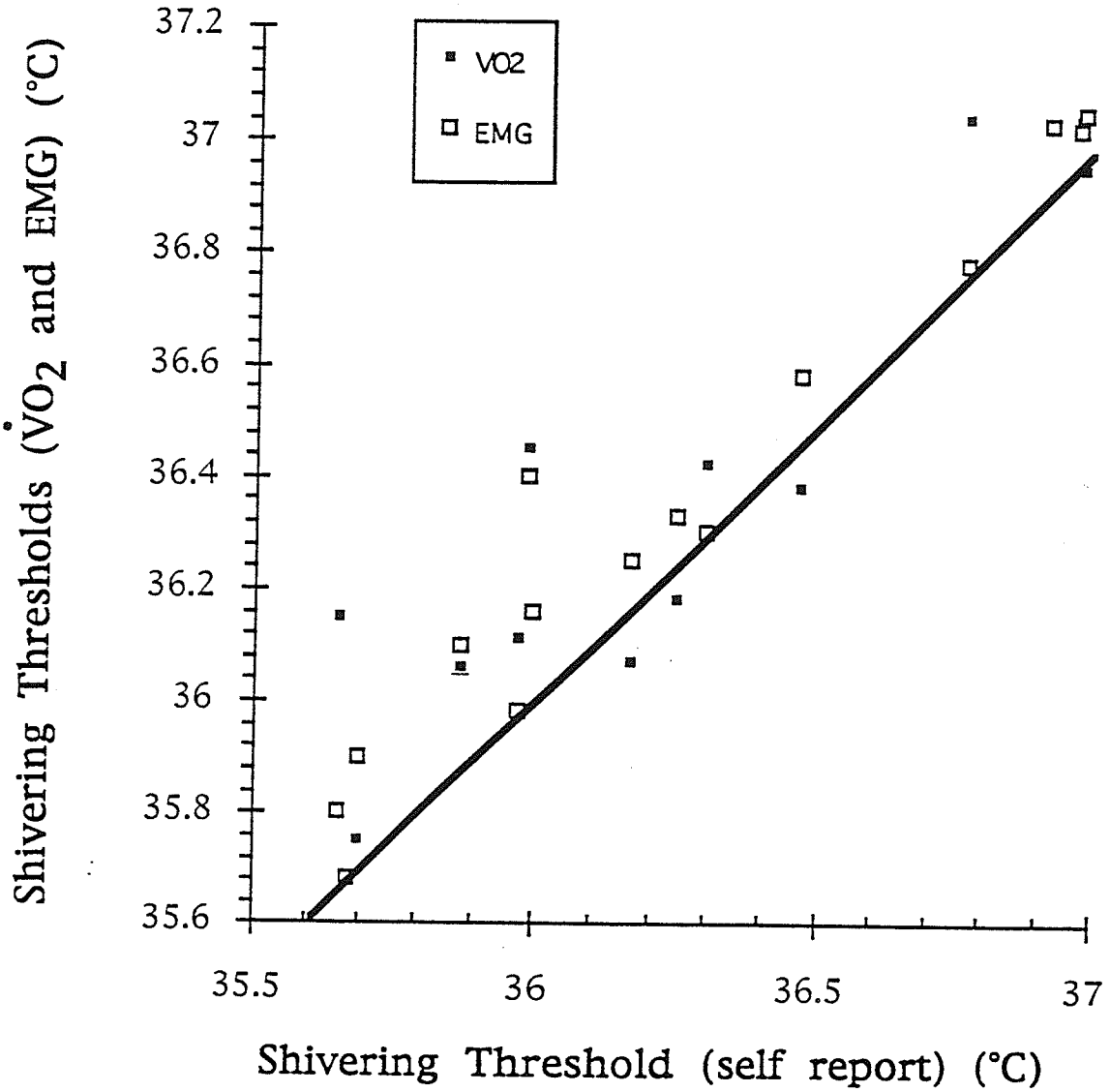

Fig. 12. A comparison of shivering thresholds as determined by $\dot{V}O2$, EMG and self report. Solid line represents the line of identity.

D. DISCUSSION

This is the first study to examine the effects of both hypocapnic hypoxia and normocapnic hypoxia on core cooling rates and cold thermoregulatory response thresholds in humans exposed to a mild cold stress by immersion in water which was gradually cooled at a rate of $4°C \cdot hr^{-1}$ from 37 to ≈ 27°C. Under these conditions, the core temperature cooling rates in the HH and NH trials were significantly increased 49% and 54% compared with control trial during the first 40 min of cooling. This result is in agreement with many previous studies showing T_{co} depression in hypoxic laboratory animals and humans (6, 13, 16, 24, 40).

Hypothermia is a normal and adaptive response to hypoxia in both ectotherms and endotherms (56). In 1936, Gellhorn and Janus (16) demonstrated that a significant decrease in barometric pressure (460-225mmHg) (i.e., reduction of the partial pressure of O_2) results in a lowering of core temperature in guinea pigs. A similar decrease in core temperature (~1°C) was demonstrated in men exposed to 10% O_2 at environmental temperatures of 11 to 22°C (26). Cipriano and Goldman (6) showed a hypoxic depression in rectal temperature of ~0.3°C at an altitude of 5,000 m and 0.2°C at 2,500 m after exposure to 15°C air for 120 min. In laboratory studies, normocapnic hypoxia causes the core cooling rate in humans to increase by 33% compared with normoxia (24).

It is well established that heat loss is increased in hypoxic animals and humans due to peripheral vasodilation (2, 6, 26, 33). Kottke et al. (26) found

that when people breathe 10% O_2, skin temperature increases, resulting in increased heat loss. Another study showed that in men at an altitude of 5,000 m, skin temperature was significantly higher by 2°C than that recorded during a comparable sea-level exposure (6). Vogel et al. (52) demonstrated a partitioning of blood flow away from the splanchnic beds and toward the skeletal muscles during moderate hypoxia. The conclusion from these studies is that the blood flow to the peripheral or body shell increases during hypoxia and results in an increased skin temperature. The results from our study support this conclusion.

Although the temperature of skin below the water surface was almost the same in the three conditions, the temperature of skin which was out of water was higher in HH and NH conditions than in the control condition (Fig. 5). This suggests that the skin blood flow in HH and NH trials was higher than the skin blood flow in the control trial, which would cause more heat dissipation from skin in HH and NH trials. Although the average heat flux during the latter half of the vasoconstriction period and the shivering period was about 8 Watts higher than in the control trial, this difference was not significant.

Shivering is a defense reaction to cold stress found in homeothermic animals. $\dot{V}O_2$ is often used to quantify shivering (25). In our experiment, the average $\dot{V}O_2$ during the shivering period increased 27.75%, 42.51% and 62.0% compared with the vasoconstriction period in the control, HH and NH conditions, respectively. During the HH condition, $\dot{V}O_2$ was lower than that in the control and NH conditions (Table 1). Similar results were found in resting people by Kottke (26) and Robinson (40). Since shivering is under the control

of the central nervous system, it may be expected that shivering will be inhibited in the conditions of moderate hypoxia. Such a depressive effect might occur through a direct effect on hypothalamic neurons. Hypoxia has been shown to increase the activity of warm sensitive neurons in the preoptic hypothalamus of anesthetized rats (50). The resulting overestimation of the integrated thermal signal in the hypothalamus, at a given T_{es} and T_{sk} combination, could result in a decrease in the threshold for shivering (see below).

In our study the highest $\dot{V}_{O2}$ was found in NH trial before and during shivering. This is not surprising for the following reasons. First, hypocapnia causes cerebral vasoconstriction therefore reducing O_2 delivery to the brain (47). Normocapnia may blunt this effect. On the other hand, the pH (7.44 ±0.02) during the cooling in NH trial was significantly ($P<0.05$) lower than in the HH trial (7.49±0.04) ($P<0.01$). The lower pH in the NH trial would shift the oxygen dissociation curve to the right and increase the delivery of oxygen to the tissues at a given partial pressure of O_2 (49). Second, CO_2 increases ventilation. During the NH trial, we added CO_2 at an average of 100 - 420 $ml \cdot min^{-1}$ to keep the end-tidal CO_2 constant. The ventilation was significantly higher in NH trial than that in control and HH trials during the periods of vasoconstriction and shivering. The increased energy expenditure of respiratory muscles may be responsible for the increase in $\dot{V}_{O2}$.

The increase in heart rate during hypoxia in this study follows the same pattern as many previous studies (22, 40, 44, 45). One explanation for this may be an increase of the sympathetic nervous activity. Rowell et al. (43) found that when hypoxia was imposed during exercise, plasma norepinephrine

concentration increased. For resting people even severe hypoxemia causes little or no increase in sympathetic nervous activity. This may be because the central effector mechanisms that increase sympathetic nervous activity are blunted by severe hypoxemia (42). When no additional stress is present, the lack of increase in plasma norepinephrine during hypoxemia indicates that either neuronal reuptake of the transmitter is facilitated or its release is inhibited (44). Another reason may be that hypoxemia in resting subjects raises heart rate to approximately 100 beats·min^{-1} by vagal withdrawal (41). Hypoxia induces a compensatory tachycardia that increases cardiac output and improves oxygen delivery (51).

Although many studies show that hypoxia increases ventilation (4, 8, 9, 28, 37), this was only seen in the NH trial in our study. There was no significant difference between HH and control trials prior to onset of shivering. Our subjects were resting during the whole experiment. The ventilatory response to mild hypocapnic hypoxia has been shown to be minimal at rest (18, 40). Another study (8) showed that ventilatory response to normocapnic hypoxia in adults exhibited some biphasic features. During 20-25 min of normocapnic hypoxia, ventilation increases initially and then declines to a plateau value that still remains higher than the control levels. We did not observe a similar phenomenon in our study. Although during the HH trial in our experiment, average ventilation increased from 9.8±2.8 during baseline (air) to 10.3±2.8 L·min^{-1} after 10 min hypocapnic hypoxia and then decreased to 9.2±3.0 L·min^{-1} in the vasoconstriction period, this change was not significant. This may be because different protocols were used in these two studies. We used continuous hypoxia to lower the O_2 saturation to 80%. This process lasted about 10 minutes. The duration of hypoxia was about 2-3 hours. However, in

the other study, O_2 saturation abruptly decreased to 80% in 1-2 min and only lasted about 25 min.

In agreement with the study of Johnston et al. (24), our results showed that normocapnic hypoxia has a large effect on ventilation. This is because CO_2 acts synergistically with hypoxia to increase ventilation (48). Also, high ventilation caused an increase in respiratory heat loss. This may explain the highest core cooling rate in the NH trial.

Johnston et al. (24) found that normocapnic hypoxia increased the rate of core cooling by 33% and lowered the core temperature thresholds for vasoconstriction and shivering. Our study showed the similar result in core cooling rate but the opposite result in the core temperature threshold for shivering (i.e., increased threshold) during both hypocapnic hypoxia and normocapnic hypoxia conditions. Several studies in rats, cats, dogs and humans showed a depression of shivering by hypoxia (12, 14, 26). On the other hand, some studies reported that although hypoxia caused $\dot{V}_{O2}$ to decrease, shivering measured by EMG (40) or visual observation (2) was actually increased during hypoxia.

There are several differences between the study of Johnston et al. and our study: 1) our subjects were resting through out the entire protocol, but in their study, subjects completed 25 min of sub-maximal exercise; 2) in that study water temperature was constant (28°C) and skin temperature was clamped at the same value from exercise until shivering. However, we changed water temperature at a rate of $4°C \cdot h^{-1}$ and skin temperature changed from 37°C to 31-33°C (at a rate of $\approx 3°C \cdot h^{-1}$); 3) in the present study, the rate of core cooling was

slower, 0.4-0.6°C·h^{-1} vs 1.4-1.8°C·h^{-1}, and the time to shivering from onset of core cooling was longer (70-90 min vs 40-50 min) than the previous study; and finally, 4) our core temperature threshold was corrected for changing skin temperature based on the fractional contribution of skin to the thermoregulatory responses. On the other hand, the actual core temperature was used by Johnston et al. to indicate response thresholds (24).

Several mechanisms may help us to explain why our study showed that the core temperature threshold for shivering actually increased during hypoxia. First, our core threshold was measured by a corrected value based on ß (the contribution of the skin to the response) which may increase during hypoxia. According to Cheng et al. (5), there is a linear relationship between skin and core temperature contributions to thermoregulatory responses, and our ß value was based on 20% cutaneous contribution to vasoconstriction and shivering thresholds. We do not know whether this linear function still remains during the condition of hypoxia. In a study of awake rats, Giesbrecht et al. (17) used an abdominal heat exchanger to produce isolated core cooling with clamped surface temperatures and alternately to cool the surface while core temperature was maintained at a stable level. The cold sensitivity for isolated core cooling (indicated by change in $\dot{V}_{O_2}$ for change in temperature) was 11 ml $O_2 \cdot °C^{-1}$ in room air and dropped to 2 ml $O_2 \cdot °C^{-1}$ in hypoxia (FI_{O_2} = 0.12) within core temperatures ranging from 37 to 33°C. On the other hand, the sensitivity of skin cooling decreased from 1.06 ml $O_2 \cdot °C^{-1}$ in room air to 0.28 ml $O_2 \cdot °C^{-1}$ in hypoxia in the range of ambient temperatures from 28 to 10°C. Hypoxia caused a 40% increase in the skin contribution to cold-induced heat production (ß) from 8.8% in room air to 12.3% in hypoxia. If we assume a similar effect in humans and changed the ß value from 0.2 to 0.3 for the hypoxia conditions,

shivering thresholds were still elevated compared to control. Therefore, this is not a likely explanation for our divergent results.

Second, hypoxia could increase the sensitivity of thermoregulatory control systems to the rate of change in core temperature. In the study of Lopez et al. (29), there is no difference in shivering threshold when core cooling rate changed from 0.7 to 1.7°C·h^{-1} at the same skin temperature during normoxia. This indicates that the sensitivity of central control systems is not affected by changes in cooling rates of this magnitude. Johnston et al. (24) found that the core cooling rate increased during normocapnic hypoxia (1.8°C·h^{-1}) compared with normoxia (1.4°C·h^{-1}), and the shivering threshold decreased when skin temperature was kept the same. In our study, the core cooling rates were lower during both normoxia (0.4°C·h^{-1}) and hypoxia (0.6°C·h^{-1}) conditions and skin temperature changed at a rate of 3°C·h^{-1}. It is unlikely that hypoxia increased the sensitivity to core cooling rate at these lower core cooling rates [as indicated in the study of Johnston et al. (24)] but hypoxia may have increased sensitivity to skin cooling. In the study on the thermosensitivities of preoptic neurons in anaesthetized rats (50), it was found that the activity of some of a large group of warm-sensitive neurons and a small group of cold-sensitive neurons was increased during hypoxia. It is possible that a combination of effects of hypoxia on central neurons could result in an increased sensitivity to skin cooling. Even if this were to occur, the effect would likely be small.

It should be recognized that although the hypoxia induced increase in shivering threshold is significant, it is practically very small. Future studies should focus on the effect of hypoxia on the gain and maximal intensity of the

shivering response as these factors have a more important effect on long term cooling and thermoregulation.

Gautier et al. (13, 14) in their studies on cats, assessed the effects of hypocapnia on thermoregulation by normalizing end-tidal CO_2 levels during inhalation of 12% O_2. Hypoxia decreased shivering activity and $\dot{V}O_2$, and this suppression was reversed when end-tidal CO_2 was normalized. Shivering and $\dot{V}O_2$ again decreased when CO_2 was withdrawn. Based on their studies, we expected that HH would have more effect on the responses to thermal stimuli than NH in our study. Our results, however, showed that there was no meaningful difference between HH and NH. Richardson et al. (39) demonstrated that acute hypocapnic hypoxia in humans resulted in an increase in cardiac output, heart rate and forearm blood flow in humans. They observed that when hypocapnia was abolished by adding CO_2 to 8% O_2 in inspired air, the cardiac output and heart rate returned to the control level. However, addition of CO_2 also increased the arterial oxygen tension. Therefore, it is possible that the normalization of cardiovascular variables was due to the increased PaO_2 and not the addition of CO_2. Another study showed that because addition of CO_2 stimulates further hyperventilation and increases PaO_2 during hypoxia, inspiring 10.5% O_2 during CO_2 replacement in the condition of normocapnic hypoxia resulted in the same PaO_2 as during 12% O_2 in hypocapnic hypoxia (21). In our study, the PaO_2 was not significantly different between HH and NH conditions. This suggests that the inspired PO_2 in the NH trial might be lower than in the HH trial. We added N_2 as required to control SaO_2. Consequently, SaO_2 was the same during the entire NH trial.

$PaCO_2$ during immersion in the NH trial (34.5±5.1 mmHg in vasodilation and 34.1±4.1 mmHg in cooling periods) was higher than in the HH trial (31.0±7.7, and 30.0±3.3 mmHg), but it is still significantly lower ($P<0.05$) than in the Control trial (40.3±4.6, and 37.1±2.7 mmHg). The reason may be the hyperventilation in the NH trial. This caused a smaller difference in $PaCO_2$ than desired and minimized any differences that were expected between NH and HH trials. These results explain the difficulty in maintaining true arterial normocapnia during periods of high ventilation even though end-tidal CO_2 values are kept constant.

We determined our actual core temperature threshold by considering a combination of self-report, EMG and $\dot{V}_{O2}$. An increase in EMG activity is a common method of detecting shivering. This is a very sensitive method but it can be confounded by mechanical and technical artifact. An increase in $\dot{V}_{O2}$ has been adopted in many studies (5, 24, 32) to determine shivering threshold. We also introduced self-report and found very good correlation among shivering threshold values determined by the 3 methods. Therefore, we feel the shivering threshold values are valid.

There are several possible mechanisms for the effects of hypoxia observed in the present study: 1) change of central/hypothalamic integrative and control processes, 2) altered sympathetic nervous system activity; 3) limitation of O_2 supply to shivering muscle; 4) peripheral chemoreceptor function and 5) increased respiratory heat loss and skin heat dissipation.

Central/ hypothalamic effects. Support for this hypothesis comes from a study on the thermosensitivities of preoptic neurons in anaesthetized rats

(50). It was found that during hypoxia the baseline activity and thermal sensitivity of 35% of warm-sensitive neurons was increased. This suggests that preoptic thermosensitive neurons may play a role in our results. Gautier et al. (14) stated that hypoxia acts on the central nervous system to suppress shivering and carotid sinus nerve afferents appear to counteract this direct effect. This result was confirmed later by Bonora and Gautier (3), who found that in conscious cats the T_{es} threshold temperature for thermal tachypnea is lowered by hypoxia. They concluded that this result comes from a central effect of hypoxia because the effect persists after carotid body denervation.

Altered sympathetic activity. Hypoxia alters overall sympathetic activity. Regional differentiation of sympathetic efferents has been known to be evoked by hypoxia. In decerebrated rabbits, cutaneous sympathetic activity increased during hypoxia [as cited in (50)]. In man, cardiac output and HR increases during hypoxia are reduced by half by beta-adrenergic blocking agents. This suggests the involvement of increased sympathetic activity during hypoxia (38). When hypoxia is imposed during exercise, Rowell et al. (44) observed an increase in plasma norepinephrine concentration and tachycardia. Later, Rowell et al. (43) examined the effect of arterial hypoxemia on the sympathetic nervous system and its control of warm responses. The study showed that acute moderate hypoxemia exaggerated increases in catecholamines and heart rate during hyperthemia, indicating increased peripheral autonomic function. However, for resting humans severe hypoxia may blunt the sympathetic nervous activity because the norepinephrine concentration does not increase when arterial PO_2 is reduced as low as 27 mmHg (42). In intact rabbits, 8% inspired O_2 results in a rise of

ear skin temperature and a corresponding decrease in sympathetic activity [as cited in (50)].

Limitation of O_2 supply to shivering muscle. Hypoxia may impair normal shivering thermogenesis by limiting O_2 supply to thermogenic effector organs (17). In cats, shivering is impaired at levels of hypoxia (15% inspired O_2) that produced little fall in arterial O_2 content, and O_2 limitation in shivering muscle may begin to contribute to the impairment of shivering only when inspired O2 is < 11% (14). Higher CO_2 levels in the NH trials were unlikely to cause a significant change in tissue O_2 delivery. The addition of CO_2 to maintain normocapnia will shift the O_2-dissociation curve to the right, thus lowering the SaO_2 for a given PaO_2. On the other hand, CO_2 also provided some additional ventilatory stimulation with a consequent increase in PaO_2.

Peripheral chemoreceptors. Early studies proposed that peripheral chemoreceptors were the site of action for hypoxia. Von Euler and Söderberg (10) and Mott (34) found that the stimulation of arterial chemoreceptor activity could inhibit shivering in anesthetized adult cats. Later, Bonora and Gautier (3) observed that peripheral chemoreceptors could inhibit the increase in breathing frequency in response to heat stress. However, the enhancement of panting and the inhibition of shivering by hypoxia persist after carotid body denervation, and the CO breathing caused decrease SaO_2 without stimulating chemoreceptors (14). This indicates that these effects are independent of the peripheral chemoreceptors and must therefore originate in central integrative structures that receive many inputs related to thermoregulation (15).

Respiratory heat loss and skin heat dissipation. In this experiment, the highest cooling rate was in the NH trial. Normocapnic hypoxia resulted in a significant hyperventilation ($\dot{V}_E$ = 13.5 L·min^{-1} during hypoxia vs. 9.6 L·min^{-1} during control for the 70 min of cooling). This increase in ventilation may have enhanced core cooling in two ways. First, total respiratory heat loss (due to evaporation and gas warming) would be greater during the normocapnic hypoxia exposure. Although temperature and humidity of the respired gases were not directly measured, it was assumed that the inspirate was at ambient temperature (22°C) and saturated, because it was bubbled through water. Expired gas was assumed to be saturated and 37°C. It was therefore possible to calculate respiratory heat losses. The increase in evaporative respiratory heat loss, based on the difference in water content between saturated inspirate (19.4 mg·l^{-1} at 22°C) and expirate (43.8 mg·l^{-1} at 37°C) and the heat of vaporization of water (0.576 kcal·g^{-1}), was ~3.3 kcal·h^{-1} (~4 W). The increase in conductive respiratory heat loss, based on the difference in temperature between the inspirate and expirate (15°C) and the specific heat of the respired gas (0.34 cal·l^{-1}·°C^{-1}), was ~1.2 kcal/h (~1.5 W). Thus the total respiratory heat loss in the present study was increased by an estimated ~4.5 kcal·h^{-1} (~5.5 W). Given the average mass of our subjects (~85 kg) and the specific heat of body tissue (0.83 kcal·kg^{-1}·°C^{-1}), the increased respiratory heat loss could account for a small decrease in mean body temperature of ~0.074°C over 70 min. Second, the increase in respiratory movements during the normocapnic hypoxia exposure would be also increase convective heat loss from the body surface to the water in which temperature is below core temperature, although the magnitude of this effect cannot be estimated. On the other hand, in the hypocapnic hypoxia trial, the average heat flux was about 8 Watts (~6.9 kcal·h^{-1}) higher than the control trial during the cooling. Given the specific heat and average mass of

our subjects, the increased heat dissipation from skin could account for a small decrease in mean body temperature of ~0.079 °C over 70 min. Although the increase in heat flux was not statistically significant in this study, increased skin heat loss during HH has been reported in other studies and must be considered as a possible mechanism for the increased core cooling rate.

In summary, our study is the first time to demonstrate the effects of hypocapnic hypoxia and normocapnic hypoxia on core cooling rate and cold thermoregulatory response thresholds in humans exposed to a mild cold stress. Hypocapnic hypoxia and normocapnic hypoxia significantly increase the core cooling rate by 49% and 54%. This may be explained in part by the increase of heat loss from hyperventilation in the normocapnic hypoxia condition and the increase of cutaneous heat loss in hypocapnic hypoxia. The high core cooling rate would be an advantage to initiate shivering earlier. The T_{co} thresholds of vasoconstriction and shivering in hypocapnic and normocapnic hypoxia conditions occurred at higher skin temperature compared with the control trial, even though the water cooling rates are the same. There are no significant differences in the responses to cold exposure between hypocapnic hypoxia and normocapnic hypoxia except for the higher $\dot{V}_{O2}$ and $\dot{V}_E$ in the NH condition. The corrected core thresholds for shivering in this study were higher during hypoxia than normoxia. Compared with the study of Johnston et al. (24), our study showed that different physiologic responses result from different protocols. In the hypoxia condition, thermoregulatory responses are more complicated than can be explained by the model of Matsukawa et al. (30). Further studies are needed to solve this issue, such as: 1) to determine if hypoxia changes the ß value for humans; 2) to compare the effect of constant skin temperature with the changing skin temperature on the shivering

threshold in hypoxia and normoxia conditions; and 3) to prolong the protocol to produce greater water and skin cooling in order to measure, not only thresholds, but also the gain and maximal intensities of the shivering responses. For this study, 5% CO_2 in 12% O_2 should be inspired in the NH trial to ensure that $PaCO_2$ values are near baseline levels.

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APPENDIX I. PILOT STUDIES

A. INTRODUCTION

We carried out three pilot studies before we adopted our final protocol. In the first pilot study, we used the protocol of Mekjavic et al. (12) which uses exercise in 28°C water to elevate T_{co} past the sweating threshold followed by a rest period during which T_{co} falls below the shivering threshold. This type of protocol allows determination of the thresholds for sweating, vasoconstriction and shivering while maintaining a constant and uniform skin temperature. For the second protocol, subjects rested in thermoneutral air until they were peripherally vasodilated and then were cooled slowly in water. In the third pilot study, we used water immersion at the Critical Water Temperature to initiate peripheral vasodilation and then we cooled the water slowly until subjects shivered.

B. GENERAL MEASUREMENT METHODS

In the three pilot studies, we measured core temperature, oxygen consumption, skin temperatures and heat flux (at 5 or 12 sites), heart rate, sweat rate and peripheral finger blood flow.

Core temperature was measured using a Mon-a-therm® esophageal thermocouple (Mallinckrodt, St. Louis, MO) inserted through a nostril to the level of the heart. Probe insertion depth was determined from sitting height according to the formula of Mekjavic and Remple (11). Heart rate was monitored continuously with a DC battery-operated 43100A Defibrillator/ECG monitor (Hewlett-Packard) with leads in a modified V5 arrangement.

Sweat rate was measured using a ventilated capsule (~5.0 x 3.5 cm) placed on the forehead. Anhydrous compressed air was passed through the capsule over the skin surface. Air flow was controlled at 1 $L \cdot min^{-1}$ by a Brooks 5850 Mass Flow Controller (Emerson Electric, Hatfield, PA). Vapour density of the effluent air was determined based on the relative humidity and temperature of the air as measured by an Omega HX93 Humidity and Temperature sensor (Omega Engineering, Stanford, CT) that was previously calibrated by placing it above saturated salt solutions. Sweat rate was the product of the difference in water content between effluent and influent air and the flow rate. This value was adjusted for the skin surface area under the capsule to give a value in $g \cdot m^{-2} \cdot hr^{-1}$. Flow meters in the inlet and outlet tubing of the capsule allowed the detection and correction of any leaks in the system.

Oxygen consumption ($\dot{V}O_2$) was determined by analysis of the O_2 and CO_2 content of the expired air. Expired air was collected in a rubber facemask with one-way valves and directed to a 10 L fluted mixing box via corrugated plastic tubing. Mixed expired air was continuously sampled from the mixing box at the rate of 500 $ml \cdot min^{-1}$ and analyzed by a Beckman OM-11 O_2 sensor (Beckman, Anaheim, CA) and at a rate of 200 $ml \cdot min^{-1}$ and analyzed by a DATEX 253 Airway Gas Monitor (Datex Instrumentarium Corp., Helsinki, Finland) for O_2 and CO_2 content, respectively. Minute ventilation was monitored by a pneumotachometer (Hewlett Packard 47304A Flow Transducer) in the expiratory circuit proximal to the mixing box.

Cutaneous heat flux (in $W \cdot m^{-2}$) and skin temperature (in $^{\circ}C$) were measured from five sites or twelve sites (depending on the protocol) by thermal flux transducers (Concept Engineering, Old Saybrook, CT). The transducers were calibrated using a Rapid-k instrument (Dynatech, Cambridge, MA) (4). Flux was defined as positive when heat traversed the skin toward the environment (15). Initially five sites were used with the following regional percentages assigned based on those of Layton et al. (8), head 6%, chest 19%, arms 19%, back 19% and legs 37%. Because measurements of heat flux and average skin temperature are subject to errors resulting from regional differences in temperature and flux, as well as errors in estimating regional skin areas (5), we later increased measuring sites from 5 to 12 to minimize these errors. In the later case, the following regional percentages were assigned based on those of Hardy and DuBois (6): forehead 7%, upper chest 8.7%, abdomen 8.8%, scapula 8.7% and lower back 8.8%, anterior thigh 9.5%, posterior thigh 9.5%, shin 6.5%, calf 6.5%, dorsum of the foot 7%, dorsum of the hand 5%, and upper arm 14%. Body surface area (BSA) was calculated [area (m^2) = $weight^{0.425}(kg) \bullet height^{0.725}(cm) \bullet 0.007184$] (3). Flux values from each transducer ($W \cdot m^{-2}$) were then converted into $W \cdot region^{-1}$ [flux at region (Watts) = transducer flux ($W \cdot m^{-2}$) X body surface area (m^2) X regional percentage X 0.01].

Peripheral vessel tone at the fingertip was also assessed using an Ohmeda Biox 3700 Pulse Oximeter (Ohmeda, Louisville, CO) with a clamp-type oximeter probe placed on the fourth finger. The pulse oximeter data was collected on-line and graphically displayed using a portable PC with custom software supplied by Ohmeda. This method of measuring peripheral blood flow has been validated against absolute blood flow as measured by volume

plethysmography. The rate of blood flow ($ml \cdot min^{-1}$) can be calculated from the equation: Log (perfusion) = 0.98 · Log (flow) + 0.04, $r^2 = 0.88$ (13).

End-tidal CO_2 was monitored with a DATEX 253 Airway Gas Monitor (Datex Instrumentarium Corp. Helsinki Finland). Expired gas was sampled from the mouthpiece at 200 $ml \cdot min^{-1}$ and returned to the breathing circuit proximal to the pnemotachometer. The analog output was monitored on a chart recorder. Gas analyzers were calibrated against gases of known concentration prior to each experiment.

Analog data from the thermocouples and gas analyzers were acquired using an electrically isolated Macintosh IIci computer equipped with a NB-MIO-16L 16-channel analog-digital converter (National Instruments, Austin TX). Data were digitized asynchronously at 2 Hz, averaged over 5 seconds, and scaled using appropriate corrections. The results were averaged, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk at 30 second intervals. The process was controlled by a "virtual instrument" written using LabVIEW 2 graphical signal processing software (National Instruments, Austin TX).

C. PILOT STUDY #1

UNDERWATER EXERCISE FOLLOWED BY SLOW PASSIVE COOLING

PROTOCOL

As in studies by Mekjavic et al. (12) and Johnston et al. (7), three subjects (1 male and 2 female) participated in one maximal exercise test and two experimental trials (control and hypocapnic hypoxia), each on a separate day. In each test, the subjects sat in a semi-recumbent position on an underwater cycle ergometer immersed to the clavicles in 28°C water. During the experimental trials, the subjects exercised (at 50% of their previously determined maximum workload) to elevate their T_{co} and initiate sweating. They then cooled passively, allowing determination of T_{co} cooling rate and the T_{co} thresholds for sweating, vasoconstriction and shivering. The ergometer consisted of a bicycle frame submersed in a tank of water and connected with a 1:1 gear ratio to a mechanically-braked cycle ergometer (Monark) supported above the water tank (1).

Maximal Exercise Trial

Each subject performed a graded exercise test to exhaustion pedaling at 60 rpm. Workload started at 0 kp and was increased 0.75 kp (male) or 0.5 kp (females) every two minutes until subjects could no longer maintain a cadence of 60 rpm. The workload for the exercise period in the subsequent experimental trials was 50% of the maximum workload achieved during this session.

Experimental Trial

Each subject then participated in a control and a hypocapnic hypoxia trial. Subjects reported to the laboratory following a minimum four hour fast and were instructed to abstain from alcohol, caffeine and heavy exercise prior to the test session. During the instrumentation period (~30 minutes) subjects were covered with a cotton blanket and rested on a chair. Skin temperatures and heat flux were measured at 5 sites. After a 20 min baseline period, subjects were immersed in 28°C water to the clavicles and sat on the underwater cycle. They then pedaled at 60 rpm for 25 min at 50% maximum workload. In all cases, this exercise bout was sufficient to elevate T_{co} past the sweating threshold and establish a high sweat rate. Immediately following the exercise period, subjects rested their left forearm on a shelf just above water level and the pulse oximeter probe was attached to the middle finger to monitor peripheral vessel blood flow. Subjects remained seated on the ergometer in the circulated water and cooled passively until T_{co} dropped below the thresholds for vasoconstriction and finally, shivering. Immersions were terminated when shivering was continuous and vigorous for 30 min.

Throughout the control trial, subjects inspired humidified room air. In the hypocapnic hypoxia trial, subjects inspired humidified gas containing 12%O_2/balance N_2. Subjects inspired the hypoxic gas mixture for the final 5 min of exercise and throughout the entire cooling period.

RESULTS AND DISCUSSION

The results were highly variable. Sweating, vasoconstriction and shivering thresholds increased in subject 2 during the hypocapnic hypoxia trial compared with the control trial. In contrast, all three thresholds

decreased for subject 3 during the hypocapnic hypoxia trial. For subject 1, the shivering threshold increased slightly but sweating and vasoconstriction thresholds decreased during the hypocapnic hypoxia trial compared with the control trial (Fig. 13, 14, 15). One possible reason for this variability could be the effect of exercise. Lopez et al.(9) found that exercise per se reduces the sweating threshold significantly (~0.7°C). The reason may be the increasing sympathetic nervous system activity during exercise or other exercise related factors. Because of the possible complications caused by exercise, we decided to confine our observations to subjects resting in water (28°C).

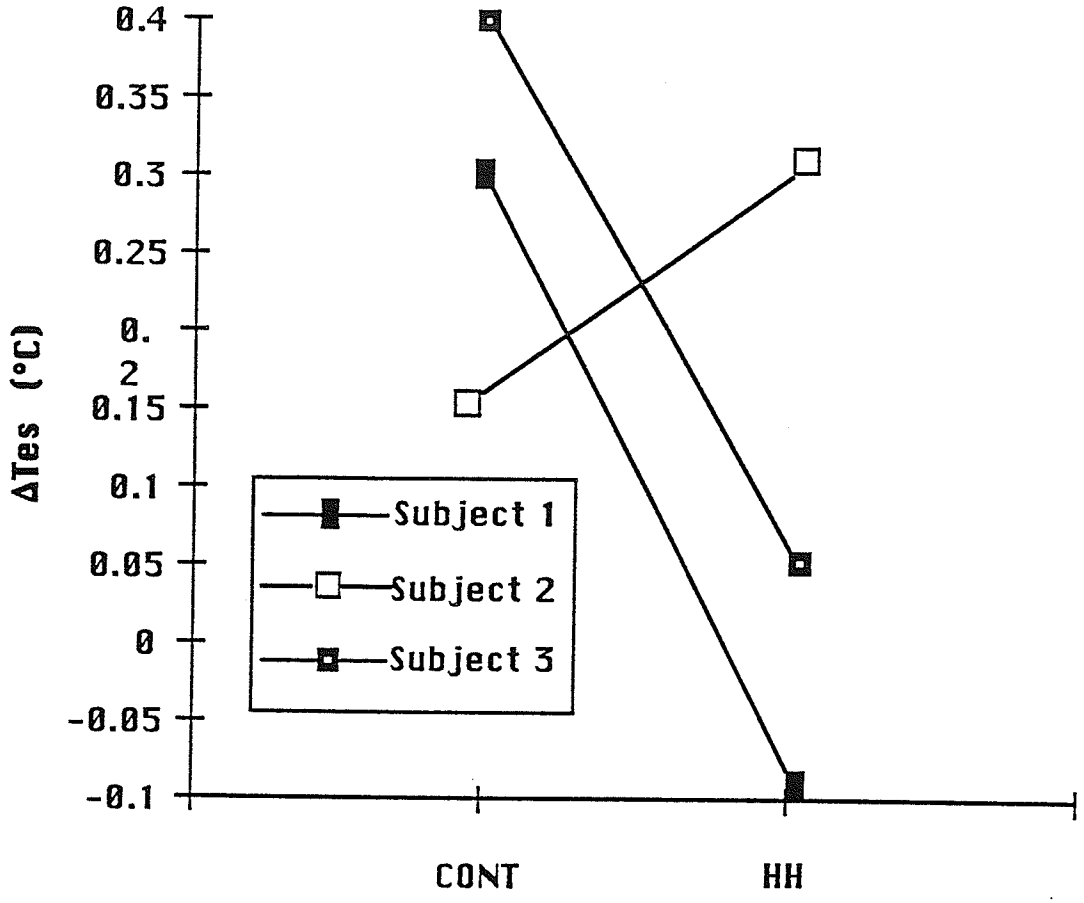

Fig. 13. Individual core temperature thresholds for sweating in control (Cont) and hypocapnic hypoxia (HH) conditions. Thresholds are plotted as change in Tes from preimmersion baseline (ΔTes)

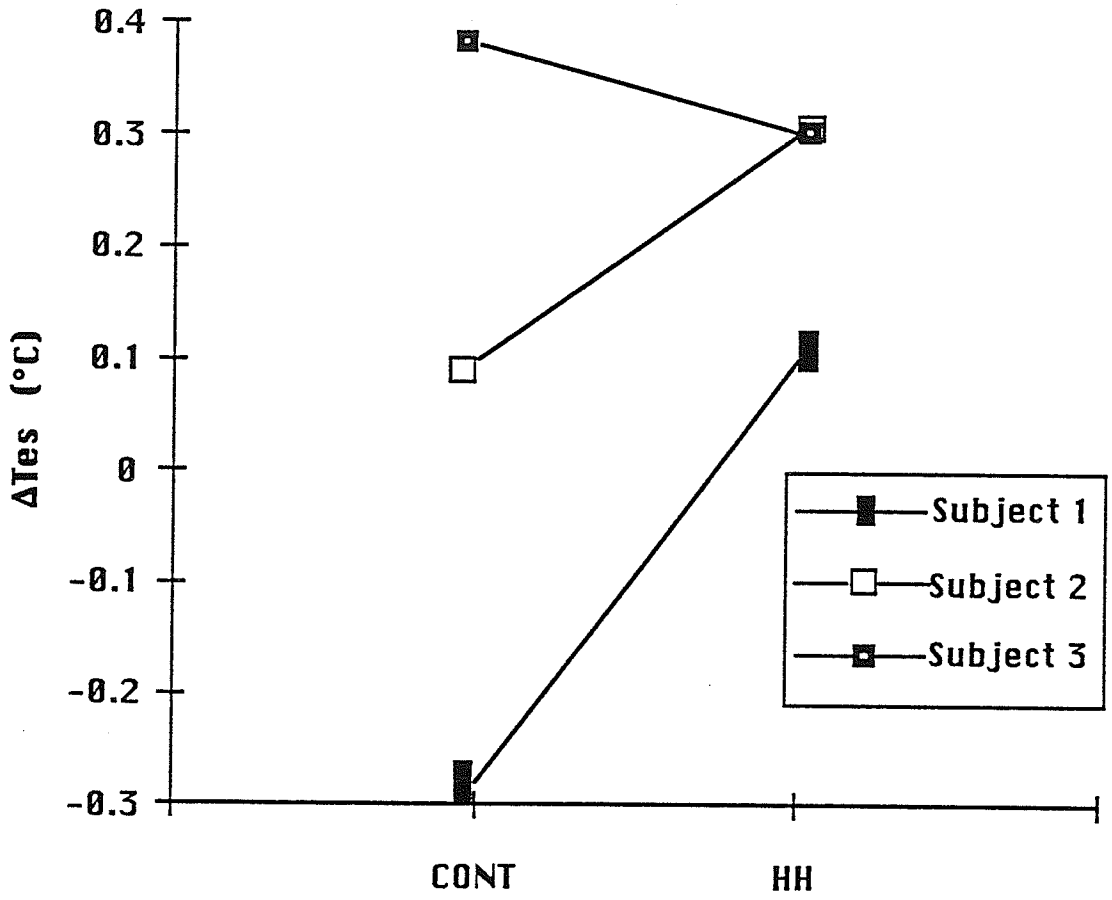

Fig. 14. Individual core temperature thresholds for vasoconstriction in control (Cont) and hypocapnic hypoxia (HH) conditions. Thresholds are plotted as change in Tes from preimmersion baseline (ΔTes).

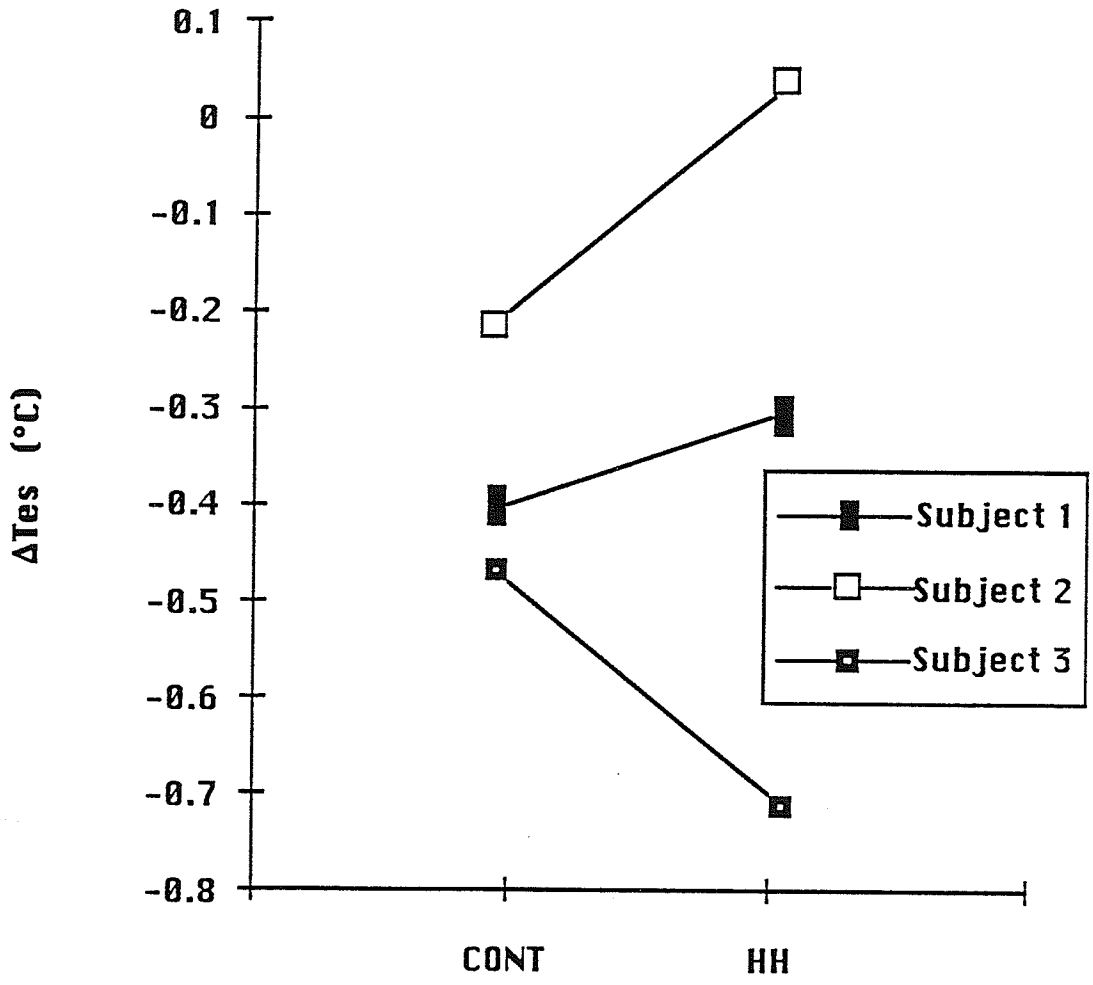

Fig.15. Individual core temperature thresholds for shivering in control (Cont) and hypocapnic hypoxia (HH) conditions. Thresholds are plotted as change in Tes from preimmersion baseline (ΔTes).

D. PILOT STUDY #2

RESTING IN THERMONEUTRAL AIR AND SLOW PASSIVE COOLING IN WATER

PROTOCOL

In this study, we deleted the sweating portion because exercise would not be used and core temperature would not passively rise above the sweating threshold. Therefore, only vasoconstriction and shivering thresholds were studied. Three male subjects took part in this pilot study. They entered a climatic chamber after instrumentation. The climatic chamber (CONVIRON-C810) has a volume of 13.6 m^3 (2.7 m long, 2.4 m high and 2.1m wide). It has a temperature range from -20°C to +40°C with full humidity control at ambient temperatures above 5°C. In our experiments, the ambient temperature was 29°C and relative humidity was 50%. Subjects sat motionless in the chamber for about 1 hour until peripheral vasodilation occurred. Then, subjects came out of the chamber and immediately entered the 28°C water. Immersions were terminated when shivering was continuous and vigorous for 30 min.

Throughout the control trial, subjects inspired humidified room air. In the hypocapnic hypoxia trial, subjects inspired humidified gas consisting of a 12% O_2 balance N_2 mixture. In the normocapnic hypoxia trial, subjects also inspired gas consisting of a 12% O_2 balance N_2 mixture and additional CO_2 was added to the inspirate to bring expired CO_2 to normal levels. In both hypoxia trials, subjects inspired the hypoxic gas mixtures for the final 10 min in the environmental chamber and throughout the entire immersion period.

RESULTS AND DISCUSSION

The problem with this procedure was that it was difficult to determine the vasoconstriction threshold because of the large and rapid change of skin temperature immediately after subjects entered the water. When subjects came out from chamber, their average skin temperature was about 33°C. Fingertip vasoconstriction occurred in each subject soon after they entered the 28°C water. This is likely because of the large and rapid decrease in skin temperatures following immersion (Fig. 16). These results made it impossible to compare vasoconstriction thresholds in the 3 conditions. To solve this problem, we canceled the period of sitting in chamber (T_{am} = 29°C) and asked the subjects to enter the water directly after collecting baseline data while they were seated in the laboratory (T_{am} = 22°C).

The next issue was to choose a suitable water temperature allowing determination of the T_{co} thresholds for both vasoconstriction and shivering. Rennie et al. (14) introduced the concept of "Critical Water Temperature" (T_{cw}) which was defined as the lowest water temperature subjects could tolerate for 3 hr without shivering. We thought subjects would be vasodilated in water at T_{cw}. We could then decrease water temperature gradually to determine the vasoconstriction and shivering thresholds.

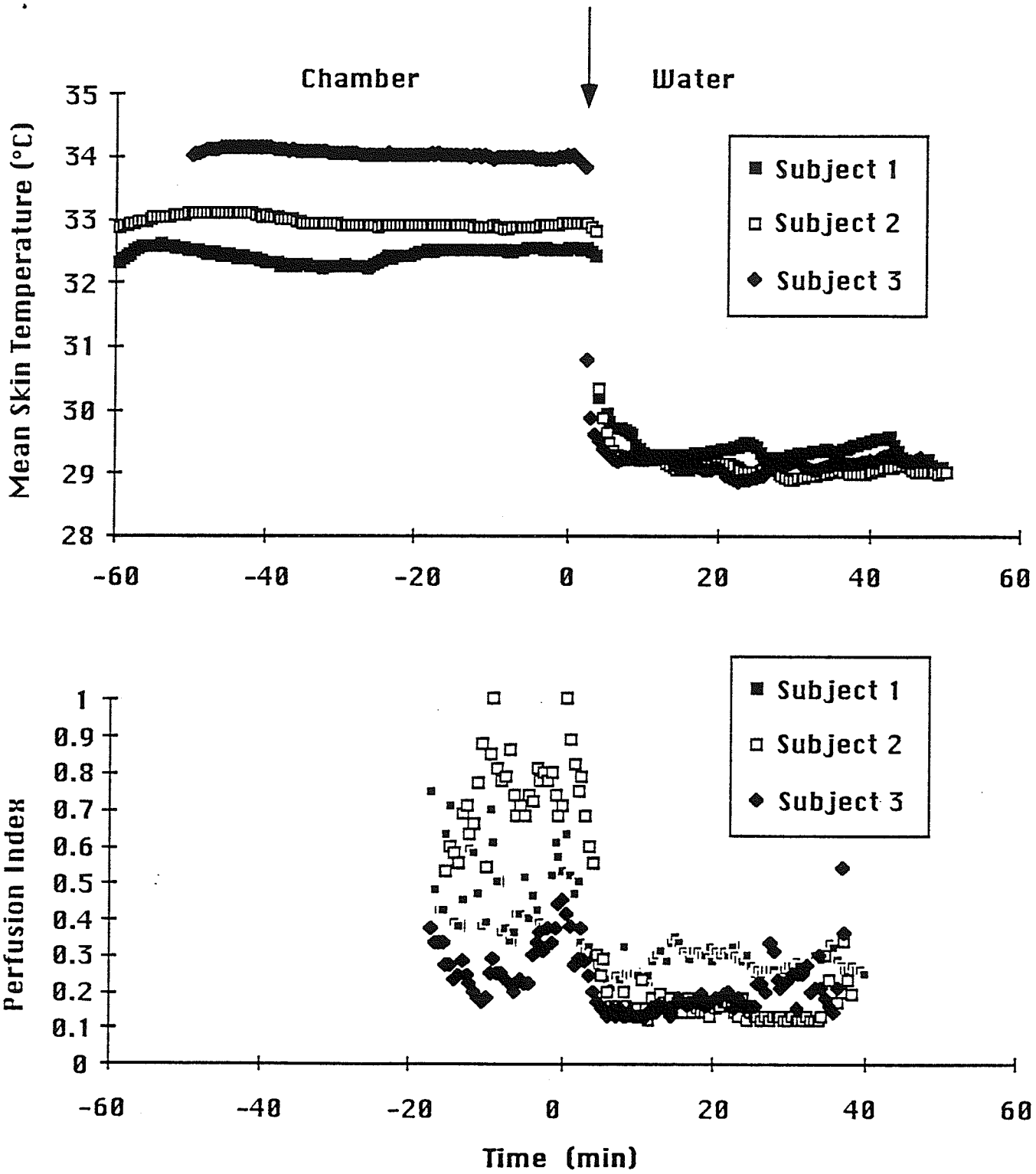

Fig. 16. Mean skin temperature (top) and Perfusion Index (bottom) for 3 subjects in the hypocapnic hypoxia condition (results were similar in the control and normocapnic hypoxia conditions). Subjects enter the water at Time = 0 min

E. PILOT STUDY #3

REST AT CRITICAL WATER TEMPERATURE FOLLOWED BY SLOW COOLING IN WATER

PROTOCOL

Smith and Hanna (16) developed the linear approximation method to calculate critical water temperature. The approximation is based on subcutaneous fat thickness. Skinfolds were measured at the following nine sites by calipers (John Bull, British Indicators Ltd.): chin, dorsal upper arm, largest part of lateral forearm, juxtanipple, midaxillary line at the level of the sternum, waist midway between umbilicus and midaxillary line, center of anterior thigh, widest part of dorsal calf, and subscapular point. The T_{cw} is calculated by the following equation: $T_{cw} = -0.237x + 35.2$ (x is the mean skinfold). Two male subjects participated in this study. Their T_{cw}'s were 32.9°C and 31.6°C respectively. After instrumentation subjects sat quietly in the laboratory (T_a = 22°C) for a 30 min baseline period. They then entered water at T_{cw} for at least one hour of immersion.

RESULTS AND DISCUSSION

We thought water at T_{cw} could keep T_{co} stable near 37°C and cause peripheral vasodilation. Although skin temperature was maintained at stable values (Fig. 17), T_{co} decreased steadily (Fig. 18). Again fingertip blood flow decreased soon after immersion and vasodilation did not occur following 60 min (subject 1) and even 140 min (subject 2) (Fig. 19). It therefore seemed necessary to increase the water temperature above T_{cw} to a temperature which would initiate full vasodilation.

A recent study by Cheng et al. (2) showed that vasoconstriction and shivering thresholds are a linear function of skin and core temperature, with skin contributing ~ 20% to the responses. Using this relationship, Matsukawa et al. (10) developed a equation which gives a method to compare the integrated thermal signals to the thermoregulatory system when skin and core temperatures are both changing. With this method, changes in skin temperature are compensated for (i.e., by designating a common skin temperature) and equivalent core temperatures are calculated at the various thermoregulatory thresholds. Based on their study, we fixed our final protocol in which the initial water temperature was increased to 37°C to stimulate peripheral vasodilation. The water was then decreased at $4°C \cdot hr^{-1}$ until shivering was continuous for half an hour.

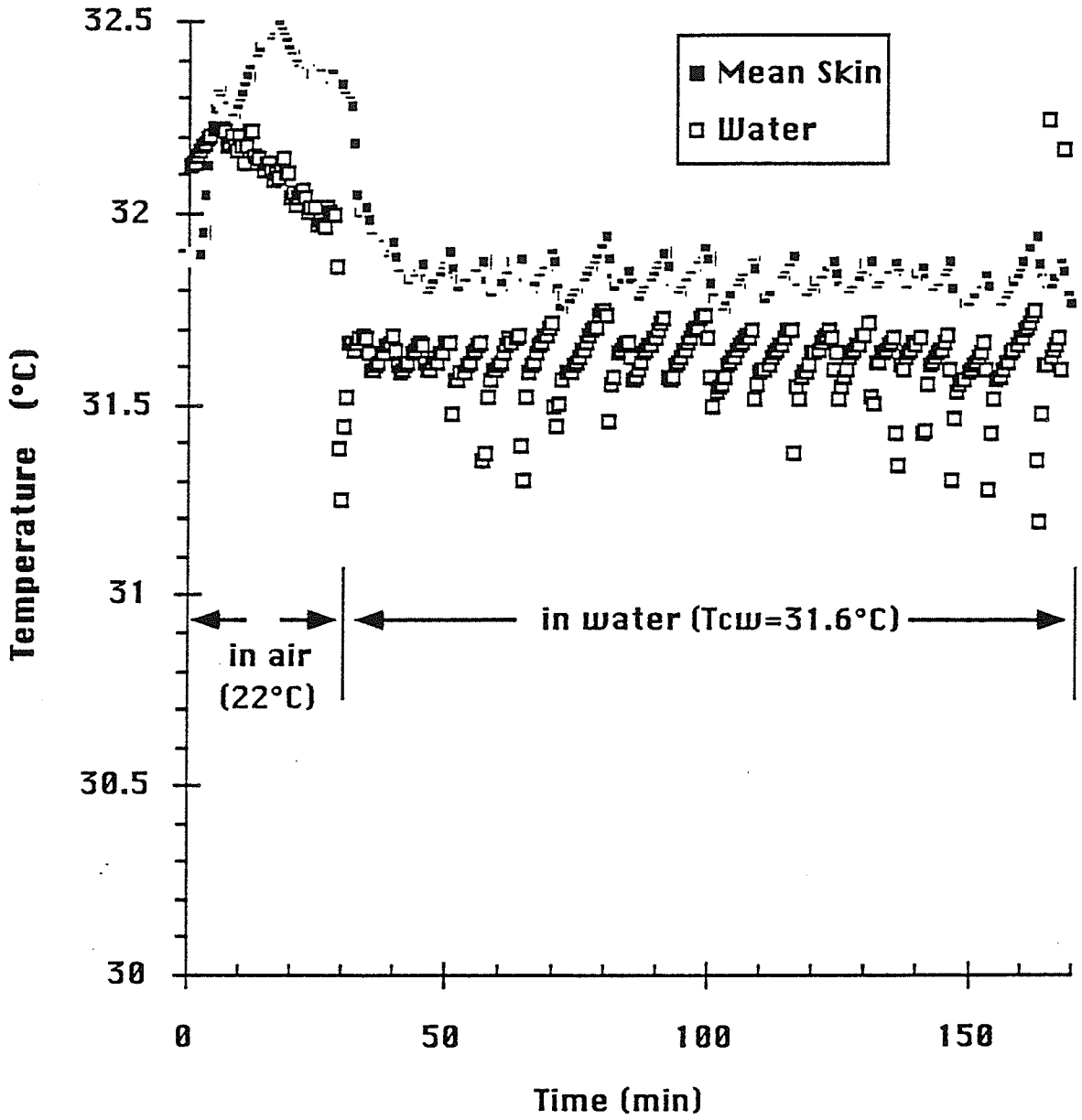

Fig. 17. Mean skin and water temperatures for one representative subject (#2) under control (i.e. respiring room air) condition. Note, the periodic small decreases in temperature are caused by addition of small amounts of ice to prevent water temperature from rising.

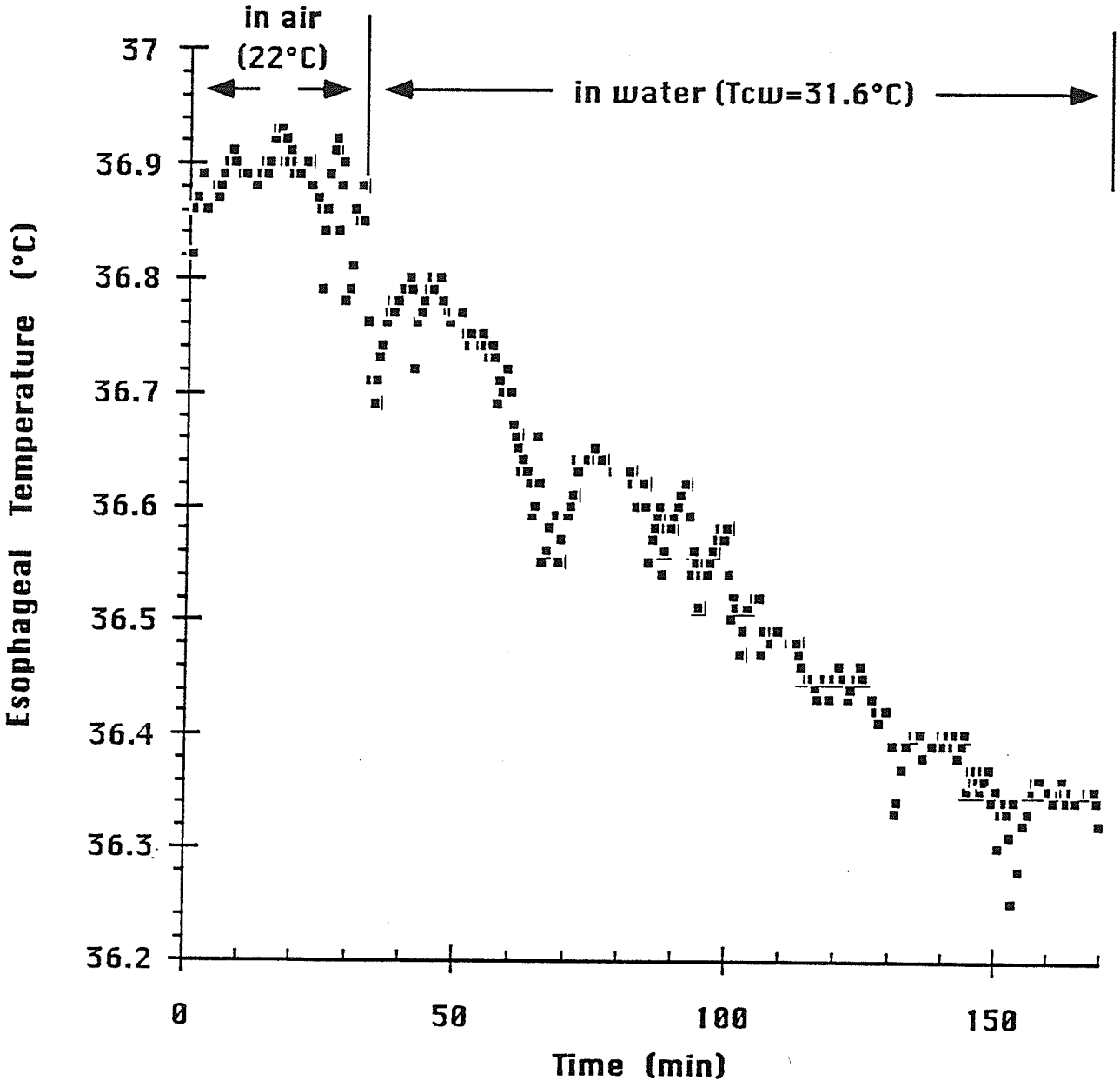

Fig. 18. Esophageal temperature for one representative subject (#2) under control condition.

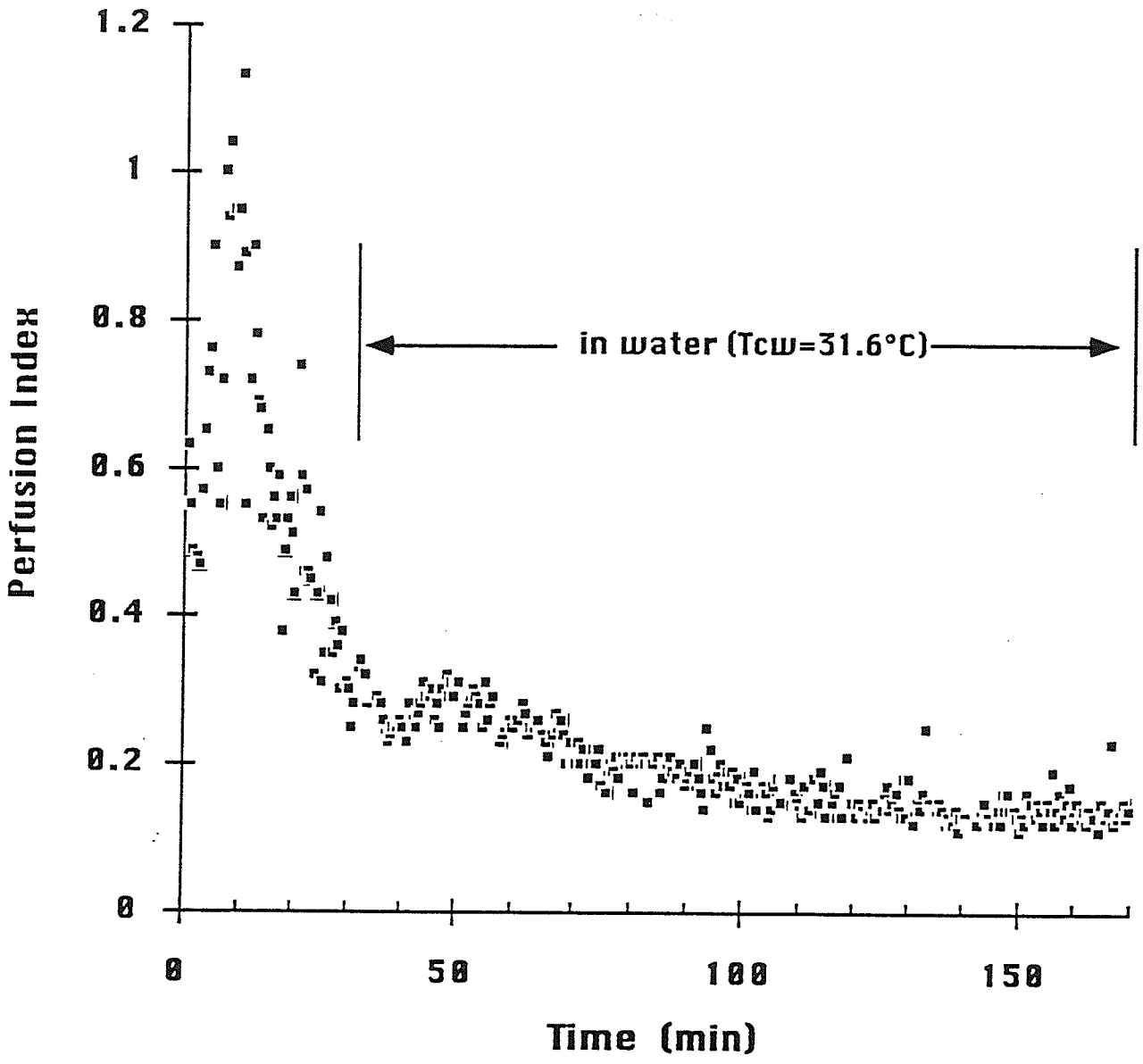

Fig. 19. Perfusion index for one representative subject (#2) under control condition

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