THE EFFECTS OF EUCAPNIC HYPOXIA AND HYPERCAPNIA ON HUMAN TEMPERATURE REGULATION

BY

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Religion
- General 0318
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Theology 0469

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Anthropology
- Archaeology 0324
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Economics
- General 0501
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- Commerce-Business 0505
- Finance 0508
- History 0509
- Labor 0510
- Theory 0511

Folklore 0358
Geography 0366
Gerontology 0351
History
- General 0578
- Ancient 0579
- Medieval 0581
- Modern 0582
- Black 0328
- African 0331
- Asia, Australia and Oceania 0332
- Canadian 0334
- European 0335
- Latin American 0336
- Middle Eastern 0333
- United States 0337

History of Science 0585
Law 0398
Political Science
- General 0615
- International Law and Relations 0616
- Public Administration 0617

Recreation 0814
Social Work 0452
Sociology
- General 0626
- Criminology and Penology 0627
- Demography 0938
- Ethnic and Racial Studies 0631
- Individual and Family Studies 0628
- Industrial and Labor Relations 0629
- Public and Social Welfare 0630
- Social Structure and Development 0700
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Transportation 0709
Urban and Regional Planning 0999
Women's Studies 0453

THE SCIENCES AND ENGINEERING

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Agriculture
- General 0473
- Agronomy 0285
- Animal Culture and Nutrition 0475
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- Food Science and Technology 0359
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- Plant Pathology 0480
- Plant Physiology 0817
- Range Management 0777
- Wood Technology 0746

Biology
- General 0306
- Anatomy 0287
- Biostatistics 0308
- Botany 0309
- Cell 0379
- Ecology 0329
- Entomology 0353
- Genetics 0369
- Limnology 0793
- Microbiology 0410
- Molecular 0307
- Neuroscience 0317
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- Physiology 0433
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- Veterinary Science 0778
- Zoology 0472

Biophysics
- General 0786
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Geochemistry 0996
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Geophysics 0373
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- General 0566
- Audiology 0300
- Chemotherapy 0992
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- Education 0350
- Hospital Management 0769
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- Immunology 0982
- Medicine and Surgery 0564
- Mental Health 0347
- Nursing 0569
- Nutrition 0570
- Obstetrics and Gynecology 0380
- Occupational Health and Therapy 0354
- Ophthalmology 0381
- Pathology 0571
- Pharmacology 0419
- Pharmacy 0572
- Physical Therapy 0382
- Public Health 0573
- Radiology 0574
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- Speech Pathology 0460
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Home Economics 0386

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- General 0485
- Agricultural 0749
- Analytical 0486
- Biochemistry 0487
- Inorganic 0488
- Nuclear 0738
- Organic 0490
- Pharmaceutical 0491
- Physical 0494
- Polymer 0495
- Radiation 0754

Mathematics 0405
Physics
- General 0605
- Acoustics 0986
- Astronomy and Astrophysics 0606
- Atmospheric Science 0608
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- Electronics and Electricity 0607
- Elementary Particles and High Energy 0798
- Fluid and Plasma 0759
- Molecular 0609
- Nuclear 0610
- Optics 0752
- Radiation 0756
- Solid State 0611

Statistics 0463

Applied Sciences
Applied Mechanics 0346
Computer Science 0984
Engineering
- General 0537
- Aerospace 0538
- Agricultural 0539
- Automotive 0540
- Biomedical 0541
- Chemical 0542
- Civil 0543
- Electronics and Electrical 0544
- Heat and Thermodynamics 0348
- Hydraulic 0545
- Industrial 0546
- Marine 0547
- Materials Science 0794
- Mechanical 0548
- Metallurgy 0743
- Mining 0551
- Nuclear 0552
- Packaging 0549
- Petroleum 0765
- Sanitary and Municipal 0554
- System Science 0790

Geotechnology 0428
Operations Research 0796
Plastics Technology 0795
Textile Technology 0994

PSYCHOLOGY
General 0621
Behavioral 0384
Clinical 0622
Developmental 0620
Experimental 0623
Industrial 0624
Personality 0625
Physiological 0989
Psychobiology 0349
Psychometrics 0632
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TABLE OF CONTENTS

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LIST OF FIGURES

Figure — Page

CHAPTER I. OVERVIEW

A. ABSTRACT

Humans employ a range of thermoregulatory responses to maintain body temperature homeostasis when exposed to thermal stress. In some cases, other environmental stresses such as atypical inspired gas composition may be experienced in conjunction with thermal stress. For example, hypoxia (low O_2 tension) may result from altitude exposure or certain disease states and divers may experience periods of hypercapnia (high CO_2 tension) due to inadequate CO_2 removal. Hypoxia and hypercapnia are both known to alter the basic thermoregulatory responses of laboratory animals. In cold-exposed animals, hypoxia increases core temperature (T_{co}) cooling rate and suppresses shivering and non-shivering thermogenesis. Similarly, inhalation of 3-10 % CO_2 impairs thermal homeostasis in animals by attenuating shivering and promoting heat loss through peripheral vasodilation. Experimental results with humans are equivocal. Consequently, two studies were conducted to determine the effects of eucapnic hypoxia and hypercapnia on warm and cold thermoregulatory responses and T_{co} cooling during mild cold stress. For each study, we examined the sweating , vasoconstriction and shivering responses as well as T_{co} (esophageal) cooling rates, of eight subjects immersed in 28°C water. Subjects exercised on an underwater cycle to elevate T_{co} past the sweating threshold and then cooled until shivering was manifest. For the eucapnic hypoxia trial, subjects inspired 12% O_2/balance N_2 with added CO_2 to produce eucapnia. For the hypercapnia trial, subjects inspired 4% CO_2/20.9% O_2/balance N_2 throughout the cooling period. The control inspirate was room air. Eucapnic hypoxia lowered the T_{co} thresholds for vasoconstriction and shivering by approximately 0.14°C and 0.19°C,

respectively and increased T_{co} cooling rate by 33%. Hypercapnia also increased T_{co} cooling rate by ~25% and lowered the mean T_{co} shivering threshold by approximately 0.13°C. These results demonstrate that both eucapnic hypoxia and hypercapnia affect the basic thermoregulatory processes of humans and may contribute to the etiology of hypothermia by accelerating core cooling.

B. INTRODUCTION

Early models of human thermoregulation state that core temperature (T_{co}) is maintained at a set-point by the counteracting processes of heat loss and gain (2). Thus, an upward deflection of T_{co} from the set-point would result in heat dissipation through peripheral vasodilation and sweating, and a drop in T_{co} below this point would result in decreased heat dissipation through vasoconstriction and increased heat production via shivering and nonshivering thermogenesis (NST). Recently, Mekjavic *et al.* (32) have supplied convincing evidence that there is a difference on the order of 0.5°C between the set-points for sweating and shivering. This suggests that human core temperature is regulated about a "null zone" of temperatures rather than precisely controlled at a single, specific set-point.

Other groups of researchers using the procedure developed by Mekjavic *et al.* (32) and other protocols have begun examining the effects of various perturbations including anesthetics (34, 43), alcohol (27) and blood glucose status (35) on the T_{co} response thresholds for sweating, vasoconstriction and shivering. The protocol that was used by Mekjavic *et al.* (32) and that will be employed in this study, 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 skin temperature constant. There has not been any examination of the effects of hypoxia or hypercapnia on these thermoregulatory thresholds.

At altitude, decreased inspired P_{O2} results in arterial hypoxemia. It is well known that hypoxemia alters the basic thermoregulatory responses to cold challenge. In animals, hypoxemia delays the onset of shivering (4), decreases the maximal shivering response (16, 17, 21) and inhibits NST (16). Hypoxemia is also associated with an increased rate of T_{co} cooling in conscious cats (17). In humans, hypoxemia elicits peripheral vasodilation (with consequent increases in skin temperature and surface heat loss) and inhibits heat production (11, 37). The effects of hypoxemia on total heat balance are not so clear. Core temperature has been reported to either remain constant (5) or decrease (11, 37) during hypoxic cold exposure.

Hypercapnia may also affect basic thermoregulatory responses. Early animal studies have shown that inhalation of gas mixtures containing 3 to 10% CO_2 during cold exposure impairs thermal homeostasis by attenuating shivering and promoting heat loss through peripheral vasodilation (45). The effects of hypercapnia in humans under similar conditions are less clear. Inhalation of 2.5 to 4% CO_2 mixtures has been reported to transiently suppress shivering without affecting T_{co} cooling rate (8), to increase cooling rate without affecting shivering by impairing NST (48) or to have no significant effect on either shivering or core cooling (30).

There are several limitations to previous work on the effects of hypoxia and hypercapnia on human thermoregulation. In addition to inconsistent results during cold stress, little is known about the thermoregulatory effects of inspiring these gas mixtures during heat

challenge. Also, the effects of hypoxia and hypercapnia on warm and cold response thresholds are unknown. Finally, the hypoxic stimulus has not been isolated from that of arterial hypocapnia subsequent to hypoxic hyperventilation in human subjects.

STATEMENT OF THE PURPOSE

To determine the effects of eucapnic hypoxia and hypercapnia on T_{co} thresholds for warm and cold thermoregulatory responses as well as T_{co} cooling rates during mild cold stress.

IMPORTANCE OF THE STUDY

This study is important on two accounts. First, it will provide independent validation of the methods used by Mekjavic *et al.* (32) and thereby provide further evidence in the set-point vs. null zone debate. To date, no other laboratory has replicated these methods to test their validity. Second, this study will help to further elucidate the effects of both eucapnic hypoxia and hypercapnia on human thermoregulation. Specifically, the effect of these gases under conditions of heat stress or mild cold stress at a constant skin temperature have never been examined. Since skin temperature provides a powerful input to the hypothalamic centers, it must be controlled.

HYPOTHESES

Eucapnic Hypoxia

It is expected that eucapnic hypoxia will promote peripheral vasodilation and delay shivering, thereby depressing the T_{co} thresholds for

vasoconstriction and shivering. The depression in these cold response thresholds with hypoxia may increase T_{co} cooling rates. The effect of hypoxia on the sweating threshold cannot be predicted although the vasodilation expected with hypoxia may increase the sweating response. These effects may be small, since end-tidal CO_2 levels will be normalized.

Hypercapnia

Inspiring a hypercapnic gas mixture should delay the onset of shivering. This may cause an increase in the T_{co} cooling rate. The effect of hypercapnia on the T_{co} threshold for vasoconstriction, sweating response and null zone size cannot be predicted.

ASSUMPTIONS

The most important assumption is that the "null zone" is a real physiological phenomenon and not simply a product of the experimental protocol developed by Mekjavic *et al.* (32). This assumption seems justified, since other researchers (8, 42) using different protocols have also demonstrated a range of core temperatures between the thresholds for sweating and shivering. A second assumption is that using exercise to increase T_{co} will not change the pattern of thermoregulatory responses to cold stress or alter the effect of the different gases on these responses. Although T_{co} may be elevated for a period of time following exercise, there is no research suggesting fundamental changes in temperature regulation following a 25 minute exercise bout. The changes in thermoregulatory control mechanisms due to exercise are expected to be slight. Since exercise is part of all experimental trials, comparisons between trials will still provide valuable information. Third, it is assumed that changes in fingertip blood flow accurately reflect the pattern of whole body peripheral blood flow.

Finally, it must be assumed that the subjects will not confound the results by indulging in prohibited behaviour (*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 will be invited to participate in this study. This may limit the generalizability of the results to this specific group.

2) Exercise will be used as a warming procedure, since no other non-invasive method exists of elevating core temperature while keeping skin temperature constant. Exercise may change the thermoregulatory control mechanisms, although this effect, if any, should be slight.

3) Core cooling will be achieved by application of a mild cold stress (immersion in 28°C water).

4) Arterial hypoxemia will be achieved by inhalation of 12% O_2 balance N_2. This was chosen as the lowest oxygen fraction that would allow completion of the exercise without compromising the oxygen saturation and therefore, health of the volunteers.

5) End-tidal CO_2 will be maintained during hypoxia by addition of CO_2 to the inspirate, creating a eucapnic condition.

5) The hypercapnic gas mixture will be 4% CO_2, 20.9% O_2 balance N_2.

6) Esophageal temperature will be used as an indicator of T_{co}.

DEFINITION OF TERMS

1) The **core temperature response threshold** is the core temperature at which a given thermoregulatory (heat dissipating or conserving) mechanism is initiated.

2) The **thermoregulatory null zone** (32) is the range of T_{co} between the thresholds for sweating and shivering.

3) The **interthreshold range** is the range of T_{co} between the thresholds for sweating and vasoconstriction. Sessler (42) has suggested that this represents the range of T_{co} over which no active thermoregulation occurs. However, active thermoregulation does occur in this zone, which truly represents a range of temperatures within which thermoregulation is limited to responses of the peripheral vasculature.

4) **Hypoxia** is the condition in which the oxygen supply to the tissues is below physiological levels .

5) **Eucapnia** is the condition in which the carbon dioxide tension of the blood is normal.

6) **Hypercapnia** is the condition in which the carbon dioxide tension of the blood is above normal.

7) **Nonshivering thermogenesis** is the metabolic production of heat without mechanical work via brown fat oxidation (42).

C. REVIEW OF RELATED LITERATURE

INTRODUCTION

This review is intended to serve two purposes. First, the evolution of the current model of thermoregulatory control will be briefly discussed. Next, the effects of hypoxia and hypercapnia on thermoregulation in both experimental animals and humans exposed to thermal stress will be examined in detail.

SET POINT OR NULL ZONE?

Much debate has existed for decades regarding the best model of the thermostatic control of T_{co} in mammals. Two general models have been proposed: the set-point model and the null zone model.

Basically, the set-point model assumes that T_{co} is regulated around a hypothalamic set-point (2). When T_{co} increases above the set-point, heat dissipating mechanisms are invoked to reduce T_{co}, maintaining thermal homeostasis. Thus, even a small increase in central temperature from the set-point would produce a error signal in the hypothalamus and result in peripheral vasodilation and sweating. A drop in T_{co} below the set-point would result in decreased heat dissipation through vasoconstriction and behavioural mechanisms and increased heat production via shivering (or non-shivering thermogenesis in small mammals and neonates). Evidence for the set-point hypothesis has come from experiments on both experimental animals (26) and humans (10). Cabanac and Massonet (9) warmed their subjects in a 40°C bath and transferred them to 28°C water for cooling. T_{co} response threshold were determined during both warming and cooling protocols. With this protocol, the threshold for shivering occurred at a

slightly higher T_{co} than the sweating threshold, although this overlap was insignificant (~0.05°C). Benzinger (2) also used the term set-point to describe his observations of human sweating and shivering responses at various skin temperatures. His results indicated, however, that there was a range of T_{co} between the thresholds for sweating and shivering (33). One of the fundamental problems with these human studies was the large difference in skin temperature between the warming and cooling protocols. Since cutaneous information is one of the major inputs to the hypothalamic integrating center, it is possible that these results were skewed by the inconstant skin temperature.

Other experimental work seems to indicate the existence of a range of core temperatures devoid of active thermoregulation, or a null zone. Early experiments often examined the responses to either high or low environmental temperatures but not to both. Sweating responses were analyzed by increasing T_{co} via exercise or application of exogenous heat (*e.g.*, warm bath immersion). Shivering control was observed by increasing heat loss with exposures to cold air or cold water. When experimental observations of warm and cold thermoregulatory responses, as measured in different protocols, were plotted together versus T_{co}, they included a dead band. This dead band was considered to represent a "neutral thermal zone" or a range of core temperatures in which active thermoregulation was absent (10).

Recent studies have convincingly demonstrated a thermoregulatory null zone in human subjects. Mekjavic and Bligh (33), attempted to replicate the findings of Cabanac and Massonet (10) by warming subjects in a 40°C bath and cooling them in 28°C water. In direct contrast to the earlier study, they found a considerable range of core temperatures (~0.6 °C)

between the sweating and shivering thresholds. Although these authors were unable to induce shivering thermogenesis during cooling, T_{co} fell significantly below the threshold for sweating, indicating that a null zone must exist between the sweating and shivering thresholds. This null zone was also evident when exercise, instead of warm water immersion, was used as a method to elevate T_{co}. The thresholds for sweating and shivering as determined by the two warming protocols were similar. When warm water immersion was used to elevate T_{co}, a hysteresis or difference of ~0.3°C was observed between sweating onset and offset during cooling. Cabanac and Massonet (10) reported a hysteresis in sweating of only 0.06°C with warm water immersion. Exercise produced less hysteresis in sweating onset and offset than warm water immersion and allowed for maintenance of a more constant skin temperature during warming and cooling (33). Therefore, in a follow-up study from the same laboratory, underwater exercise (28°C H_2O) was used to elevate T_{co} while maintaining skin temperature constant (32). Under these conditions a thermoregulatory null zone of approximately 0.5°C was clearly and convincingly demonstrated. Other laboratories have also demonstrated a null zone of similar magnitude using this protocol (27) and others that maintain skin temperature and alter T_{co} by intravenous infusion of cold saline (43).

In summary, carefully controlled and elegantly designed studies have recently provided powerful evidence that the null zone model provides a more accurate description of human thermoregulation than the set-point model. The term null zone does not imply that no thermoregulation occurs in this zone. Rather, this zone represents the range of temperatures in which T_{co} is defended exclusively by autonomic responses of the peripheral vasculature. To clarify this point, Sessler (42) has coined the term

interthreshold range. The interthreshold range is the range of T_{co} between the thresholds for sweating and vasoconstriction and represents the zone where active thermoregulatory processes are truly absent.

Protocols such as the one developed by Mekjavic *et al.* (32) should prove very useful for examining the effects of environmental perturbations on thermoregulatory processes. By applying warm and cold stress during the same procedure, information on both warm and cold response thresholds can be readily determined. For example, the effects of hypoxia or hypercapnia on the T_{co} thresholds for sweating, vasoconstriction and shivering at constant skin temperature have not been examined.

EFFECTS OF HYPOXIA ON THERMOREGULATORY RESPONSES

The interactions between hypoxia and temperature regulation have been studied frequently in the last sixty years. Most research has focused on the impact of hypoxia on the thermoregulatory responses to cold exposure. This focus in the literature on cold rather than warm stress stems from the practical implications of sojourn to altitude, where the partial pressure of oxygen in the air and the ambient temperature are both usually low. The following section will deal first with the effect of hypoxia on thermoregulatory responses to cold stress, second with the limited data available on the effect of hypoxia on warm responses and finally with the possible mechanisms underlying the impact of hypoxia on thermoregulation.

During Cold Exposure

Body Temperature/Hypothermia

Some of the earliest studies in this field focused mainly on the effect of hypoxia on the body temperature of man and other animals exposed to

cold stress. Gellhorn and Janus (20) demonstrated that guinea pigs cooled more rapidly when exposed to reduced barometric pressures. Secondarily, they demonstrated that this thermal impairment was specifically due to hypoxia and not hypobaria. Guinea pigs became hypothermic just as quickly with normobaric hypoxia as with hypobaric hypoxia.

Subsequent experiments from the same laboratory in mice, rats and guinea pigs exposed to low atmospheric pressures (hypobaric hypoxia) and high and low temperatures indicated the protective function of hypoxia-induced hypothermia (19). Survival of hypothermic animals in hypoxia was high but when the drop in body temperature was prevented by higher ambient temperatures survival was greatly reduced. The greatest drop in T_{co} was observed in the animals with the largest surface area:mass ratio, indicating perhaps that the effect of hypoxia was to increase heat loss from the body's surface. The protective nature of lowered body temperatures with hypoxia was also acknowledged by Kottke *et al.* (29) who observed a lowering of body temperature in mice, dogs and man with hypoxia. The mice showed the largest alteration in temperature control, becoming essentially poikilothermic when hypoxic. In these mice, T_{co} was on average less than 1°C above air temperature for ambient temperatures ranging from 4 to 24 °C. Body temperature fell on average 1.3°C in dogs and about 1°C in humans exposed to 6% and 10% O_2, respectively.

Similar, more recent observations in pigeons (22, 1), rats (21, 15), cats (17, 16) and humans (5, 11, 37) have led to general acceptance that hypoxia impairs the thermoregulatory response to cold stress. The lowering of T_{co} by hypoxia may be the result of impaired thermogenesis (shivering or non-shivering) or enhanced heat loss (vasodilation) or a combination of both of these factors. Evidence for each will be examined in turn.

Heat Production

Shivering

Kottke *et al.* (29) showed that shivering was inhibited by hypoxia in mice, dogs and man. At an atmospheric pressure of <250mm Hg, mice became essentially poikilothermic and showed no evidence of shivering or voluntary muscular activity. In both dogs and men, shivering was abolished or greatly inhibited by inhalation of 10% O_2 and was reestablished immediately upon reintroduction of room air. T_{co} also rose as shivering and oxygen consumption attained normoxic levels (29).

The lowered oxygen consumption with hypoxia in dogs and man could have resulted from a reduction in overall metabolic rate as well as an inhibition of shivering. Later work with non-shivering, anesthetized or decerebrate cats at a controlled T_{co} showed that mild hypoxia (<13% O_2) does not affect basal metabolic rate until 3-5% O_2 is reached, apparently refuting notions of overall metabolic suppression with mild hypoxia (24). In shivering cats, shivering was markedly reduced only below 12% O_2 and was entirely absent at oxygen tensions <6% .

The most elegant and convincing series of studies have been performed recently on cats and rats by Gautier and his colleagues. In the first of these, chronically instrumented cats were exposed to levels of hypoxia from 11 to 17% O_2 (17). Shivering activity was reliably monitored using both neck muscle EMG and the vibration of a flexible platform supporting the animal. Hypoxia produced a progressive decrease in shivering activity during cold exposure. This hypoxia-induced shivering suppression resulted in a drop in T_{co}.

Longer duration hypoxic cold exposure showed that hypoxia initially reduced shivering and T_{CO} but that shivering resumed at a lower T_{CO} although not as vigorously as in controls (70%). At this point of shivering resumption, T_{CO} had fallen ~0.2°C from baseline. The authors suggested that this indicates the achievement of a "new quasi-steady state at a lower body temperature" (17). Viewed from the perspective of the null-zone model, this resumption of shivering at a lower T_{CO} may also suggest a lowering of the T_{CO} threshold for shivering thermogenesis by hypoxia.

In a follow-up study, Gautier *et al.* (16) showed, again in conscious cats, that hypoxia depresses shivering metabolism in the cold. Shivering index was linearly related to $\dot{V}_{O_2}$ under all thermal and gaseous conditions and hypoxia reduced $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at thermoneutrality by ~20%, suggesting a hypoxic suppression of overall metabolism independent of hypoxic suppression of thermogenesis.

The effects of hypoxia on $\dot{V}_{O_2}$, shivering and non-shivering thermogenesis in normal and cold-acclimatized rats have also been examined in the same laboratory (15). Shivering was evaluated using hind-limb EMG as an index. As shown for cats and other species, hypoxia resulted in an immediate, marked reduction in shivering and $\dot{V}_{O_2}$. As demonstrated in cats, a gradual recovery in $\dot{V}_{O_2}$ and shivering was observed so that after 35-45 minutes of hypoxia, the shivering averaged 98 ± 5% of control. Again, this could indicate a resetting of the threshold for shivering thermogenesis to a lower T_{CO}. When the rats were exposed to stepwise decreases in the temperature of a water bath, the ambient temperature threshold for shivering was similar in normoxia and hypoxia. However, rats cooled more quickly with hypoxia and thus the T_{CO} threshold for shivering had decreased by ~1°C.

The thermoregulatory system of birds, like that of mammals, is sensitive to hypoxia. At 10% O_2, shivering is markedly reduced and sometimes inhibited in pigeons, whereas at 7% O_2 shivering is eliminated (22). The FI_{O2} that begins to inhibit thermogenesis appears to be lower in birds than in mammals, perhaps because of the better ability of the bird to increase intrapulmonary gas and blood O_2 convective transports when exposed to hypoxia (1).

In contrast to the bulk of evidence for hypoxic shivering depression, a few studies have suggested that hypoxia does not alter shivering thermogenesis. In one study of dogs, hypoxia (12% O_2) immediately reduced the cold-induced increase in oxygen consumption by abolishing shivering (5). This effect was transient, however, since shivering resumed in about 20 minutes. The transient nature of the shivering suppression again suggests a reduction in the T_{co} threshold for shivering, since T_{co} continued to fall during the period of suppressed shivering. Because shivering resumed yet $\dot{V}_{O_2}$ remained ~25% below normoxic levels, these authors concluded that nonshivering thermogenesis (NST) may have been selectively abolished by hypoxia. This conclusion is suspect for two reasons. First, NST is thought to be insignificant, if not absent in larger, adult mammals. Second, the quantification of shivering in this study was unreliably based on a subjective rating of visible shivering intensity according to a simplistic 4 point scale.

A similar rationale and the same method of quantifying shivering led these investigators to similar conclusions regarding the effects of hypoxia on human thermoregulation (5). Oxygen consumption was reduced at altitude, but visual shivering was not, leading to the assumption that hypoxia preferentially impairs non-shivering thermogenesis. This conclusion is

suspect because NST in adult humans is thought to be minimal. For hypoxic reduction of NST to explain these results, NST must have a) accounted for 21% of total body metabolism and b) be totally abolished by moderate hypoxia. One other study has also suggested that hypoxia does not suppress shivering but rather impairs NST in humans (37). In this study, shivering was apparently increased by hypoxia although the choice of the sternocleidomastoid muscle for EMG recording may have biased this result due to the background hypoxic hyperventilation. The authors suggest, using similar logic to Blatteis and Lutherer (5), that a decrease in $\dot{V}_{O_2}$ despite increased shivering indicated a specific reduction in the NST component of thermogenesis by inhibition of the aerobic catabolism of fat stores. A major flaw in this study is that the time of shivering onset is not reported. Instead, the mean EMG value for the entire cooling period is given. It is possible that in humans, as has been reported for dogs (5) and rats (15), hypoxia only transiently suppresses shivering. If the shivering under hypoxic conditions recovered with time to a level higher than for normoxia, the average EMG index may appear to indicate greater shivering throughout hypoxia, although a temporary hypoxic suppression of shivering actually was present.

Non-shivering Thermogenesis

The contribution of NST to maintenance of body temperature in small and infant mammals is well-established and accepted (12). It has been demonstrated that hypoxia induces hypothermia in newborn rabbits (3) and other small mammals (15, 25) by inhibiting NST. Gautier *et al.* (15) showed in the rat that hypoxia suppressed both shivering and NST. As rats acclimatized to a cold environment and became more reliant on NST as a thermogenic mechanism, the hypoxic depression of NST became more

evident. In nonshivering cats, however, hypoxia had no effect on metabolic rate as indicated by $\dot{V}_{O_2}$ (24). This suggests a species difference with respect to the importance NST as a thermogenic mechanism and hence the effect of hypoxia on the non-shivering thermogenic responses to the cold.

More controversial, however, is the effect of hypoxia on NST in larger adult mammals including humans. In three studies that suggest that NST is preferentially suppressed by hypoxia in dogs (4) and humans (5, 37), the evidence is indirect and circumstantial. Since overall metabolism, as measured by $\dot{V}_{O_2}$, was depressed while shivering thermogenesis was reported as constant or increased, by elimination it was assumed that the decrease in metabolism represented suppression of NST. As discussed above, there are several reasons to doubt this hypothesis. It may be possible, for example, that there were errors in shivering measurement or that hypoxia decreases tissue metabolism in general due to a reduced supply of oxygen to the tissues.

Blood Flow

In addition to impairing thermogenesis, hypoxia also seems to enhance heat loss to the environment by altering the normal vasoconstriction response to cold exposure. Gellhorn (19) observed in a multi-species study that the greatest drop in T_{CO} occurred in animals with the largest surface area:mass ratio, indicating perhaps that hypoxia increased heat loss from the body's surface. Although this author failed to speculate on the mechanism for this enhanced surface heat loss, it is conceivable that peripheral vasodilation with hypoxia could explain his observations. Humans also may have markedly elevated skin temperatures when exposed to cold and breathing a hypoxic gas mixture (29). Kottke *et al.* (29) also cited

unpublished data showing increased lower leg peripheral blood flow, as measured by plethysmography, with hypoxia.

Despite the development of plethysmographic techniques for measuring limb blood flow in the 1940's, later researchers continued to infer the effects of hypoxia on peripheral blood flow from changes in skin temperature (T_{sk}). For example, Cipriano and Goldman (11) observed that the T_{sk} of human volunteers exposed to cool air was ~2°C higher at an altitude of 5000m than at sea level. Also, surface temperature showed a graded response with the T_{sk}'s at 2500m being consistently between those at 5000m and sea level. This suggested that hypoxia accelerated heat loss increasing the temperature gradient between the body surface and the environment by increasing skin blood flow.

In a similar study of humans at altitude, T_{sk} stabilized at higher values at altitude, probably indicating sustained cutaneous vasodilation or inhibited/delayed vasoconstriction (5). In this study, however, the authors conclude that the difference in T_{sk} may have been due to the effect of lowered barometric pressure on convective heat exchange rather than an increase in peripheral blood flow.

Studies of blood flow during hypoxia under thermoneutral conditions rather than during cold exposure have generally contradicted these findings in humans. In one study, hand blood flow, as measured by volume plethysmography, showed a marked reduction at altitude in both residents and sojourners (13). This suggests that altitude exposure produces a vasoconstriction that effectively redistributes blood volume from the extremities to the internal organs. Hypoxia induced by inhalation of low oxygen gas mixtures also results in peripheral vasoconstriction although this effect is prevented if hypoxic hypocapnia is prevented (49). Similar results

have been obtained in rabbits and dogs (47). Clearly more direct measurements of blood flow in humans exposed simultaneously to cold and hypoxia are required.

The Effect of Simultaneous Hypocapnia

Several studies of the effects of hypoxia on thermoregulation have attempted to separate the effect of hypoxia *per se* from that of hypocapnia subsequent to hypoxic hyperventilation. In general, it appears as if the inhibitory effects of hypoxia are very dependent on hypocapnia. In studies of conscious cats, Gautier *et al.* (16, 17) assessed the effects of hypocapnia by normalizing end-tidal CO_2 levels during inhalation of 12% O_2. Hypoxia produced a decrease in shivering activity and this suppression was reversed when end-tidal CO_2 was normalized. Shivering was again suppressed when CO_2 addition was withdrawn. Apparently, the effect of ambient hypoxia required hypocapnia. In pigeons, 7% hypocapnic hypoxia eliminated shivering (1). During normocapnic hypoxia, however, shivering persisted at ~50% of the normoxic intensity. The persistence of shivering appeared to result from the maintenance of higher levels of arterial PO_2 and CO_2 content with normocapnia. T_{co} dropped with both normocapnia and hypocapnia, although the decrease with normocapnic hypoxia was slightly less (0.04 vs. 0.09 °C).

CO_2 may lessen the depressive effect of hypoxia on thermoregulation by elevating PCO_2 levels in the blood. Elevated PCO_2 may increase cerebral blood flow, increasing the ability of the central neural structures to process and deliver thermoregulatory information (17). Conversely, hypocapnia may reduce the oxygen available to the tissues by inducing a left-shift in the oxyhemoglobin dissociation curve (Haldane effect).

During Heat Stress

As mentioned previously, little research has been conducted on the effect of hypoxia on the responses to elevated ambient or core temperatures. Some data exists, however, suggesting that hypoxia changes the normal heat dissipating responses of panting, sweating and vasodilation.

Panting/Sweating

Cats respond to an elevation in T_{co} by dissipating heat via increased respiratory frequency to enhance respiratory heat loss. Bonora and Gautier (6) have shown that for any given T_{co}, respiratory frequency was greater with hypoxic (hypocapnic) hypoxia than with air. A smaller though similar shift was observed with eucapnic hypoxia. Hypoxia appeared to facilitate heat loss by lowering the threshold for thermoregulatory panting (6). This is consistent with previous observations on cats during cold exposure (17) which suggested that hypoxia lowers the position of the thermoregulatory null zone (*i.e.*, lowers both sweating and shivering thresholds).

A hypoxic reduction in heat dissipation might be protective in the same sense that hypoxia-induced hypothermia may be. That is, the increased heat loss, resulting from lowered thresholds for sweating and vasodilation, may lower T_{co} and increase survival time of hypoxic animals by reducing metabolic rate and therefore O_2 demand according to the Q_{10} effect (6).

In humans, the T_{co} threshold for sweating has been shown to be unaffected by altitude and by extension, hypoxia (28,38). Altitude does, however, decrease the sensitivity of the sweating response by ~40% (28). The reduced sensitivity of sweating may be a direct effect of lowered O_2 tension on the sweat gland, possibly affecting synthesis of transmitter

substance, thereby reducing synaptic transmission (14). It is possible that studies of onset of sweating with chronic altitude exposure may be confounded by the dehydration that accompanies long-term sojourn to altitude.

Vasodilation

The normal vasodilatory response appears to be somewhat impaired by hypoxia. Humans at altitude display a reduced sensitivity of the skin vasodilatory response as well as a lowering the T_{co} threshold for vasodilation by ~0.3°C (28). Other studies have failed to show any effect of breathing a hypoxic gas mixture on cutaneous blood flow (39). However, the input to peripheral thermal receptors is different at altitude than when breathing hypoxic mixtures at sea level due to the different heat transfer characteristics of air in hypobaric conditions. This may account for the difference between the responses observed in these studies.

Possible Mechanisms for the Action of Hypoxia

In summary, hypoxia appears to impair thermoregulation in general by altering the thermoregulatory responses to both warm and cold challenge. There are several possible mechanisms underlying this hypoxic alteration in temperature control including: 1) limitation of O_2 supply to effector organs,2) disruption of hypothalamic function, 3) activation of peripheral chemoreceptors and 4) altered sympathetic nervous system activity.

Effector Organs

Shivering depends upon an adequate supply of O_2 to the shivering muscles. It is possible that a severe reduction in O_2 supply to the

muscles may result in the impairment of shivering observed with hypoxia. Studies on anesthetized dogs have observed that the O_2 consumption of exercising muscle decreases only at arterial O_2 tensions below 50 Torr (44). However, shivering is impaired in cats at levels of hypoxia (15% O_2) that produce little change in arterial O_2 levels (17). Clearly, electromechanical uncoupling produce by muscular hypoxia cannot explain the shivering impairment produced in this and other studies of mild hypoxia. Gautier *et al.* (17) predict that the lack of O_2 supply to shivering muscle may only begin to contribute to the impairment of shivering when inspired O_2 is less that 11% in intact animals.

Central/Hypothalamic

One possible explanation for the alteration in thermoregulation with hypoxia is that hypoxia produces a "coordinated readjustment of thermoregulatory processes, of which the suppression of shivering is only one manifestation" (17). Hypoxia might decrease shivering and body temperature through an alteration or a resetting of hypothalamically-controlled thermoregulatory processes. This suggestion is consistent with the hypoxic reduction in the thresholds for shivering (17) and panting (6). In support of this hypothesis, it has been shown that hypoxia induced changes in the thermosensitivity of preoptic hypothalamic neurons in anesthetized rats (46). Specifically, the activity of the warm-sensitive neurons was increased, perhaps explaining the decrease in the response thresholds observed with hypoxia and predicting a similar reduction in the warm response thresholds. Although far fewer cold sensitive neurons were examined (7 vs. 45), they appeared to show the same increase in activity with hypoxia as their warm-sensitive counterparts.

It is also possible that low O_2 content does not change the excitation thresholds within the hypothalamus but rather alters the neural traffic from intercranial neural structures (24). For example, decreased efferent signals to shivering muscles could explain the suppression of shivering. Changes in hypothalamic response thresholds, however, better explain the transient shivering suppression sometimes observed.

Peripheral Chemoreceptors

A second possible site of action for hypoxia is the peripheral chemoreceptors. If hypoxia affected the activity of these receptors and their signal traffic to the thermoregulatory centers, it could alter the pattern of temperature regulation. To address this possibility, Gautier *et al.* (17) exposed conscious cats to hypoxic hypoxia and carbon monoxide (CO) hypoxia. CO exposure and ambient hypoxia reduced shivering in the same manner, indicating that the action of hypoxia is on structures other than peripheral chemoreceptors which are little affected by CO.

Altered Sympathetic Activity

A final possibility is that hypoxia could alter overall sympathetic activity by inducing a generalized stress response. Human subjects tend to rate exercise or cold exposure during hypoxia as much more stressful or unpleasant than during normoxia (28). The elevations in heart rate and systolic blood pressure during hypoxia may also be evidence of increased sympathetic activity (37). Rowell *et al.* (38) examined the effect of arterial hypoxemia on the sympathetic nervous system and its control of warm responses. Hypoxemia did not block the reflex effects of hyperthermia on alpha-, beta- adrenergic, cholinergic or peptidergic effector systems. From

this study, it appears that acute moderate hypoxemia does not diminish the effectiveness of neuronal transmission in parts of the autonomic nervous system that are not activated by hypoxemia alone (38).

EFFECTS OF HYPERCAPNIA ON THERMOREGULATORY RESPONSES

The bulk of the experimental literature on hypercapnia, like that for hypoxia, deals with the effects of high CO_2 levels on temperature regulation during cold exposure. For this reason, this review will focus on the impact of hypercapnia on thermogenic and heat conserving mechanisms. Comparisons between studies in this field are difficult to make due to the large range of experimental models, cooling protocols and degrees of hypercapnia that have been examined. In general, it appears that hypercapnia does have a slight disruptive effect on maintenance of body temperature and that this effect is more pronounced in smaller mammals than in man.

During Cold Exposure

Body Temperature/Hypothermia

Early examinations of body temperature control under different gas regimes hinted at a hypothermic effect of CO_2 (20). Gellhorn (19) examined the effect of 3% CO_2 on T_{co} at various barometric pressures and various oxygen tensions in mice, rats and guinea pigs and showed that the fall in T_{co} was greater in the presence of CO_2 than in its absence. Most animal studies have been conducted on rats, rabbits, dogs and cats and all produce similar results (45).

The hypothermic response to CO_2 appears to be dose dependent. In rats at 24°C ambient temperature, there is a fairly linear relationship between the CO_2 concentration in the inspired air (from 0.03% to 20%) and the hourly decrease in T_{co} (45). A similar dose dependent hypothermia has been observed in rabbits (45) and guinea pigs. Guinea pigs, however, appear less sensitive to mild hypercapnia. During cold exposure, 5% CO_2 produced no change in T_{co} but exposure to 15% CO_2 produced a fall in T_{co} (41). The decreased oxygen consumption during hypercapnic cold exposure indicates that CO_2 may precipitate hypothermia by impairing some component of thermogenesis.

Studies of human subjects are less conclusive. Some have found an hypothermic effect of mild hypercapnia regardless of ambient temperature, despite no evidence of thermogenic impairment (48). Others have observed attenuation or delay of shivering thermogenesis with hypercapnia but no alteration in T_{co} cooling (30, 31). This discrepancy may be related to the degree of cold stress accompanying the hypercapnia. The studies showing a decrease in T_{co} have exposed subjects to cold air (5°C), while studies showing no decrease used cool water (15°C) as a cold stress (30, 31). It is possible that the high cooling rate in the water (~2°C/hr) masked the slight effects of hypercapnia on T_{co}.

Shivering

The most pronounced effect of hypercapnia, if any is observed, is usually a delay in the onset or an attenuation of shivering. In rats, inhalation of CO_2 in concentrations between 3 and 15% clearly suppressed shivering in cold environments (45). Similar results have been obtained in rabbits (45) and dogs (23) in which the observed decrease in oxygen consumption has

been linked to a suppression of the normal shivering response. In guinea pigs, inhalation of 15% CO_2 delayed the onset of shivering and suppressed shivering (41). In these experiments, some recovery in muscle activity was observed near the end of the 1 hour cold exposure period. The transient nature of shivering suppression has also been observed in rats breathing 4% CO_2 (18), and may indicate a downward shift in the T_{co} threshold for shivering with hypercapnia.

The effects of acute hypercapnia are reversed with chronic (3 day) exposure to high CO_2 levels in guinea pigs (41). These findings are consistent with those in dogs, in which 5% CO_2 decreased the hypothalamic set-point for shivering (36). That 5% CO_2 was adequate to impair thermoregulation in dogs, whereas 15% CO_2 was required for impairment in guinea pigs suggests a species difference in the sensitivity of the thermoregulatory system to hypercapnia.

The effect of hypercapnia on the shivering response in humans is less clear. Bullard and Crise (8) exposed subjects to an ambient temperature of 5°C while they inspired gas mixtures ranging from 2.5-6% CO_2. They observed a dose-dependent suppression of shivering. At 6% CO_2, shivering was eliminated in half the subjects and greatly reduced in the others. Upon reintroduction of room air, vigorous shivering immediately resumed. When inhalation of 6% CO_2 was continued, a rebound or breakthrough of shivering was observed after ~15 minutes. These observations suggest that CO_2 lowers the hypothalamic shivering threshold. As T_{co} dropped during the 15 minutes of shivering suppression, the total thermal drives to the hypothalamus were increased so that the thermostat could be activated at its depressed setting. These results suggest that CO_2 depressed shivering by lowering the shivering threshold.

In contrast, Wagner *et al.* (48) found that inhalation of 4% CO_2 neither delayed the onset of shivering in response to cold nor reduced shivering once it began in humans exposed to 5°C air. In fact, the authors suggested a slight increase in shivering in the later stages of hypercapnic cooling. The rate of T_{co} cooling was enhanced by breathing 4% CO_2, a fact difficult to explain when thermogenesis and cutaneous heat loss were unaffected. The small effect of increased respiratory heat loss would likely be compensated by the increased metabolic work associated with hyperventilation. By elimination, the authors implicate the increased convective heat loss due to hyperventilatory thoracic movements. It is more likely that the method used to quantify shivering was insensitive to the slight changes occurring with hypercapnia. Shivering tremor was measured using an accelerometer attached to the chair in which the subjects sat. The increased thoracic movements due to hyperventilation may have been picked up by the accelerometer, masking the decrease in shivering that may have occurred with hypercapnia.

Lun *et al.* (30) also failed to show an effect of 4% CO_2 on shivering of men immersed in 15°C water using EMG as an index of shivering. However, when subjects were cooled to a given core temperature (36.5 °C) and then switched to the hypercapnic gas mixture, the normal increase in shivering activity with decreasing T_{co} was markedly attenuated in under 1 minute (31). This effect was transient, with normoxic-levels of shivering returning in several minutes. Since the rate of core cooling remained constant during the hypercapnic period, the attenuation of shivering was not of large enough magnitude or duration to affect thermal balance.

Blood Flow

It was suggested as early as 1935 that hypercapnia had a vasodilatory effect on peripheral blood vessels during cold exposure (for review see (45)). Most experiments provide no evidence of this. In humans, measurements of skin temperatures have been used to indicate peripheral blood flow changes and have shown no effect of inhalation of 4% CO_2 (30, 48) or 6% CO_2 (8) on vessel tone in 15°C water or 5°C air. When measured in humans, skin heat flux (30) and forearm blood flow (48) have also been unchanged by hypercapnia during cold exposure. No studies have examined peripheral blood flow responses to hypercapnia under mild cold stress or at thermoneutrality

Although from these results it appears unlikely that hypercapnia affects peripheral vessel tone, it is possible that the degree of cold stress in these studies masked a small vasodilatory effect of CO_2. Studies of hypercapnic vessel tone during mild cold stress may clarify this issue.

During Heat Stress

Very few studies have examined the effects of hypercapnia on thermoregulation during heat stress. This likely stems from practical considerations. The conditions under which humans may be exposed to elevated levels of CO_2, during diving for example, are also situations in which hypothermia not hyperthermia is the main threat to performance and survival. However, some limited data is available on the panting and sweating responses during hypercapnia.

Panting/Sweating

Rats kept under hot (43°C) conditions and exposed to high CO_2 levels display impaired thermoregulation (45). Concentrations of CO_2 from 3-28%

augment the increase in T_{co} by 2-5°C compared with normocapnia. In dogs, hypercapnic hyperthermia appears to be connected with a prevention of the onset of panting in response to elevated temperatures. Unlike the hypothermic response, the hyperthermic action of CO_2 in these animals does not appear to be dose dependent (45). That is, the same response was observed from 3-28% CO_2.

In man, CO_2 inhalation also may disrupt the sweating response. Stupfel (45) reviewed early studies that reported spontaneous sweating onset when inhaling hypercapnic gas mixtures at neutral temperatures. This may be a simple stress response related to the hyperventilation accompanying hypercapnia or may in fact be due to an alteration of the signals or set-point of the hypothalamus.

No information is available on the effect of hypercapnia on the sweating behaviour of humans under heat stress or on thermoregulatory vasodilation. Clearly, more work is required on the effects of various levels of CO_2 on the thermoregulatory responses to heat challenge.

Possible Mechanisms for the Action of Hypercapnia

In summary, hypercapnia appears to promote a lowering of body temperature in certain species under certain cooling protocols. No effect on peripheral blood flow is usually evident despite an obviously negative heat balance in these studies. The hypothermic action of CO_2 may be due to increased respiratory heat loss, or changes in the control of shivering by the hypothalamus in response to acidosis or neuroendocrine disruptions.

Increased Respiratory Heat Loss

In his studies with animals, Gellhorn (19) initially proposed that the hypothermic effect of CO_2 was due to hyperventilation and an accompanying increase in respiratory heat loss. This theory has often been advanced as an explanation for increased heat loss in studies that observed a drop in T_{co} with no change in shivering or peripheral blood flow. However, experiments in which animals breathed 10% CO_2 at normal oxygen tension showed no changes in body temperature (19). Partitional heat balance calculations have indicated that respiratory heat loss can only account for a fraction of the difference in cooling rates between normocapnia and hypercapnia (48).

Acidosis

It is possible that the effects of CO_2 on thermoregulation result from the elevated carbonic acid levels in the blood as a result of CO_2 excess. If the inhibitory effects of CO_2 arise as a result of a drop in blood and CSF pH, then adequate buffering of these fluids may explain the absence of inhibitory effects in some studies (48). Lun *et al.* (30) suggested that the transient nature of shivering suppression observed by Bullard and Crise (8) and others may be the result of the time lag in compensation for the respiratory acidosis by plasma bicarbonate levels which rise significantly only after some delay (30). The delay in shivering onset observed by Lun *et al.* (30) corresponds well with the time required for plasma bicarbonate levels to rise satisfactorily to buffer the acidosis stemming from inhalation of 7-10% CO_2 (7).

Neuroendocrine

Evidence for hypercapnia-induced changes in neuroendocrine output comes mainly from studies in guinea pigs (41). Specifically, the fall and

subsequent rise in the threshold for shivering with chronic hypercapnia has been linked to a corresponding fall and rise in the norepinephrine concentration within the hypothalamus (40). Injection of norepinephrine into the hypothalamus also increased T_{co} and the shivering threshold of these animals (50).

SUMMARY AND CONCLUSIONS

Hypoxia and hypercapnia influence temperature regulation in most, if not all, mammals. In general, studies with animals have agreed that both of these environmental stresses impair the thermoregulatory responses to both cold and heat stress. The effects of hypoxia appear to be more pronounced than those of hypercapnia in most species and O_2 and CO_2 levels seem to interact to produce the observed effects of these gases.

The effects of hypoxia on human thermoregulation remain unclear. In humans, it is difficult to generalize from the results of many, disparate studies. More work is required using human volunteers, especially during heat stress, to accurately determine the effects of hypoxia and hypercapnia on temperature regulation. Basic research may shed some light on the possible mode of action of these gas mixtures in the thermoregulatory systems of humans.

To better clarify the effects of eucapnic hypoxia and hypercapnia on the warm and cold thermoregulatory responses of humans, two studies were conducted. These studies examined the T_{co} response thresholds for thermoregulatory responses in humans exposed to mild cold stress (28°C water immersion). In the first study, volunteers inhaled 12% O_2 balance N_2

with end-tidal CO_2 levels maintained at baseline (eucapnia) during the experimental trial and in the second study they inhaled 4% CO_2, 20.9% O_2 balance N_2.

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CHAPTER II. HYPOXIA LOWERS COLD THERMOREGULATORY RESPONSE THRESHOLDS AND ACCELERATES COOLING IN HUMANS

A. ABSTRACT

Hypoxia, which may result at high altitude or during certain disease states, alters the basic thermoregulatory responses of animals and humans. In cold-exposed animals, hypoxia increases core temperature (T_{co}) cooling rate and suppresses shivering and non-shivering thermogenesis. Experimental results in humans are equivocal. To determine the effects of eucapnic hypoxia on warm and cold thermoregulatory responses and T_{co} cooling during mild cold stress, we examined the sweating , vasoconstriction and shivering responses as well as T_{co} cooling rates of eight subjects immersed in 28°C water. Subjects exercised on an underwater cycle ergometer to elevate T_{co} past the sweating threshold. They then rested and cooled until shivering was manifest. The control inspirate was room air. For the experimental trial, subjects inspired 12% O_2/balance N_2 with added CO_2 to produce eucapnia. Eucapnic hypoxia lowered the T_{co} thresholds for vasoconstriction and shivering by approximately 0.14°C and 0.19°C, respectively and increased T_{co} cooling rate by 33%. These results demonstrate that eucapnic hypoxia enhances the T_{co} cooling rate in humans during mild cold stress and that this may be attributed in part to a delay in the onset of vasoconstriction and shivering.

Key words: sweating, shivering thermogenesis, vasoconstriction, normoxia, temperature regulation

B. INTRODUCTION

In humans, arterial hypoxemia may often occur in conjunction with increased thermal stress or a malfunctioning thermoregulatory system. For instance, hypoxemia may result from ambient hypoxia in military (*i.e.*, high altitude flight), recreational (*i.e.*, mountaineering) or diving (*i.e.*, inadequate air supply) activities. During these activities, hypoxia is often accompanied by thermal stress. For example, the military flight ensemble may include flight suits, chemical defense suits, life preservers, parachutes or even dry suits (in overseas flights). This increased insulation combined with radiant heating within the aircraft canopy may present a significant heat stress to the pilot. On the other hand, cold stress almost always accompanies high altitude mountaineering or diving in cold and/or deep water.

Hypoxemia may also occur in patients with diseases such as primary hypoventilation or interstitial lung disease. These patients are often elderly and may already experience thermoregulatory impairment. Hypoxia may further reduce their capacity to maintain temperature homeostasis during thermal stress. It is therefore important to fully understand the effects of hypoxia on human thermoregulation during warm or cold stress.

Hypoxia is thought to disrupt the thermoregulatory processes of both animals and humans. Experiments on guinea pigs (12), mice, dogs (19), rats (9) and pigeons (13) have shown that hypoxia results in a lowering of core temperature (T_{co}) during cold exposure in animals. A hypothermic effect of hypoxia has also been demonstrated in humans breathing hypoxic gas mixtures at cool and thermoneutral temperatures (28) and at altitude in the cold (7).

The lowering of T_{co} by hypoxia may be due to impaired thermogenesis, enhanced heat loss, or both. In laboratory animals, hypoxia

delays the onset of shivering (3) and reduces the maximal shivering response in the cold (9, 13, 19). The hypocapnia accompanying hypoxic hyperventilation appears to contribute to this thermoregulatory impairment since prevention of hypocapnia reduces the effect of the hypoxia in rats and cats (10, 11). Hypoxia also inhibits nonshivering thermogenesis (NST) in newborn rabbits (2), and small adult mammals (9, 14).

Human studies have produced equivocal results. Shivering has been reported to increase (28), remain constant (4) or decrease (19) during hypoxic cold exposure. NST may be inhibited by hypoxia although the evidence for this is indirect and circumstantial (4, 28). Studies at altitude have demonstrated elevated skin temperatures, suggesting that heat conservation by peripheral vasoconstriction may also be reduced by hypoxia (4, 7). However, more reliable measurements of blood flow in hypoxic humans are required to confirm these suggestions.

Although few studies have been conducted at high ambient temperatures, hypoxia also appears to affect the thermoregulatory responses to heat challenge. In cats, hypoxia shifts the threshold for thermal polypnea to a lower T_{co} and this response is reduced when hyperventilatory hypocapnia is prevented (5). In humans, altitude exposure reduces the sensitivity (rate of change of response with changing T_{co}) of the sweating and vasodilation responses but has no effect on the T_{co} threshold for sweating (18, 29). The T_{co} threshold for vasodilation is lowered by altitude exposure (18) but hypoxia has not been shown to affect cutaneous blood flow (30).

There are several limitations to previous work on the effects of hypoxia on human thermoregulation. In addition to inconsistent results during cold stress, little is known about the thermoregulatory effects of

hypoxia during heat challenge. The responses to heat and cold stress are often examined in separate studies rather than during a single procedure. Also, the effects of hypoxia on warm and cold response thresholds are unknown. Finally, the hypoxic stimulus has not been isolated from that of arterial hypocapnia subsequent to hypoxic hyperventilation in healthy human subjects. The purpose of this study was to determine the isolated effects of hypoxia (by maintaining end-tidal CO_2 at the baseline level) on T_{co} thresholds for warm and cold thermoregulatory responses as well as T_{co} cooling rates during mild cold stress. Accordingly, on two separate days human subjects were immersed in 28°C water and exercised to elevate their T_{co} and then cooled passively, allowing determination of T_{co} cooling rate and the T_{co} thresholds for sweating, vasoconstriction and shivering. On one day subjects breathed room air (control). On the other day they breathed 12% O_2/balance N_2 with CO_2 titrated to maintain eucapnia (eucapnic hypoxia).

C. METHODS

Subjects

With approval from our Faculty Human Ethics Committee, eight healthy, physically active subjects with no history of cardiovascular or respiratory disease (2 female, 6 male) volunteered to participate in this study after giving their written, informed consent. Subjects were (mean ± SD) 28.4 ± 6.3 years old, 1.75 ± 0.86 cm tall, weighed 68.2 ± 9.3 kg and had a sum of 4 skinfolds of 51.4 ± 17.0 mm (6). Female subjects were tested during the follicular phase (days 1-9) of their menstrual cycle.

Instrumentation

Esophageal temperature was measured using a Mon-a-therm® esophageal thermocouple (Mallinckrodt, St. Louis, MO) inserted through a nostril to the level of the heart. This site provides the best noninvasive representation of core blood temperature (8). Probe insertion depth was determined from sitting height according to the formula of Mekjavic and Remple (24). Heart rate was monitored continuously with a DC battery-operated 43100A Defibrillator/ECG monitor (Hewlett-Packard) with leads in a modified V_5 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 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.

Peripheral vessel tone, as indicated by fingertip blood flow, was assessed using a Perfusion Index derived from a modified Ohmeda Biox 3700 Pulse Oximeter (Ohmeda, Louisville, CO) with a clamp-type oximeter probe placed on the fourth digit. Infrared light of 2 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. 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: $Log(perfusion) = 0.98 \cdot Log(flow) + 0.04$, $r^2=0.88$ (27).

Oxygen consumption ($\dot{V}_{O_2}$) was determined by an open circuit method from measurements of expired minute volume and inspired and mixed expired gas concentrations sampled from a 5L fluted mixing box. Subjects wore a snugly fitting face mask with a one-way valve that was connected to the appropriate instrumentation by a suitable length of corrugated plastic tubing. Air was analyzed by a Beckman OM-11 O_2 sensor (Beckman, Anaheim, CA) and a DATEX 254 Airway Gas Monitor (Datex Instrument Corp., Helsinki, Finland) for O_2 and CO_2 fraction, respectively. Gas analyzers were calibrated against gases of known concentration prior to each session. Ventilatory rate and volume were monitored by a pneumotachometer (Hewlett Packard 47304A Flow Transducer).

End-tidal CO_2 was determined with an End-tidIL200 CO_2 analyzer (Instrumentation Laboratory, Lexington, MA). Expired gas was sampled from the mouthpiece at 200 ml/min and returned to the breathing circuit proximal to the pnemotachometer. End-tidal CO_2 was monitored on a chart recorder and maintained at resting baseline levels by adding CO_2 to the inspired gas line as needed.

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

Protocol

Subjects participated in one maximal exercise test and two experimental trials (control and eucapnic hypoxia), each on a separate day. In each test, the subject 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.

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 (males) 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 experimental trials was 50% of the maximum workload achieved during this session.

Experimental Trials

Each subject then participated in a control and a eucapnic hypoxia trial. These trials were conducted on separate days in a balanced order. 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. Time of day was standardized for each subject. During the instrumentation period (~30 minutes) subjects were covered with a cotton blanket and rested on a chair. Subjects remained seated for a 20 minute period to determine baseline levels for $\dot{V}_{O_2}$ and T_{co}. Subjects were then immersed in 28°C water to the clavicles and sat on the underwater cycle. They then pedaled at 60 rpm for 25 minutes 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 at water level and the pulse oximeter probe was attached to the middle finger to monitor peripheral vessel tone. Subjects remained seated on the ergometer in the circulated water and cooled passively until T_{co} dropped below the thresholds for sweating, vasoconstriction and finally, shivering. Immersions were terminated if shivering was continuous and vigorous or if T_{co} fell below 35.5°C.

Throughout the control trial, subjects inspired humidified room air. In the eucapnic hypoxia trial, subjects inspired humidified gas containing

12%O_2/balance N_2 with CO_2 added as required to maintain baseline end-tidal CO_2 levels. Subjects inspired the hypoxic gas mixture for the final 5 minutes of exercise and throughout the entire cooling period.

Statistical Analysis

Sweat rate, blood flow and $\dot{V}_{O_2}$ responses were plotted versus the change in T_{co} from the pre-immersion baseline (ΔT_{co}). Response thresholds were determined from these plots by three independent investigators blinded to trial and T_{co}. The sweating threshold was defined as the T_{co} at which sweat rate stabilized at the baseline level (~50 $g \cdot m^{-2} \cdot hr^{-1}$) (reference). The threshold for vasoconstriction was defined as the T_{co} at which fingertip blood flow reached its minimum (reference). The shivering threshold was indicated by a sustained elevation in $\dot{V}_{O_2}$ above the baseline level (22). This latter method has been validated in our laboratory against shivering threshold as determined by the self-report of subjects and increase in EMG activity (unpublished data). Thresholds are reported as the change in T_{co} from the baseline levels rather than absolute T_{co} to adjust for the daily variability in resting T_{co}. Subjects were required to rest in the lab until their T_{co} was stable and a baseline level could be confidently determined. Cooling rate was calculated by regression analysis of core temperature data from the end of exercise to the onset of shivering. Paired t-tests were used to test for significant differences in the response thresholds and the T_{co} cooling rates between the control and eucapnic hypoxia conditions (α=0.05). Sweat rate, $\dot{V}_{O_2}$, blood flow (PIavg), heart rate and minute ventilation ($\dot{V}_E$) were compared in the two trials at four times during the cooling period using paired t-tests. The probability of type I error was set at 5% and adjusted for

multiple comparisons over time (Bonferroni). Group data are presented as mean ± SD unless otherwise indicated.

D. RESULTS

Core Temperature Responses

The 25 minute exercise period elevated T_{co} by 0.71 ± 0.13 °C and 0.77 ± 0.3 °C during the control and eucapnic hypoxia trials, respectively. After completion of exercise the mean T_{co} cooling rate was 33% greater ($P<0.05$) during hypoxia (1.83 ± 0.72 °C·hr^{-1}) than during control (1.38 ± 0.85 °C·hr^{-1}) (Fig. 1).

$\dot{V}_{O_2}$, Sweat Rate and Blood Flow

Immediately after the completion of the exercise period, $\dot{V}_{O_2}$ was 1367 ± 319 ml/min during the control trial and 1124 ± 320 ml/min during the eucapnic hypoxia trial. $\dot{V}_{O_2}$ followed a nearly identical pattern in both trials, rapidly falling to resting levels and stabilizing at 442 ± 76 and 448 ± 134 ml/min by 20 min. in the control and eucapnic hypoxia trials respectively. In both trials, $\dot{V}_{O_2}$ increased slowly with time as core temperature decreased (Fig. 2).

Sweat rate was monitored throughout exercise and during the first 20-30 minutes of the cooling period. The ventilated capsule was removed as soon as sweat rate had fallen and stabilized at the baseline level. The magnitude and pattern of sweating varied widely from subject to subject and no significant differences existed between the conditions. Immediately following exercise, sweat rate was 465 ± 191 g·m^{-2}·hr^{-1} during the control

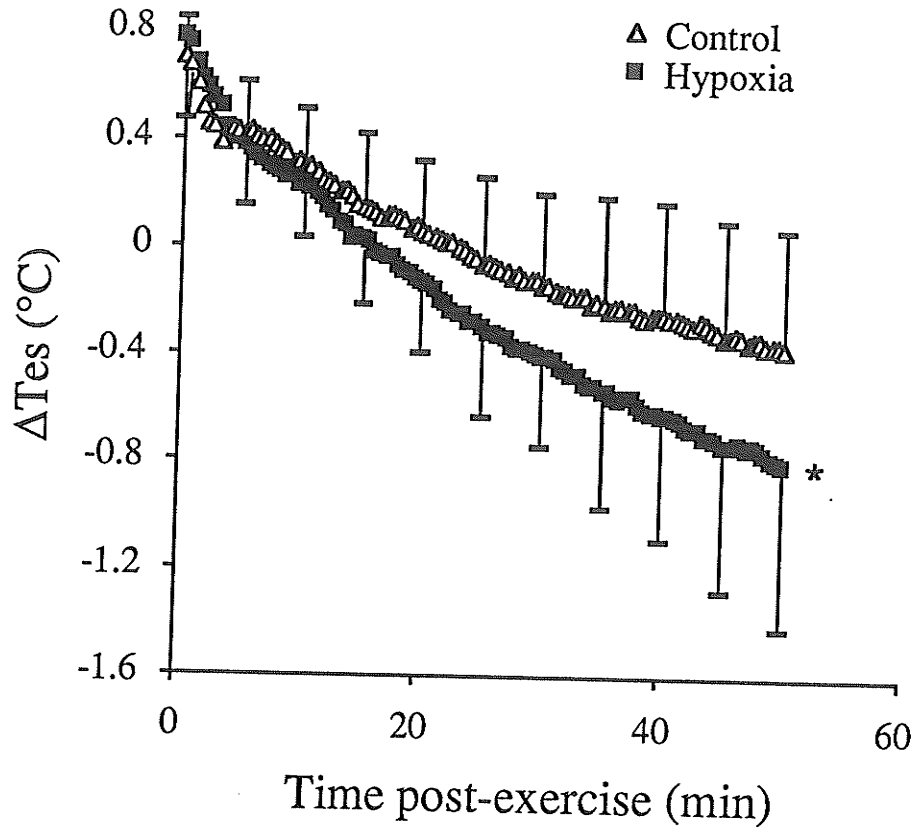

Figure 1. Group data (n=8) for esophageal temperature during post-exercise cooling in 28° C water. Data is presented as difference from baseline values. (Bars, SEM; *Rate of cooling greater during eucapnic hypoxia than during control, $P<0.05$).

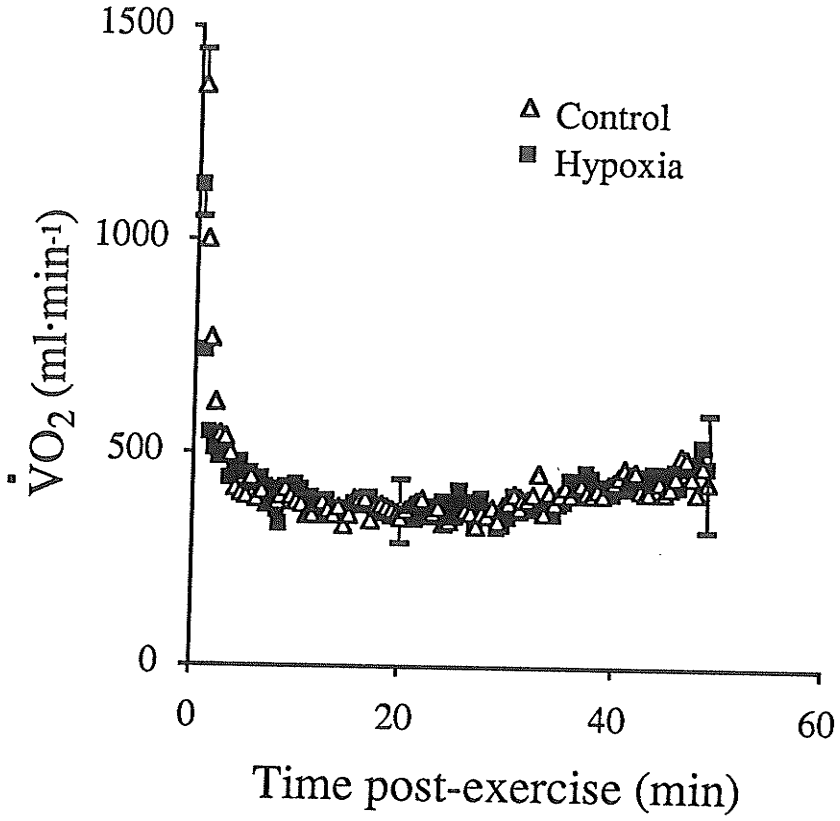

Figure 2. Mean oxygen uptake ($\dot{V}_{O2}$) during post-exercise cooling in control and eucapnic hypoxia trials (n=8).

trial and 498 ± 164 $g \cdot m^{-2} \cdot hr^{-1}$ during the eucapnic hypoxia trial. Sweat rate declined at a similar rate and in a similar pattern in the two conditions (Fig. 3).

Perfusion index data is only presented for 15 minutes following cooling since fingertip blood flow had fallen dramatically and stabilized at a low level by this time. When plotted against time, there was no difference in the maximal fingertip blood flow or the pattern or rate of decline of blood flow in the two conditions (Fig. 4).

Heart Rate and ($\dot{V}_E$)

Heart rate and ($\dot{V}_E$) both tended to be higher during eucapnic hypoxia than during the control trial. Heart rate immediately following exercise was 113 ± 23 $beats \cdot min^{-1}$ during the control trial and 116 ± 25 $beats \cdot min^{-1}$ during eucapnic hypoxia. In both trials, heart rate fell throughout the cooling period, reaching 73 ± 17 and 87 ± 7 $beats \cdot min^{-1}$ by 20 minutes during control and hypoxia trials, respectively. After 50 minutes of cooling, the heart rate was 65 ± 13.6 $beats \cdot min^{-1}$ during the control trial and 76 ± 3 $beats \cdot min^{-1}$ during eucapnic hypoxia (Fig. 5). These differences were not significant.

($\dot{V}_E$) followed a similar pattern to heart rate. Immediately following exercise the ($\dot{V}_E$) was similar in the 2 conditions but was significantly different at 15, 30 and 50 minutes post-exercise ($P<0.05$). After 50 minutes of cooling, ($\dot{V}_E$) was 11.8 ± 2.3 $L \cdot min^{-1}$ during the control trial and 26.0 ± 12.7 $L \cdot min^{-1}$ during eucapnic hypoxia (Fig. 6).

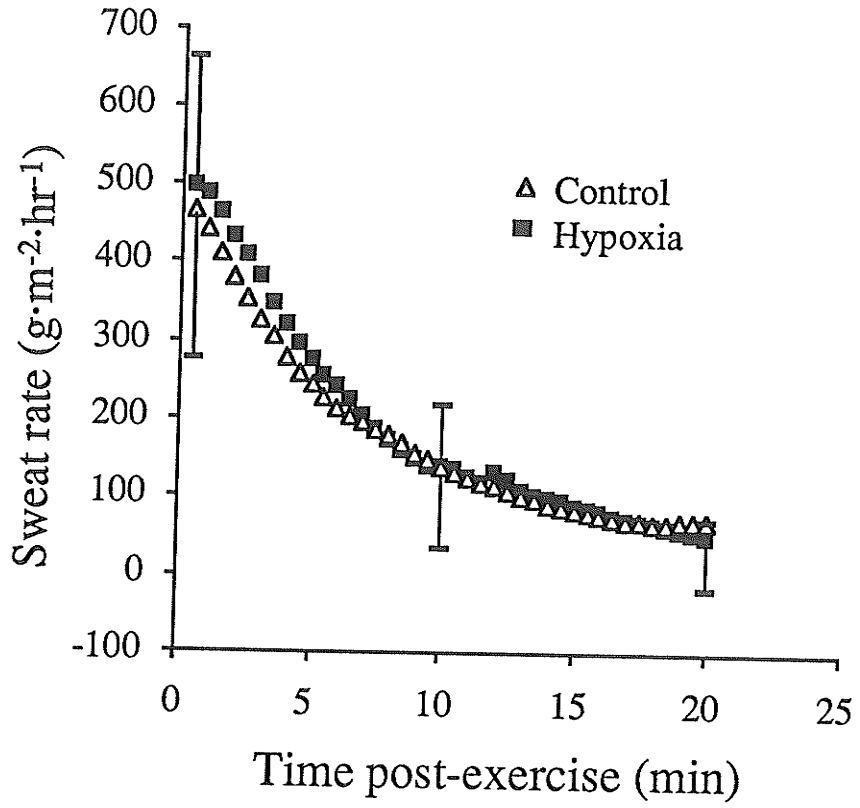

Figure 3. Mean sweat rate during post-exercise cooling in control and eucapnic hypoxia trials (n=8).

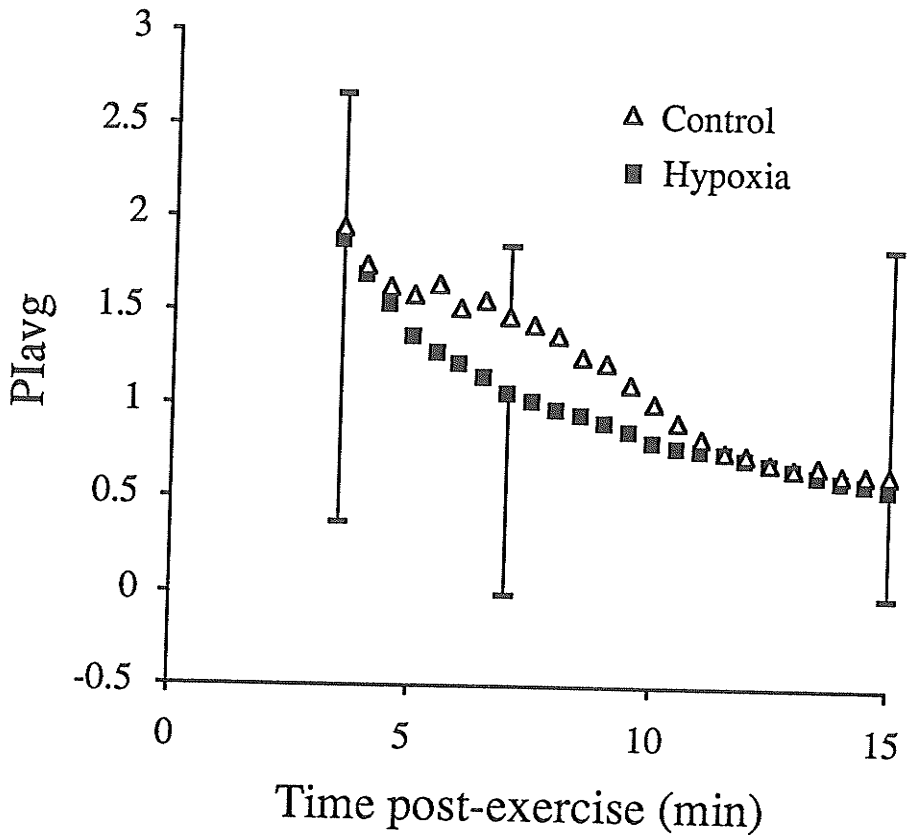

Figure 4. Fingertip blood flow, as indicated by a pulse oximeter-based perfusion index (PIavg), during post-exercise cooling in control and eucapnic hypoxia trials (n=8).

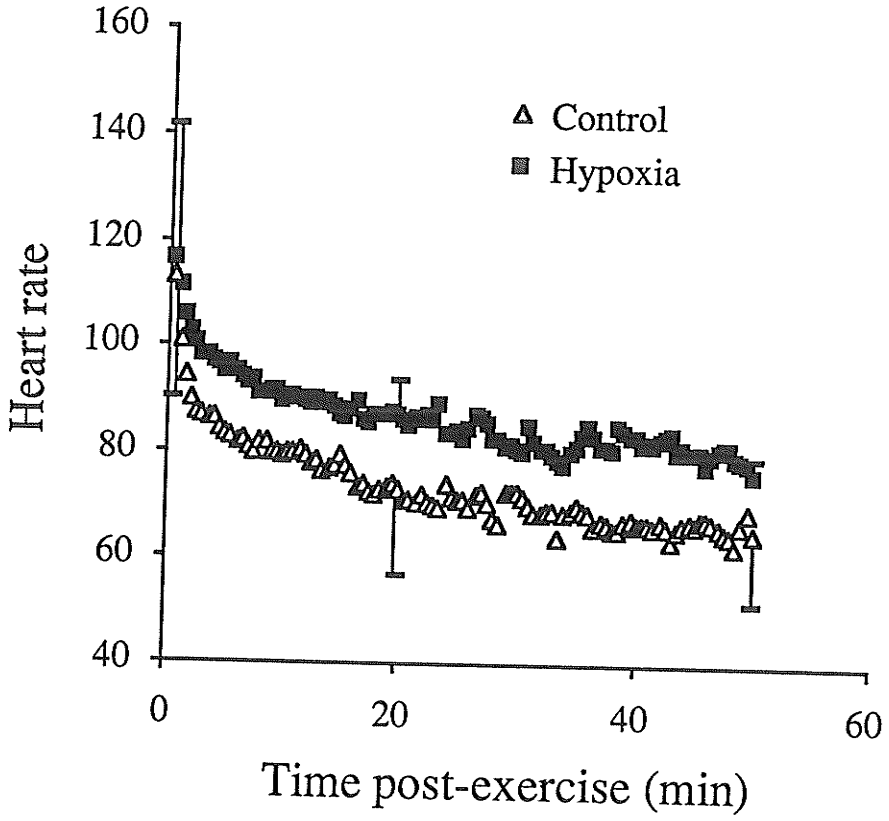

Figure 5. Mean heart rate during post-exercise cooling in control and eucapnic hypoxia trials (n=6).

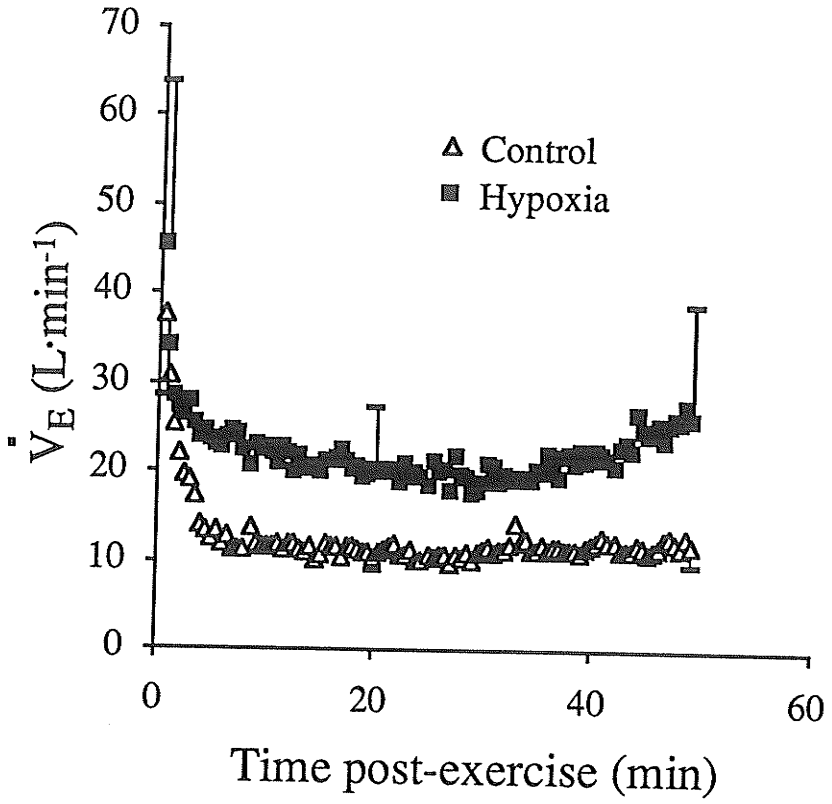

Figure 6. Mean minute ventilation ($\dot{V}_E$) during post-exercise cooling in control and eucapnic hypoxia trials (n=8).

Thermoregulatory Response Thresholds

Thermoregulatory response thresholds are reported as the change in core temperature (ΔT_{co}) relative to the baseline resting level (22). The vasoconstriction threshold was decreased by hypoxia in 4 of 8 subjects and unchanged in 4. As a result, the mean T_{co} threshold for vasoconstriction and was significantly reduced by hypoxia from 0.18 ± 0.21 °C above baseline during control to 0.05 ± 0.30 °C above baseline during hypoxia ($P<0.05$). Hypoxia lowered the shivering threshold in 7 of 8 subjects, and significantly reduced the mean shivering threshold from 0.44 ± 0.28 °C below baseline during control to 0.62 ± 0.25 °C below baseline during eucapnic hypoxia ($P<0.05$) (Fig. 7). Hypoxia lowered the sweating threshold in 3 subjects, raised the threshold in 1 subject and had no effect on the sweating threshold in 4 subjects. Although there was a tendency towards a lower mean sweating threshold with eucapnic hypoxia, the sweating threshold during eucapnic hypoxia (0.05 ± 0.33 °C above baseline) was not significantly different than during control (0.21 ± 0.12 °C above baseline). As a result of the parallel shifts in sweating and shivering thresholds, the size of the thermoregulatory null zone defined by Mekjavic *et al.* (22) was similar during control (0.64 ± 0.22 °C) and eucapnic hypoxia (0.67 ± 0.20 °C). The size of the interthreshold range was 0.02 ± 0.19 °C and 0.00 ± 0.36 °C during control and eucapnic hypoxia respectively.

E. DISCUSSION

This is the first study to isolate the effects of eucapnic hypoxia on core cooling rates and warm and cold thermoregulatory response thresholds in humans exposed to a mild cold stress (28°C water). Under these conditions, eucapnic hypoxia increases the rate of core cooling by 33%. This increased

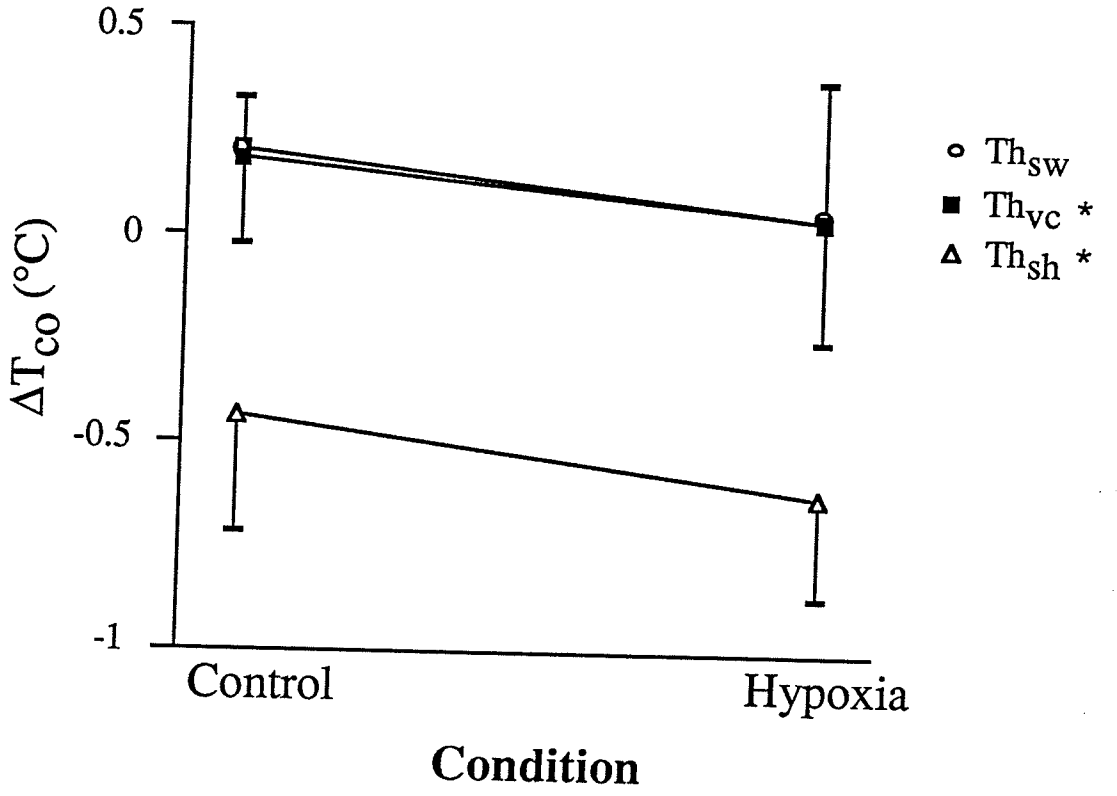

Figure 7. Mean core temperature response thresholds (plotted as change in esophageal temperature from pre-immersion baseline, or ΔT_{co}) under control and eucapnic hypoxic (12%O_2) conditions (Th_{sw}=sweating threshold, Th_{vc}=vasoconstriction threshold, Th_{sh}=shivering threshold,* $P<0.05$).

cooling may be linked to a delay in the initiation of heat conservation and production responses, since hypoxia lowered the thresholds for both vasoconstriction and shivering.

The experimental protocol, developed by Mekjavic *et al.* (22) and used in this study, has two considerable advantages. First, whole body water immersion effectively clamps skin temperature (T_{sk}) at approximately water temperature, removing the possible complication of changing cutaneous drive to the central thermoregulatory processing areas. This enabled the determination of the thermoregulatory responses to changes in T_{co} alone. Second, exercising and cooling while immersed in water is a safe, non-invasive method for manipulating T_{co} without changing T_{sk} compared with other available methods such as intravenous cold saline infusion (21) or the use of epidural anesthesia (17) in combination with external warming.

Our demonstration of a 33% increase in core cooling rate during eucapnic hypoxia is in agreement with previous work showing T_{co} depression in hypoxic animals and humans (7, 11, 12, 19, 28). In the present study, T_{co} after 55 minutes of immersion was significantly lower (~0.3 °C) during hypoxia than control ($P<0.05$). Following 60 minutes of exposure to 15°C air, Cipriano and Goldman (7) showed a hypoxic depression in rectal temperature (T_{re}) of approximately 0.3 °C at an altitude of 2500m and 0.45 °C at 5000m. Robinson and Haymes (28) also observed a depression in T_{re} of ~0.2 °C in humans breathing a 12% O_2 mixture for 90 min. at an ambient air temperature of 9°C.

Our data suggest that the increased rate of core cooling may be due to a downward shift in the T_{co} thresholds for vasoconstriction and shivering. Although no other studies have specifically examined these response thresholds during eucapnic hypoxia, several authors have reported a transient

depression of shivering by hypoxia in rats, cats and dogs (4, 9, 11). In retrospect, these findings may be explained by a hypoxic reduction of the threshold for shivering, with a resumption of shivering once T_{co} decreased to the new lower threshold temperature. The vasoconstriction response to cold exposure has also been reported to be blunted by hypoxia in humans, although the evidence for this is indirect. At altitude (2500, 5000m), T_{sk} stabilized at higher values than at sea level in air environments from 10-21 °C. The authors concluded that the increase in T_{sk} indicated increased peripheral blood flow due to a reduced vasoconstriction response (4, 7).

We observed a tendency for the sweating threshold to be reduced by eucapnic hypoxia. However, due in part to high inter-subject variability in the sweating response (25), this reduction was not statistically significant. Given the variability in the sweating response, the probability of type II error is acknowledged. This is consistent with earlier reports suggesting that the sweating threshold in humans is not significantly affected by altitude (18, 29).

As a result of the parallel downward shifts in the sweating, vasoconstriction and shivering thresholds, the size of the thermoregulatory null zone (range of T_{co}'s between sweating and shivering thresholds) and the interthreshold range (range of T_{co}'s between sweating and vasoconstriction thresholds) were unchanged by eucapnic hypoxia. In the present study the null zone was 0.64 ± 0.22 °C during control and 0.66 ± 0.20 °C during eucapnic hypoxia. Mekjavic *et al.* (22) reported a similar value of 0.58 ± 0.23 °C during 28 °C water immersion under conditions similar to our control trial. In a subsequent study, Mekjavic and Sundberg (25) reported a similar null zone of 0.59 ± 0.27 °C during a control trial and a significant increase in the null zone to 0.95 ± 0.50 °C with inhalation of 30% nitrous

oxide. Therefore, we are confident that eucapnic hypoxia has little effect on the null zone value. The size of the interthreshold range in the present study was 0.02 ± 0.19 °C and 0.00 ± 0.36 °C during control and eucapnic hypoxia respectively. In contrast, Lopez *et al.* (21) reported an interthreshold range of ~0.2 °C. There are two possible explanations for this discrepancy. First, using exercise to elevate T_{co}, rather than external warming (as performed by Lopez *et al.* (21)), may have produced different patterns of sweating and/or vasoconstriction. Second, the present study defined the sweating threshold as the T_{co} where sweat rate fell to baseline levels while Lopez *et al.* (21) measured the T_{co} at sweating initiation. A hysteresis is often observed between sweating initiation and offset, with initiation occurring at a higher T_{co} (23). This may therefore explain the difference in the interthreshold ranges between these studies.

The small effect of eucapnic hypoxia on human thermoregulatory responses is not surprising. In studies of conscious cats, Gautier *et al.* (10, 11) demonstrated a reduction in shivering activity by hypocapnic hypoxia (FIO_2=12%, hypocapnia resulting from hypoxic hyperventilation) and a significant reversal of this effect when end-tidal CO_2 was normalized. Shivering was again suppressed when the hypocapnic condition was restored. Similarly, in pigeons hypocapnic hypoxia eliminated shivering while during eucapnic hypoxia shivering persisted at 50% of the normoxic intensity (1). It is likely that hypocapnic hypoxia may produce more striking changes in human thermoregulation than those observed in this study. This may be expected since hypocapnia causes cerebral vasoconstriction which would limit blood flow and therefore O_2 supply to the thermoregulatory centers (31). In addition, hypercapnia (4% CO_2) in isolation has been shown

to cause a reduction in the shivering threshold similar to that observed with eucapnic hypoxia (16).

There are several possible mechanisms for a hypoxic depression of the cold response thresholds and enhancement of core cooling rates observed in the present study including: 1) limitation of O_2 supply to effector organs, 2) decreased efferent output to effector organs and 3) disruption of central thermoregulatory control centers.

First, hypoxia may impair normal shivering thermogenesis by limiting O_2 supply to thermogenic effector organs, although this is unlikely to fully explain our results. In cats, shivering is impaired at levels of hypoxia (15% O_2) that produce little fall in arterial O_2 content (11). Although a lower FIO_2 (12%) was used in this study, a suppression of shivering metabolism due to a limited O_2 supply would not be consistent with observations in exercising muscle (15). Gautier *et al.* (11) predicted that the lack of O_2 supply to shivering muscle may only begin to contribute to the impairment of shivering when inspired O_2 is less than 11%.

Second, it is possible that hypoxia decreased efferent output to effector organs by affecting peripheral chemoreceptors, skin temperature sensors or spinal reflexes. It is unlikely that hypoxia-induced increases in peripheral chemoreceptor drive fully explains our observations. Although chemoreceptor stimulation has been shown to inhibit shivering in anesthetized rabbits (26), shivering suppression is also observed with carbon monoxide hypoxia and carotid body denervation, neither of which affect peripheral chemoreceptor output (10, 11). The specific effect of hypoxia on skin temperature receptors has not been tested and cannot be predicted, because hypoxia has been shown to increase activity in some groups of neurons and decrease activity in others (32). Spinal

intersegmental reflex mechanisms and outputs are unaffected by hypoxia and are therefore unlikely to explain the results of this study (20).

Third, hypoxia might produce its depressive effects on T_{co} response thresholds through a direct effect on hypothalamic neurons, altering their integrative control function and subsequent efferent signaling. Hypoxia has been shown to change the thermosensitivity of preoptic hypothalamic neurons in anesthetized rats (32). Specifically, hypoxia increases the activity of warm-sensitive neurons which would tend to lower the cold response thresholds as the integrated signal in the hypothalamus would be overestimated at a given T_{co}.

Despite the relatively small reductions in the cold response thresholds, the rate of core cooling during mild cold exposure was markedly enhanced by eucapnic hypoxia in this study. The enhanced heat loss with hypoxia may be partly explained by an increase in respiratory heat loss due to hypoxic hyperventilation. Although the inspirate was humidified to reduce respiratory heat loss, ($\dot{V}_E$) doubled during eucapnic hypoxia (11.8 ± 2.3 $L \cdot min^{-1}$ vs. 26.0 ± 12.7 $L \cdot min^{-1}$ at 50 minutes post-exercise). This increased ventilation could have increased respiratory heat loss or convective heat loss to the water due to increased thoracic movements. This increase in respiratory heat loss coupled with a delay in the initiation of heat conserving (vasoconstriction) and producing (shivering) mechanisms likely explains the increased cooling rate with eucapnic hypoxia.

In summary, we provide the first demonstration of the effects of eucapnic hypoxia on the T_{co} thresholds for warm and cold thermoregulatory responses and core cooling rate in humans exposed to mild cold stress. Eucapnic hypoxia lowered the core temperature thresholds for vasoconstriction and shivering. Although these changes were small, the rate

of core cooling increased by 33%. It is possible that hypocapnic hypoxia (as would be experienced at altitude) would produce an even greater effect on the responses to cold exposure.

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CHAPTER III. HYPERCAPNIA LOWERS THE SHIVERING THRESHOLD AND INCREASES CORE COOLING RATE IN HUMANS

A. ABSTRACT

Hypercapnia, which may be encountered by patients during general anesthesia with spontaneous respiration or during diving operations, alters the basic thermoregulatory responses of animals and humans. In cold-exposed animals, 3-10 % CO_2 impairs thermal homeostasis by attenuating shivering and promoting heat loss through peripheral vasodilation. Experimental results with humans are equivocal. To determine the effects of hypercapnia on warm and cold thermoregulatory responses and core cooling rates during mild cold stress, we determined the core temperature (T_{co}) thresholds for sweating, vasoconstriction and shivering as well as body core cooling rates of eight subjects immersed in 28°C water. Subjects exercised on an underwater cycle to elevate T_{co} above the sweating threshold. They then terminated exercise and passively cooled until shivering was manifest. Subjects breathed either room air (control) or 4% CO_2/20.9% O_2/balance N_2 (hypercapnia) throughout the cooling period. There was a significantly greater rate of core cooling during hypercapnia (1.74 $\pm$ 0.8 °C·hr^{-1}) (mean $\pm$ SD) than during control (1.39 $\pm$ 0.9 °C·hr^{-1}). Hypercapnia did not alter the thresholds for sweating or vasoconstriction but lowered the threshold for shivering by approximately 0.13 $\pm$ 0.04 °C (mean $\pm$ SE). These results demonstrate that hypercapnia enhances core cooling rate during mild cold stress and that this may be attributed in part to a delay in shivering onset.

Key words: sweating, thermoregulation, vasoconstriction, carbon dioxide, temperature regulation

B. INTRODUCTION

General anesthesia inhibits human thermoregulation and disrupts thermal homeostasis partly as a result of decreasing core temperature thresholds for vasoconstriction and shivering. For example, 30% nitrous oxide has been shown to reduce the shivering threshold by ~ 0.6 °C and decrease the intensity of the shivering response (15) and halothane reduces the threshold for vasoconstriction by ~2.5 °C (19). As a result of such thermoregulatory impairment, patients may become hypothermic during surgery. Since many patients become hypercapnic during anesthesia with spontaneous respiration, it is important to know whether hypercapnia itself exerts a separate inhibitory effect on human thermoregulation and heat balance.

Early studies on laboratory animals have shown that inhalation of gas mixtures containing 3 to 10% CO_2 during cold exposure impairs thermal homeostasis by attenuating shivering and promoting heat loss through peripheral vasodilation (20). The effects of hypercapnia in humans under similar conditions are less clear. Bullard and Crise (4) exposed subjects to 5°C air for 30 minutes during which CO_2 concentrations from 2.5 - 6% were inspired. They observed a suppression of shivering proportional to the concentration of CO_2 inspired. Suppression was transient and shivering displaying a rebound with continued cold exposure. This disinhibition was attributed to increased thermal drive due to the increased respiratory heat loss resulting from hypercapnic hyperventilation. More recently, however, Wagner *et al.* (22) found that inhalation of 4% CO_2 for 60 minutes neither delayed nor suppressed shivering in cold (5°C) or thermoneutral (29°C) air environments. Lun *et al.* (11), also failed to demonstrate an effect of hypercapnia on shivering when men breathed 4% CO_2 throughout ~ 60

minutes of immersion in 15°C water. In a subsequent study subjects were cooled in 15°C water to a core temperature (T_{co}) of 36.5°C while breathing room air. Subjects were then switched to a 4% CO_2 gas mixture for 15 minutes (12). Prior to the hypercapnic period, shivering activity gradually increased with decreasing T_{co}. This consistent increase in shivering activity was attenuated by hypercapnia and resumed once the inspirate was switched back to room air.

In general, the studies showing a decrease in T_{co} with hypercapnia have used a relatively mild cold stress (5°C air) compared with those showing no hypothermic effect of hypercapnia (15°C water). It is possible that the primary inhibitory effects of hypercapnia on thermoregulation are overridden by a more severe cold stress and that these inhibitory effects may be more evident during milder cold stress. In some cases, the attenuation of the shivering response by hypercapnia may be explained by a lowering of the shivering threshold although core response thresholds during hypercapnia have not been examined. Also, little is known about the thermoregulatory effects of hypercapnia during heat challenge. Therefore, this study was performed to determine the effects of hypercapnia on core temperature thresholds for warm and cold thermoregulatory responses, as well as the rate of core cooling, during mild cold stress. Accordingly human subjects were immersed in 28°C water (to maintain a constant skin temperature) and exercised to elevate their T_{co} until sweating was manifest. They then terminated exercise and cooled passively, allowing determination of T_{co} cooling rate and the T_{co} thresholds for sweating, vasoconstriction and shivering.

C. METHODS

Subjects

With approval from our Faculty Human Ethics Committee, eight healthy, physically active subjects (2 female, 6 male) volunteered to participate in this study after giving their written, informed consent. Those on medication or with a history of cardiovascular or respiratory disease were excluded. Subjects were (mean ± SD) 28.4 ± 6.3 years old, 175.3 ± 8.9 cm tall, weighed 69.0 ± 9.9 kg and had a sum of 4 skinfolds of 49.5 ± 18.6 mm (3). Female subjects were tested during the follicular phase (days 1-9) of their menstrual cycle.

Instrumentation

Esophageal temperature was measured using a Mon-a-therm® esophageal thermocouple (Mallinckrodt, St. Louis, MO) inserted through a nostril to the level of the heart. This site provides the best noninvasive representation of core blood temperature (5). Probe insertion depth was determined from sitting height according to the formula of Mekjavic and Remple (14). Heart rate was monitored continuously with a DC battery-operated 43100A Defibrillator/ECG monitor (Hewlett-Packard) with leads in a modified V_5 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 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.

Peripheral vessel tone, as indicated by fingertip blood flow, was assessed using a Perfusion Index derived from a modified Ohmeda Biox 3700 Pulse Oximeter (Ohmeda, Louisville, CO) with a clamp-type oximeter probe placed on the fourth finger. Infrared light of 2 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. 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 (16).

Oxygen consumption ($\dot{V}_{O_2}$) was determined by an open circuit method from measurements of expired minute volume and inspired and mixed expired gas concentrations sampled from a 5L fluted mixing box. Subjects wore a snugly fitting face mask with a one-way valve that was connected to the appropriate instrumentation by a suitable length of corrugated plastic tubing. Air was analyzed by a Beckman OM-11 O_2 sensor (Beckman, Anaheim, CA) and a DATEX 254 Airway Gas Monitor (Datex Instrument Corp., Helsinki, Finland) for O_2 and CO_2 fraction,

respectively. Gas analyzers were calibrated against gases of known concentration prior to each session. Ventilatory rate was monitored by a pneumotachometer (Hewlett Packard 47304A Flow Transducer).

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

Protocol

Subjects participated in one maximal exercise test and two experimental trials (control and hypercapnia), each on a separate day. In each test, the subject 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.

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 (males) 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 experimental trials was 50% of the maximum workload achieved during this session.

Experimental Trials

Each subject then participated in a control and a hypercapnia trial. These trials were conducted on separate days in a balanced order. 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. Time of day was standardized for each subject. During the instrumentation period (~30 minutes) subjects were covered with a cotton blanket and rested on a chair. Subjects remained seated for a 20 minute period to determine baseline levels for $\dot{V}_{O_2}$ and T_{co}. Subjects were then immersed in 28°C water to the clavicles and sat on the underwater cycle. They then pedaled at 60 rpm for 25 minutes 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 at water level and the pulse oximeter probe was attached to the middle finger to monitor peripheral vessel tone. Subjects remained seated on the ergometer in the circulated water and cooled passively until T_{co} dropped below the thresholds for sweating, vasoconstriction and finally, shivering. Immersions were

terminated if shivering was continuous and vigorous or if T_{co} fell below 35.5°C.

Throughout the control trial, subjects inspired humidified room air. In the hypercapnia trial, subjects inspired humidified gas containing 4%CO_2/ 20.9%O_2/balance N_2. Subjects inspired this hypercapnic gas mixture for the final 5 minutes of exercise and throughout the entire passive cooling period.

Statistical Analysis

Sweat rate, blood flow and $\dot{V}_{O_2}$ responses were plotted versus the change in T_{co} from the pre-immersion baseline (ΔT_{co}). Response thresholds were determined from these plots by three independent investigators blinded to trial and T_{co}. The sweating threshold was defined as the T_{co} at which sweat rate stabilized at the baseline level (~50 $g \cdot m^{-2} \cdot hr^{-1}$) (reference). The threshold for vasoconstriction was defined as the T_{co} at which fingertip blood flow reached its minimum (reference). The shivering threshold was indicated by a sustained elevation in $\dot{V}_{O_2}$ above the baseline level (13). This latter method has been validated in our laboratory against shivering threshold as determined by the self-report of subjects and increase in EMG activity (unpublished data). Thresholds are reported as the change in T_{co} from the baseline levels rather than absolute core temperature to adjust for the daily variability in resting T_{co}. Subjects were required to rest in the lab until their T_{co} was stable and a baseline level could be confidently determined. Cooling rate was calculated by regression analysis of core temperature data from the end of exercise to the onset of shivering. Paired t-tests were used to test for significant differences in the response thresholds and the T_{co} cooling rates between the control and eucapnic hypoxia conditions (α=0.05). Sweat rate, $\dot{V}_{O_2}$, blood flow (PIavg), heart rate and

minute ventilation ($(\dot{V}_E)$) were compared in the two trials at four times during the cooling period using paired t-tests. The probability of type I error was set at 5% and adjusted for multiple comparisons over time (Bonferroni). Group data are presented as mean ± SD unless otherwise indicated.

D. RESULTS

Core Temperature Responses

The 25 minute exercise period elevated T_{co} by 0.83 ± 0.3 °C and 0.74 ± 0.3 °C during the control and hypercapnia trials, respectively. After completion of exercise the mean T_{co} cooling rate was 25% greater ($P<0.05$) during hypercapnia (1.74 ± 0.81 °C·hr^{-1}) than control (1.39 ± 0.88 °C·hr^{-1}) (Fig. 8).

$\dot{V}_{O_2}$, Sweat Rate and Blood Flow

Immediately after the completion of the exercise period, $\dot{V}_{O_2}$ was 1430 ± 206 ml·min^{-1} during control and 1724 ± 328 ml·min^{-1} during hypercapnia (NS). $\dot{V}_{O_2}$ followed similar patterns in both trials, rapidly falling to resting levels of 371 ± 68 and 439 ± 97 ml·min^{-1} by 20 minutes in the control and hypercapnia trials, respectively (NS). In both trials, $\dot{V}_{O_2}$ increased slowly with time as core temperature decreased (Fig. 9).

Sweat rate was monitored throughout exercise and during the first 20-30 minutes of the cooling period. There was a high sweat rate following 20 minutes of exercise that was maintained when hypercapnia was introduced. The ventilated capsule was removed as soon as sweat rate had fallen and stabilized at the baseline level.

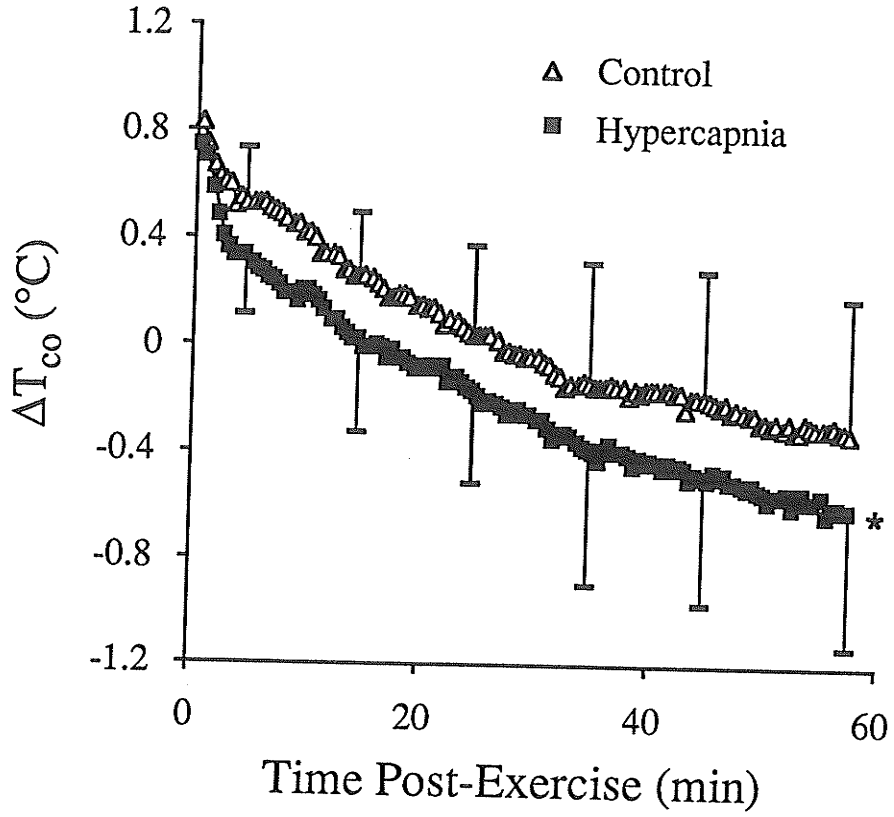

Figure 8. Group data (n=8) for esophageal temperature during post-exercise cooling in 28° C water. Data is presented as difference from baseline values. (Bars, SEM; *Rate of cooling greater during hypercapnia than during control, $P<0.05$).

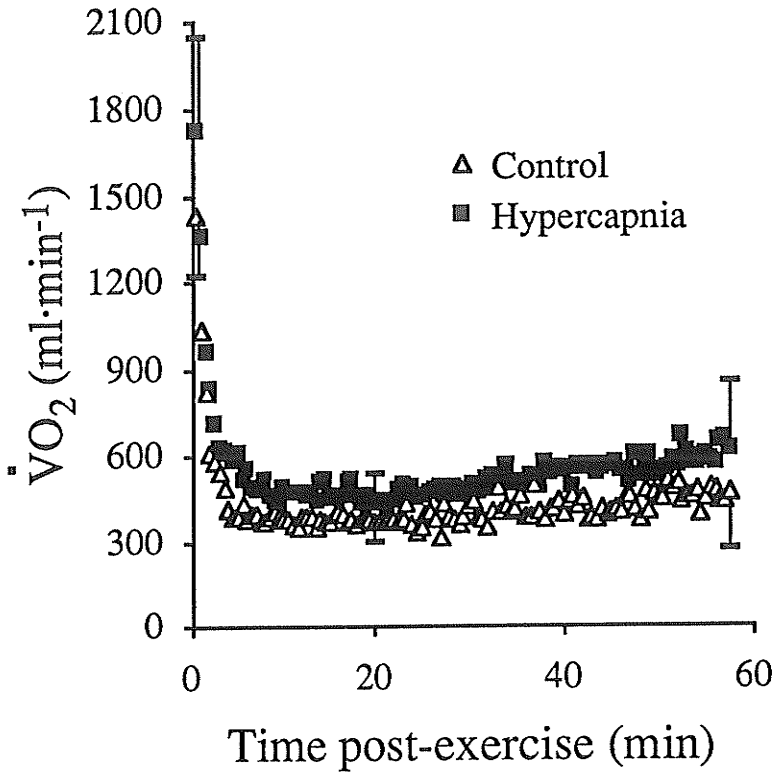

Figure 9. Mean oxygen uptake ($\dot{V}_{O_2}$) during post-exercise cooling in control and hypercapnia trials (n=8).

The magnitude and pattern of sweating varied widely from subject to subject. Immediately following exercise, sweat rate was 451 ± 212 $g \cdot m^{-2} \cdot hr^{-1}$ during the control trial and 490 ± 200 $g \cdot m^{-2} \cdot hr^{-1}$ during the hypercapnia trial (NS). Sweat rate declined at a similar rate and in a similar pattern in the two conditions (Fig. 10).

Perfusion index is only presented for 15 minutes following cooling since fingertip blood flow had fallen dramatically and stabilized at a low level by this time. When plotted against time, there was no difference in the maximal fingertip blood flow or the pattern or rate of decline of blood flow in the control and hypercapnia trials (Fig. 11).

Heart Rate and $\dot{V}_E$

The pattern of heart rate response was similar in the two trials. Heart rate immediately following exercise was 117 ± 21 $beats \cdot min^{-1}$ during control and 125 ± 14 $beats \cdot min^{-1}$ during hypercapnia (Fig. 12). In both conditions, heart rate fell throughout the cooling period, reaching 76 ± 10 and 79 ± 9 $beats \cdot min^{-1}$ after 20 minutes during control and hypercapnia trials respectively (NS). At 40 minutes post exercise, the heart rate during hypercapnia was significantly higher than control ($P<0.05$). After 58 minutes of cooling, the heart rate was 66 ± 8 during control and 71 ± 9 $beats \cdot min^{-1}$ during hypercapnia (NS).

$\dot{V}_E$ was significantly higher throughout the cooling period during hypercapnia ($P<0.05$). Immediately following exercise, $\dot{V}_E$ was 40 ± 8 $L \cdot min^{-1}$ during control and 66 ± 13 L/min during hypercapnia. $\dot{V}_E$ fell rapidly, but remained significantly higher during hypercapnia

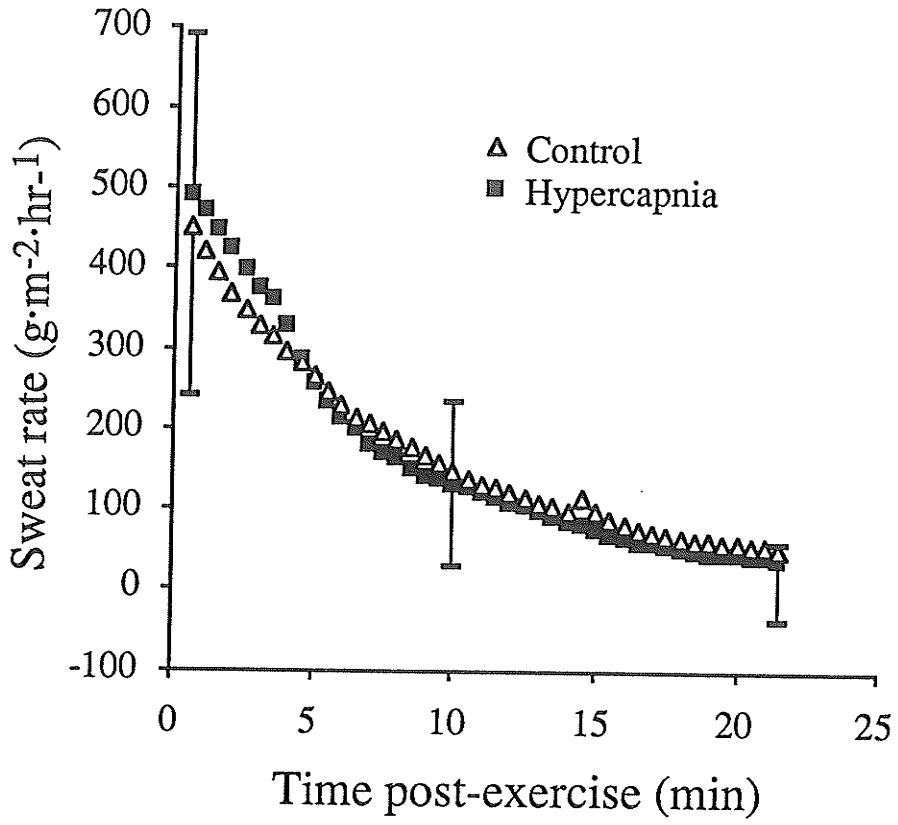

Figure 10. Mean sweat rate during post-exercise cooling in control and hypercapnia trials (n=8).

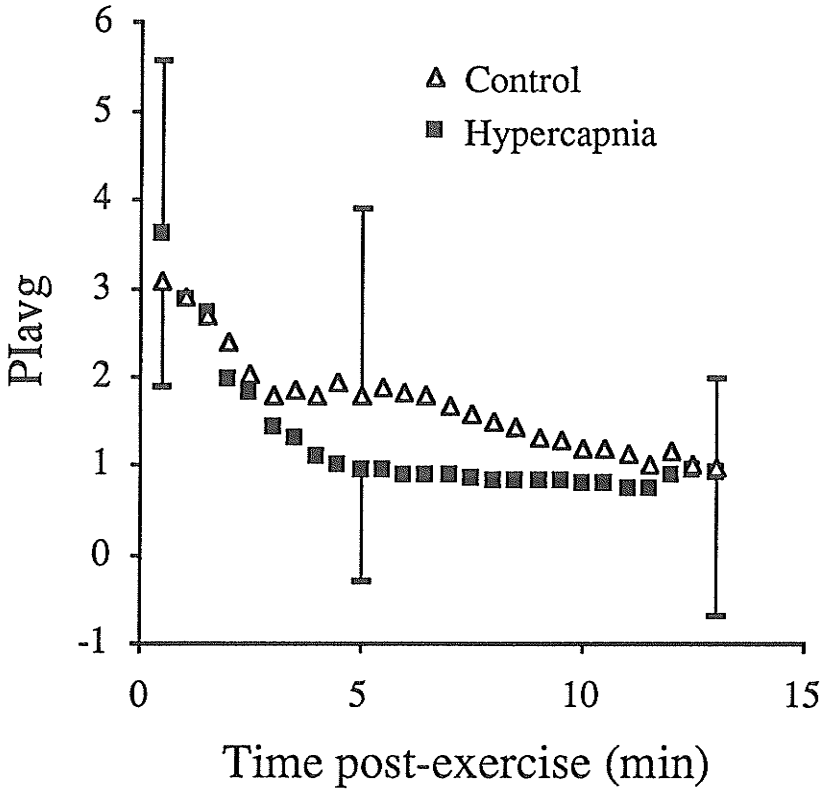

Figure 11. Fingertip blood flow, as indicated by a pulse oximeter-based perfusion index (PIavg), during post-exercise cooling in control and hypercapnia trials (n=8).

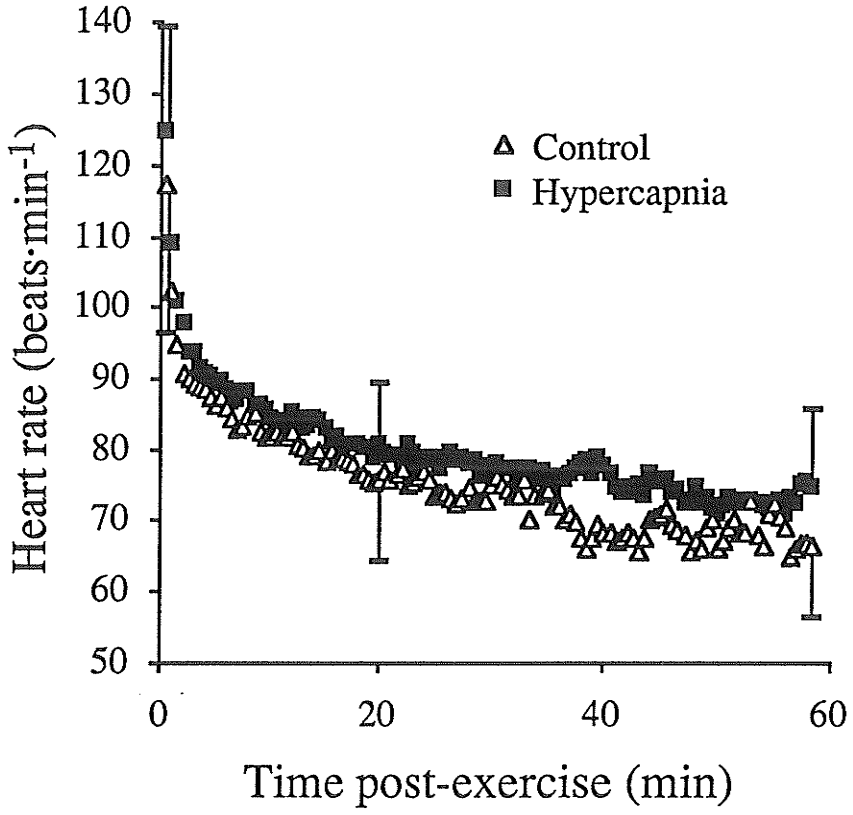

Figure 12. Mean heart rate during post-exercise cooling in control and hypercapnia trials (n=6).

(21 ± 6 L·min^{-1}) than during control (11 ± 2 L·min^{-1}) after 20 minutes. After 50 minutes of cooling, $\dot{V}_E$ was 12 ± 3 L·min^{-1} during control and 26 ± 14 L·min^{-1} during hypercapnia (Fig. 13).

Thermoregulatory Response Thresholds

Response thresholds are reported as the change in core temperature (ΔT_{co}) relative to the baseline resting level (13). The shivering threshold was decreased by hypercapnia in all subjects and the mean shivering threshold was significantly reduced from 0.35 ± 0.30 °C below baseline during control to 0.48 ± 0.36 °C below baseline during hypercapnia ($P<0.05$)(Fig. 14). Hypercapnia had a variable effect on the thresholds for sweating and vasoconstriction, in each case lowering these thresholds in five subjects and increasing them in three. As a result, hypercapnia produced no significant change in the sweating or vasoconstriction thresholds. The size of the thermoregulatory null zone (difference in T_{co} between the sweating and shivering thresholds) was similar during control (0.59 ± 0.3 °C) and hypercapnia (0.64 ± 0.2 °C).

E. DISCUSSION

This is the first study to examine the effects of hypercapnia on core cooling rates and warm and cold thermoregulatory response thresholds in humans during mild cold stress (28°C water). Hypercapnia decreased the T_{co} threshold for shivering by 0.13 °C and increased the rate of core cooling by 25 %. The delay in shivering onset likely contributed to the increased core cooling rate.

The experimental protocol, developed by Mekjavic *et al.* (13) and used in this study, has two advantages. First, whole body water immersion

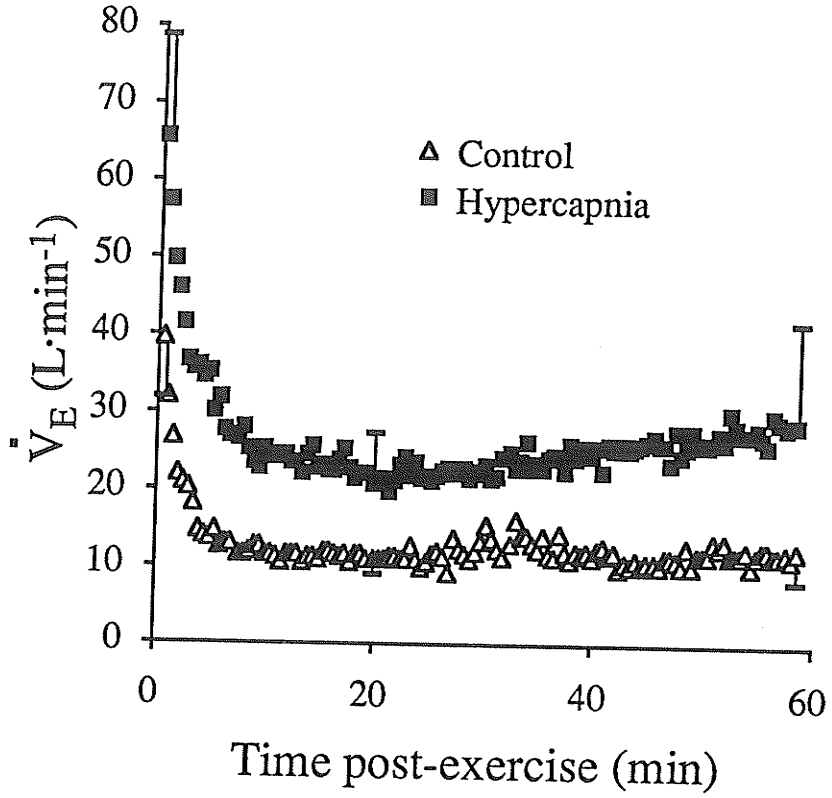

Figure 13. Mean minute ventilation ($\dot{V}_E$) during post-exercise cooling in control and hypercapnia trials (n=8).

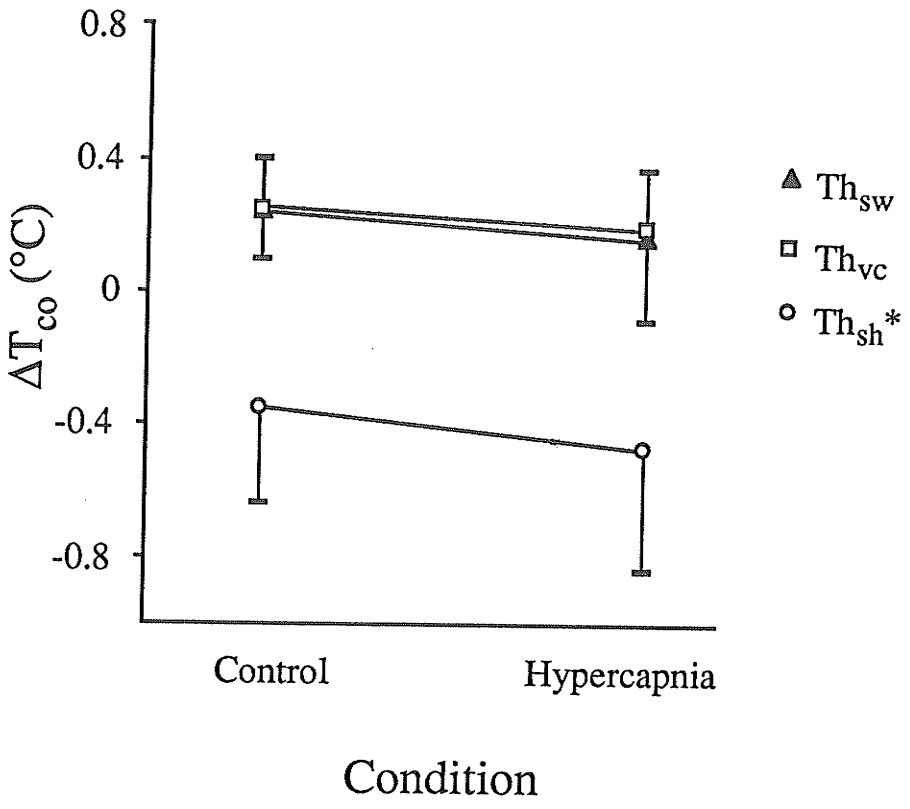

Figure 14. Mean core temperature response thresholds (plotted as change in esophageal temperature from pre-immersion baseline) under control and hypercapnic conditions (Th_{sw}=sweating threshold, Th_{vc}=vasoconstriction threshold, Th_{sh}=shivering threshold,*$P<0.05$).

effectively clamps skin temperature (T_{sk}) at approximately water temperature, removing the possible complication of changing cutaneous drive to the central thermoregulatory processing areas. This enabled us to determine the thermoregulatory responses to changes in T_{co} alone. Second, exercise followed by passive cooling while immersed in water is a safe, non-invasive method for elevating and then reducing T_{co} without changing T_{sk} compared with other available methods such as intravenous cold saline infusion (10) or the use of epidural anesthesia (9) combined with external warming.

The hypercapnia-induced increase in the rate of core cooling is consistent with previous work by Wagner *et al.* (22) who observed 0.2 °C depression (average over both conditions) in rectal temperature of men breathing a 4% CO_2 for 60 minutes. This effect was reported at both cold (5°C) and neutral (29°C) air temperatures although the magnitude of the hypercapnic depression under each ambient condition is not reported. In the present study, T_{co} was ~0.3 °C lower with hypercapnia following 1 hour of cooling in 28°C water (Fig. 8). In contrast, Lun *et al.* observed no increase in the rate of T_{co} cooling during long term (1 hour) (11) or acute (15 min.) (12) exposure to 4% CO_2 in men immersed in 15°C water. This discrepancy may be explained by the large difference in cold stress and cooling rates between these studies. Immersion in 15°C water produced core cooling rates of ~2.2-3.0 °C·hr^{-1} (11, 12). These rates are much greater than the ~0.3 °C·hr^{-1} cooling rate reported by Wagner *et al.* (22) and the rate of ~1.5 °C·hr^{-1} in this study. The high cold stress during 15 °C water immersion may have overridden the small primary effects of hypercapnia on thermoregulatory control mechanisms.

The enhanced heat loss with hypercapnia may be partly explained by an increase in respiratory (evaporative and conductive) heat loss due to hypoxic hyperventilation (6). Although the inspirate was humidified to reduce respiratory heat loss, ($\dot{V}_E$) approximately doubled during hypercapnia (12 ± 3 L·min^{-1} during control vs. 26 ± 14 L·min^{-1} during hypercapnia at 50 minutes post-exercise), increasing conductive heat loss from the respiratory passages. This increased ventilation could have increased respiratory heat loss or convective heat loss to the water due to increased thoracic movements (22). However, since the water was constantly and vigorously circulated, increased respiratory movements would have had a reduced impact on overall convective heat loss.

The lowering of the T_{co} threshold for shivering is likely one factor contributing to the hypothermic effect of hypercapnia. Inhalation of gas mixtures containing between 3 and 15% CO_2 has been reported to suppress maximal shivering responses in rats, rabbits, guinea pigs and dogs (8, 18, 20). In guinea pigs, Schaefer and Wunnenberg (18) demonstrated that 5% CO_2 had no effect on the shivering threshold However, inhalation of 15% CO_2 lowered the threshold by ~4 °C. In human subjects, a dose-dependent suppression of shivering by CO_2 concentrations from 2.5-6% has been observed by Bullard and Crise (4). This suppression was transient and shivering displaying a rebound after ~15 minutes of hypercapnia with continued cold exposure. This is consistent with our findings of a hypercapnic reduction in the shivering threshold. It is possible that as T_{co} decreased during the 15 minutes of suppressed shivering in the earlier study, the total thermal drive to the hypothalamus was increased to a level past the new threshold so that shivering was reactivated. At a cooling rate of ~2°C/hr with 6% CO_2, the 15 minute delay in the onset of shivering would

correspond to a reduction of ~0.5 °C in the shivering threshold (4) . In comparison, 4% CO_2 reduced the shivering threshold by 0.13 °C in the present study (Fig. 14). In contrast, Wagner *et al.*, found that inhalation of 4% CO_2 during exposure to 5 and 29°C air neither delayed the onset of shivering nor reduced the magnitude of shivering once it began. Lun *et al.* (11) also failed to show a reduction in shivering with 4% CO_2 in men immersed for 60 minutes in 15°C water. However, when normoxic subjects were cooled to 36.5 °C and then switched briefly to the hypercapnic gas mixture, the normal increase in shivering activity concurrent to decreasing T_{co} was attenuated (12).

We observed no significant effect of hypercapnia on the threshold for vasoconstriction. Previous studies have indicated that measurements of skin temperature (4, 22), skin heat flux (11) and forearm blood flow (22) are unchanged by 4-6% CO_2.

Limited data is available on the effect of hypercapnia on heat dissipating mechanisms. Hypercapnia delays the onset of panting in dogs exposed to heat stress (20). Our data indicate, however, that 4% CO_2 did not significantly affect the sweating threshold in humans.

There are several possible mechanisms that may explain the alteration of the shivering threshold by hypercapnia including: 1) a decrease in blood pH, 2) humoral factors and 3) disruption of central thermoregulatory control centers.

First, it is possible that the decrease in plasma pH that results from hypercapnia affects the function of central thermoregulatory structures such as the hypothalamus. Brackett and Schwartz (2) have shown that although a new steady-state of acid-base equilibrium is achieved in 10 minutes following an acute increase in CO_2 levels, extrarenal buffer mechanisms are

inadequate to defend the baseline extracellular hydrogen ion concentration. Inhalation of 4% CO_2 would be expected to elevate the concentration of hydrogen ion in the blood from ~38 to 49 nM, producing a reduction in plasma pH of ~0.1 (2). This is an unlikely mechanism, however, since a decrease in pH of 0.1 still leaves plasma hydrogen ion concentration well within the normal physiological range and there is no evidence to suggest thermoregulatory impairment by slight acidosis (7).

Second, the disruption of thermoregulation by hypercapnia may be a symptom of the humoral changes that accompany increased CO_2 levels. Evidence for these effects come mainly from studies in guinea pigs. Specifically, the acute fall and subsequent rise in the shivering threshold in these animals as they adapt to chronic hypercapnia has been linked to a corresponding fall and rise in the norepinephrine concentration within the hypothalamus (17). Also, injection of norepinephrine into the hypothalamic region has been shown to increase the shivering threshold and T_{co} in these animals (23). If norepinephrine concentrations were reduced by hypercapnia in humans and human hypothalamic neurons were similarly sensitive to norepinephrine, this could explain a reduced shivering threshold and core temperature with hypercapnia. Further studies on catecholamine levels in hypercapnic humans are required to evaluate this possible mechanism.

Finally, there is evidence to suggest that there is a direct effect of elevated plasma CO_2 levels on the activity of thermosensitive neurons within the pre-optic area of the hypothalamus. In the rat, inhalation of gas mixtures containing 4-10% CO_2 caused an increased firing rate in more than half the pre-optic area neurons, with the greatest effect observed in thermally sensitive cells (21). Although CO_2 increased the activity of both warm and cold sensitive neurons, Tamaki *et al.* (21) suggest that the increased activity

of warm sensitive neurons may affect thermoregulation more strongly because these cells are more numerous than cold-sensitive cells in the pre-optic area. This would tend to lower the Tco threshold for shivering as the integrated thermal signal in the hypothalamus would be overestimated in a given thermal condition. Consistent with this theory, generalized electrical stimulation of the pre-optic area has been shown to increase heat loss and decrease thermogenesis (1).

In summary, we provide the first demonstration that hypercapnia (4% CO_2) reduces the threshold for shivering and increases T_{co} cooling rate in humans exposed to mild cold stress. Although these effects are small compared with those of anesthesia and other thermal factors during surgery, this information may be valuable in relation to total patient management. These results may also have other practical implications. For example, in contrast to the conclusion of Lun *et al.* (12) regarding severe cold stress, we suggest that hypercapnia may contribute to the etiology of hypothermia in divers exposed to mild cold stress.

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CHAPTER IV. SUMMARY

The two studies presented in this thesis were concerned with the effects of eucapnic hypoxia and hypercapnia, two environmental stresses that are often encountered in combination with thermal stress, on human temperature regulation. These studies used an identical experimental protocol and demonstrated that inhalation of hypoxic or hypercapnic gas mixtures increases the rate of core temperature cooling during mild cold stress and as such, may contribute to the etiology of hypothermia under similar circumstances in the field. The acceleration of core cooling may be attributed in part to a decrease in the response thresholds for vasoconstriction and shivering (eucapnic hypoxia) or to a reduction in the shivering threshold alone (hypercapnia). The similar reduction in the shivering thresholds and increases in core cooling rates by these two gases may indicate a common mechanism. Although it is impossible from the data presented here to evaluate or propose a mechanism for the action of these gases on thermoregulation, a direct effect on the activities of temperature-sensitive neurons in the hypothalamus is a promising explanation and deserves further study.