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THERMAL, HORMONAL AND CARDIOVASCULAR RESPONSES TO SINGLE AND REPEATED NONHYPOTHERMIC COLD EXPOSURES IN MAN

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Abstract

The purpose of this study was to find out and compare the physiological effects of different types of non-hypothermic cold exposure tests in man. In whole-body cold exposures lightly clothed subjects were exposed to 10°C for 2 hours (single exposure), as well as repeatedly for 2 h and 1 h on ten successive days in separate studies. For local cold exposures, cold pressor tests (immersion into ice-cold water) of both hands and both feet were used. In whole-body cold exposures, several hormonal and metabolic parameters as well as cold sensations were measured. In local cold exposures the measured parameters were blood pressure, heart rate and skin temperatures.

The single 2-h whole-body cold air exposure decreased rectal and skin temperatures and body heat content, but increased the metabolic rate. At the same time the serum noradrenaline concentration increased indicating a general activation of the sympathetic nervous system. Serum free fatty acid concentration increased whereas cortisol, GH and prolactin concentrations fell. No significant changes were found in serum concentrations of adrenalin, TSH, T3, T4, testosterone or LH. Serum total proteins were enhanced apparently due to cold-induced hemoconcentration. After repeating the 2-h whole-body cold exposure for five days the increase in serum noradrenaline level was markedly lower in the cold. At the same time hemoconcentration, judged from serum protein concentrations, was attenuated and the subjects became habituated to the cold sensations. However, the results showed that the repeated 1-h cold exposure in 10°C was not sufficiently intensive to reduce the noradrenaline response.

Comparison of the hand and foot cold pressor tests to whole-body cold exposure tests showed that all tests caused significant increases in systolic and diastolic blood pressures, but that heart rate increased significantly only in the cold pressor test of feet. During the 2-h cold air exposure the heart rate fell. This caused a reduction in rate pressure product (RPP, the product of heart rate and systolic blood pressure). In both cold pressor tests the rate pressure product increased, indicating the enhancement of the O2-need in the heart muscle. The results showed no significant correlation in systolic or diastolic blood pressures between whole-body and local cooling of hands or feet. The lack of the association between local and whole-body cold exposure tests may be due to differences in severity and site of the tests: whole-body cold exposure tests cause general cold discomfort while cold pressor tests cause local cold pain.

Keywords: adrenalin, body temperature, cold exposure, cold pressor test, cold sensations, habituation, noradrenaline, pituitary hormones, thyroxine, triiodothyronine
Korhonen, Ilkka, Yksittäisten ja toistuvien lievien kylmäaltistusten vaikutukset ihmisen lämpötasapainoon, hormonitoimintaan, sekä sydän ja verenkiertominon vasteisiin
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Tiivistelmä


Toistettua kahden tunnin pituiseessa kylmäaltistuksessa seerumin noradrenalinipitoisuudessa tapahtunut kasvu oli merkitsevästi vähäisempi viiden päivän jälkeen. Samanaikaisesti seerumin proteiinipitoisuus kylmässä vähäsi ja kylmätuntemukset muuttuivat lievemmiksi. Sen sijaan yhden tunnin toistettu altistus 10°C:ssa ei ollut riittävän voimakas vähentämään kylmän aiheuttamaan veren noradrenalinipitoisuuden kasvua.


Asiasanat: kehon lämpötila, kilpirauhashormonit, kylmäaltistus, kylmäsopeutuminen, kylmävesitesti, lämpötilanvastuu, noradrenaliini, sydämen syketiheys, verenpain
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Ilkka A Korhonen


**Abbreviations**

A    adrenalin (ng/ml)
ACTH adrenocorticotrophic hormone (ng/l)
BP   blood pressure (mmHg)
CNS  central nervous system
DBP  diastolic blood pressure (mmHg)
FFA  serum or plasma free fatty acid concentration (mmol/l)
FSH  follicle stimulating hormone (IU/l)
GH   growth hormone (µg/l)
HR   heart rate (beats/min)
LH   luteotrophic hormone (IU/l)
M    metabolic heat production (W/m²)
NA   noradrenaline (ng/ml)
NST  nonshivering thermogenesis
Q    body heat content (J)
RPP  rate pressure product (of heart rate and systolic blood pressure)
S    storage of body heat (W/m²)
SBP  systolic blood pressure (mmHg)
T3   triiodothyronine (nmol/l)
T4   thyroxine (nmol/l)
TSH  thyroid stimulating hormone (mU/l)
UCP  uncoupling proteins
List of original papers

The thesis is based on the following papers, which are referred to in the text by their Roman numerals:


Some unpublished results will also be presented in this thesis.
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1 Introduction

During the cold season cold exposure is a permanent part of human life in circumpolar countries and occasionally also in the temperate zone as well. People are working outdoors in cold conditions or participating in recreational activities, e.g. winter sports. The most common outdoor occupations are construction work, agriculture, forestry, seafaring, military work and mining work. There is also considerable cold exposure is in indoor work e.g. in the food industry. It has been estimated that in Finland there are about 800 000 people working occasionally in cold conditions and for 300 000 of them the main work is predominantly performed under cold exposure (Hassi et al. 2002).

Cold can be experienced in air or water or in contact with solid materials. Unclothed or clothed parts of the body can be locally exposed to cold (hands, face and legs) or the whole-body may be cooled. The cold stimulus can be characterized by its duration, intensity and repeating times. From a physiological point of view, cold activates the human thermoregulatory system, while from a psychological point of view, cold causes unpleasant thermal sensations or even cold-induced pain, which is experienced as stressful. In a cold environment decreased mental (Palinkas 2001) or physical performance have been found (Oksa 1998). Even moderate whole-body cooling, which causes superficial but not marked deep-body cooling, increases postural sway considerably, indicating an impaired postural control (Mäkinen 2006).

Cold exposure may cause certain diseases and aggravate the symptoms of some. Diseases whose symptoms or seriousness can be made worse by the cold include high blood pressure, coronary heart disease, asthma, bronchoconstrictive diseases and Raynaud’s disease (disturbance in peripheral circulation). It has been estimated that in Finland about 1.5 million people have a chronic disease, that may be affected by exposure to cold. Some people have many concurrent diseases, that react to cold exposure and cold symptoms are also found in people who do not have any such diseases. The symptoms affected by cold are numerous and originate from several organs (Hassi & Rintamäki 2002). Recent studies have also shown an increased prevalence of cold- related morbidity in winter (Spencer et al. 1998, Danet et al. 1999, Näyhä 2002, Hajat et al. 2004).

Marked individual differences have been found in the physiological responses to cold. The individual ability to protect against cold is affected by the shape and mass of the body, the amount of subcutaneous fat, physical fitness, age, gender as well as some illnesses and medications (Stocks et al. 2004). These individual
factors can also modulate the development of cold acclimatization. Human responses to continuous or repeated exposures to cold may be either blunted (habituation) or pronounced. Responses that are not apparent in unacclimatized subjects may also be developed (Young 1996). Habituation to cold usually produces reduced thermal discomfort and changes in circulatory as well as endocrinological responses.

Over the last two decades human cold research has shown that considerable cold-related stress is experienced in everyday situations, but the type and intensity of the human responses to these situations are not sufficiently known (Hassi et al. 2001). There is a lot of variability in methods concerning temperature, time and type of the exposure (cold water or air, local or whole-body cooling), when the cold stimulus is produced in controlled laboratory studies. This makes it difficult to compare the results of these tests. This also includes studies, where habituation processes to cold are produced via repeated cold exposures. The cold-induced physiological mechanisms that produce the physiological reactions are partly same and partly different in local and whole-body cold exposures. There are not much data on direct comparison of these different exposures e.g. using the same volunteers in these experiments. New aspects have been found of the effects of genes to cold tolerance. Extremely cold conditions can have led to selection of a combination of specific genes or alleles, which have been named cold climate genes promoting adaptation to these conditions. The possible existence of cold climate genes can lead to increased thermogenesis (Fridlyand & Philipson, 2006)

The present thesis describes the effects of a standardized 2-h whole-body cold exposure method on several physiological parameters. This test was also repeated in order to evaluate the effects of habituation to cold. Comparisons were made to other whole-body cold exposure tests with shorter duration, as well as to local cold exposure tests.
2 Review of literature

2.1 Effects of whole-body cooling on heat balance, metabolism and thermal sensations

Homeothermic animals and human subjects keep their deep body temperature as stable as possible in situations when environmental temperature changes. This means that heat production by metabolism and physical activity equals with heat losses by radiation, evaporation, conduction and convection. Moreover, part of the heat is also lost from respiratory organs by evaporative and convective heat loss mechanisms. In humans, the protection against cold occurs in everyday-life by clothing with thermal insulation, which minimizes the heat loss by radiation, convection and conduction. The time spent in a cold environment can also be restricted and physical activity enhanced. This balance can be described by the heat balance equation:

\[ M \pm W = C \pm R \pm E \pm S \]

where \( M \) = metabolic rate, \( W \) = external work, \( C \) = heat exchange by convection, \( R \) = heat exchange by radiation, \( E \) = heat exchange by evaporation (evaporation of water from the skin and the surfaces of the respiratory tract) and \( S \) = heat storage (becomes zero, when heat gains and losses are equal).

Cooling of cold receptors, located in the skin, but also in the lungs, digestive tract and central nervous system cause cold sensation, which moves via afferent nerves to the hypothalamus, the main temperature-regulating center in the brain. The heat producing and maintaining mechanisms are mainly controlled via the autonomic nervous system. Body temperature can also be regulated to a minor extent by the medulla oblongata of the brain and the spinal cord. The responses to cold stimulus are starting most effectively in situations, where the cold receptors are activated at the same time both in the skin and the inner parts of the body. Activation of the cold receptors in peripheral parts of the body alone is also sufficient to activate the thermoregulatory mechanisms (Rintamäki et al. 2005).

When ambient temperature decreases below a so-called thermoneutral temperature (in unclothed humans about 28 °C), the physiological heat producing mechanisms and the mechanisms that minimize the heat loss from the body become activated. Heat production is increased by accelerated metabolism and can be measured by increased oxygen consumption and in enhanced utilization of
fuel substances, such as free fatty acids and carbohydrates. In this process most (> 80%) of the metabolic energy is released as heat and the rest is available for mechanical work. The heat producing mechanisms of the body are skeletal muscle shivering and chemical heat production (non-shivering thermogenesis, NST). In humans, the maximal heat production by shivering can be about five times greater than the heat production under thermoneutral conditions (Iampietro et al. 1960). In mild cold exposure or at the beginning of a severe cold exposure shivering means unsynchronized contraction of skeletal muscle fibers accompanied by increased muscle tonus, but if the cold exposure continues the maximal heat production by shivering is reached with synchronizing the contractions of the muscle fibers. The fuel substrates for shivering are lipids, muscle glycogen, plasma glucose and proteins (Haman et al. 2002). Lipids are the main fuel substrates in low-intensity shivering and carbohydrates under high-intensity shivering (Weber & Haman 2005), but this can also vary depending on the state in availability of fuel substrates (Haman et al. 2004). Individual differences in the capacity of shivering are great and the capacity diminishes with age, because of a decrease in the mass of skeletal muscles. Detailed aspects of shivering as a response to cold have been reported by Young (1988), Kleinebeckel & Klussman (1990), Block (1994), Hohtola (2004) and Weber & Haman (2005).

Chemical heat production is seen in the so-called brown fat (brown adipose tissue, BAT). Brown fat can liberate its chemical energy directly in the form of heat. This process requires so-called uncoupling proteins (UCP), which can be activated by thyroid hormones, catecholamines and the sympathetic nervous system (Silva & Rabelo 1997, Silvestri et al. 2005). An increased noradrenaline concentration in the blood during a cold exposure increases the production of cyclic AMP (cAMP), lipolysis and free fatty acids (FFA) in BAT. FFAs open the mitochondrial proton channel protein in BAT. Protons enter the mitochondria and inhibit ATP synthesis (uncoupling). This way, energy is transformed into heat instead of ATP. There are five types of UCPs, UCP1 being the most important for heat production of the body. In adults BAT is located especially around great vessels and spinal cord. In normal situations the heat production through NST in adult subjects is minor compared to other heat producing mechanisms. However in situations where the exposure to cold is chronic, activation of NST (Cannon & Nedergaard, 2004) and increasing amounts of brown fat (Hassi 1977) have been found. Newborns have the greatest amount of brown fat, while their other thermogenetic mechanisms, especially the ability to use shivering, are only partly
developed. Newborns can more than double their metabolism rate when subjected to cold (Brück 1961, Himms-Hagen 1995, Leppäluoto et al. 2005).

Heat loss from the body is suppressed by subcutaneous fat and clothing. The most important physiological mechanism that decreases heat loss from the body is cutaneous vasoconstriction. Vasoconstriction decreases the rate of skin circulation and thus the temperature in the skin. This minimizes the temperature gradient between the skin and cold environment. During maximal vasoconstriction heat conduction is reduced to about one third of its maximal value (Rintamäki et al. 2005).

The more severe the exposure to cold, the more marked the effects that can be observed in body heat balance. The type and severity of cooling depends on the cooling medium (cold air or cold water), its temperature and movements and the exposure site and area in the human body. Cold-water immersion is usually a much stronger cold stimulus than cold-air exposure. The effect of a cold stimulus on deep body temperature and heat content of the body is classified by Lloyd (1986) as follows:

1. Mild cold stress: Deep body temperature as well as heat content of the body normal (only skin cooling occurs).
2. Moderate cold stress: Deep body temperature normal but heat content of the body decreased.
3. Strong cold stress: Deep body temperature decreased to 35 °C.
4. Mild hypothermia: Deep body temperature 35–32 °C
5. Moderate hypothermia: Deep body temperature 32–28 °C
6. Strong hypothermia: Deep body temperature under 28 °C

Holmer (1991) has classified the types of cooling as whole-body cooling, peripheral cooling, skin cooling and respiratory cooling. LeBlanc (1988) has divided the types of human cold exposures into systemic moderate cold, systemic severe cold and local severe cold.

In human subjects the hypothermic condition usually develops in accidents or during loss of physical activity. In hypothermia, which is primarily developed as a result of an accident, the thermoregulatory system of the body functions normally, but the exposure to cold is too strong. In hypothermia, which is secondary to an accident, also a mild exposure to cold is enough to produce hypothermia, because the thermoregulatory system is not fully controlled. In induced hypothermia, the hypothermic condition is caused to patients for medical purposes in order to minimize the oxygen consumption of the body for instance during coronary
bypass surgery (Loyd 1986, Hanhela et al. 1999). Mild or moderate cold stress is found in everyday life in outdoor work or other outdoor activities.

It is noteworthy that individual physical characteristics produce a great deal of variation in the responses to cold stimulus. Increased tolerance to cold is seen in individuals with an increased amount of body fat, large size of the body, good physical fitness and as a result of adaptation to a cold environment. Increased amounts of body fat provide better insulation. If the body size is large, the ratio of body mass to skin area is better in order to maintain heat. In good physical fitness skeletal muscles have better capacity for shivering (Budd et al. 1991, Van Oijen et al. 2001, Stocks et al. 2004). Other factors producing variation in responses to cold are age, gender and certain diseases as well as medications.

Different psychological characteristics of the subjects also produce variability in the responses to cold. Extrovert persons seem to have the best defence ability against cold by effective starting of shivering and activation of the sympathetic nervous system, which is seen together with increased noradrenaline secretion (Leblanc et al. 2003, 2004).

Cold sensation is a subjective feeling about the cold stimulus. Factors affecting the sensation are the intensity and location of the cold stimulus, because the number of cold receptors varies in different parts of the body. It has been noted that cold receptors become adapted to the same stimulus in quite a short time (Hensel 1981) and during cold exposure in situations where temperature changes rapidly, the sensations of discomfort are most marked (Gagge et al. 1967).

Age produces its own effects in responses to cold. In old subjects a stronger cold stimulus in peripheral parts of the body is needed to produce the same cold sensation as in young subjects (Stevens & Choo 1998). This can be a result of a decreased cold sensitivity in the skin. The decrease in thermal sensitivity can already be seen already after 10 years age and this decrease continues linearly throughout the lifetime (Meh & Donislic 1994). Aging decreases vasoconstriction in the skin as a response to cold especially in men (Young & Lee 1997). Moreover, the decreasing mass of skeletal muscles in elderly subjects diminishes the capacity to shiver.
2.2 Effects of whole-body cooling on blood pressure and heart rate

In a cold environment the temperature of the skin and the subcutaneous layer decreases causing cold sensation, which increases the activity of the sympathetic nervous system and consequently affects tone and vasoconstriction in the vessels. This increases peripheral resistance to blood flow, so that a greater amount of blood moves to the inner parts of the body. The mediating substance between the nerve endings and smooth muscle in vessel walls is noradrenaline. In many previous studies it has been found that even a mild or a short-term whole-body exposure to cold air increases systolic and diastolic blood pressure (e.g. Budd & Warhaft 1966, Raven et al. 1970, Raven et al. 1975, Mäkinen et al. 2006).

As a consequence of increased blood pressure the cardiac load, expressed by RPP (systolic blood pressure x heart rate) tends to increase. There are variable results regarding the heart rate during mild cold exposure, when men are exposed to cold air (5–10 °C) lightly clothed. In some studies no change was found in the heart rate (e.g. Raven et al. 1970, O’Hanlon & Horvath 1970). In other studies, however, the heart rate has been increased (Thauer 1965) or decreased (Budd & Warhaft 1966). The heart rate has been noted to decrease most markedly in studies where the cold exposure is intensively directed to face (Hayward et al. 1976, LeBlanc 1975). Blowing cold air to the face has also been found to decrease the blood flow in the hands at the same time (Hayward et al., 1976). When studying the effects of different seasons on blood pressure it has been noted that healthy adults have higher blood pressure values in winter than in summer (Näyhä 1985), this difference being more pronounced in old than in young people (Brennan et al., 1982).

2.3 Effects of whole-body cooling on hormone secretion

2.3.1 TSH and thyroid hormones

Many animal studies have shown that thyroid hormone secretion is quickly activated by cold exposures (Thompson 1977). This activation of the thyroid gland can be mediated via neuronal reflexes from the hypothalamus in midbrain. Hypothalamus increases TRH (TSH-releasing hormone) secretion, which activates TSH (thyroid stimulating hormone) and thyroid hormone release. Thyroid hormones exert their major effects on obligatory thermogenesis and
resting metabolic rate and seem to stimulate almost all reactions in the intermediary metabolism leading to heat production (Silva 1993).

The findings on the effects of cold exposure on adult human thyroid function are partly controversial. It seems that the magnitude, type (cold air or water) as well as the duration of the cold exposure each have their own effect on the response. Seasons and living areas also seem to modulate the responses. In some controlled laboratory studies thyroid hormone secretion has been found to increase, while in other studies this was not observed. Goldstein-Golaire et al. (1970) and O’Malley et al. (1984) found that exposure to ambient temperature of 4°C for 30–120 minutes increased serum TSH, T3 and T4 concentrations in lightly clothed subjects. In the studies of Fisher & Odell (1971) and Hershman (1970) lightly clothed subjects were exposed to ambient temperature of 2–4 ºC lightly clothed for 1 h and they found no change in the serum TSH content. Eastman et al. (1973) found that in lightly clothed subjects four days’ exposure to an ambient temperature of 6 ºC increased their serum T3 and T4 levels.

In an exposure to cold water by Tuomisto et al. (1976) the subjects took a sauna bath and swam after that in cold water. This increased their serum TSH content. Immersion of adult subjects into cold water (12 ºC) for 10 min followed by spending 20 min in 28 ºC resulted in about twofold increases in plasma TSH (Leppäluoto et al. 1982). In a study of Weeke and Gundersen (1983) eating of ice pieces caused no changes in serum TSH concentrations.

By studying the effects of different seasons on thyroid hormone secretion Nagata et al. (1976) found a greater serum T3 content in winter than in summer in subjects who lived in a mountain district in non-heated houses. In outdoor workers, Hassi et al. (2001) found that serum TSH was at the highest in December and the serum free fraction of T3 at the lowest in February. Reed et al. (1986) studied individuals in an Antarctic expedition and found that their T3 metabolism increased in winter, seen as decreased concentrations of serum free T3 fraction. Thus it appears that more abundant amounts of thyroid hormones, especially T3, are available for tissues after cold exposure. The decreases of free fractions of thyroid hormones may be explained by increased elimination and tissue binding (Reed et al. 1990).

Darkness in wintertime can also have an effect on TSH secretion. The study of Hassi et al. (2001) demonstrated that ambient light correlated significantly with serum TSH in an inverse manner so that the highest serum TSH occurred during the darkest month (December) and the ambient outdoor temperature did not correlate with TSH at all.
2.3.2 Noradrenaline and adrenalin

Several previous studies have demonstrated that nonhypothermic exposures to cold air rapidly increase human noradrenaline secretion. Exposures of lightly clothed human subjects to 4–10 °C ambient temperatures for 1–2 hours increased serum noradrenaline concentration (Scriven et al. 1984, O'Malley et al. 1974, Wilkerson et al. 1974). At the same time in some of these studies serum adrenalin concentration didn’t change (Scriven et al. 1984, O'Malley et al. 1974) or increased (Wilkerson et al. 1974). Leppäluoto et al. (1989) found in experiments on nonhypothermic cold exposure an increase in plasma noradrenaline and dopamine concentrations at the same time. This indicates that during acute cold exposures the increased blood noradrenaline concentrations are derived from the sympathetic nerve endings. The fast increase in serum noradrenaline concentration in response to cold is useful for the heat balance of a body, because it causes vasoconstriction, which leads to decreasing skin temperatures and thus decreasing heat loss from the body. It also increases the release of fatty acids from adipose tissue to be used as energy substrates. In rodents thyroid hormones are produced by the stimulation of pituitary-thyroid axis and peripheral deiodination of T4 to T3 in response to cold exposures. Cold exposures appear to stimulate the pituitary-thyroid axis also in human newborn, but it seems that this does not occur in adults. Detailed aspects of the role of catecholamines in cold exposures are presented in the review of Leppäluoto et al. (2005)

Severe or long term whole-body exposures to cold have been found to activate the adrenal medulla. In the study of Galbo et al. (1979) the subjects swam 60 min in cold water and their serum adrenalin concentration increased. Also in the study of Purshottam et al. (1978) the subjects showed increased adrenalin secretion after spending 6 h lightly clothed in ambient temperature of 8°C.

2.3.3 Other hormones

Insulin and glucagon. The need for increasing metabolism during exposure to cold also enhances the need of free fatty acids and glucose. Especially shivering uses abundant amounts of these substrates. Insulin secretion is usually inhibited during cold exposures (Galbo et al. 1979, Seitz et al. 1981). Campbell et al. (1975) found decreased insulin secretion in winter in a group of members of an arctic expedition. The decreased secretion of insulin in a cold environment can be
a result of increased sympathetic nervous activity. Vallerand et al. (1988) showed increased sensitivity of tissues to insulin in exposure to cold, which can compensate the effects of lowered insulin secretion. Glucagon is secreted in response to cold exposures, but its contribution to cold-induced metabolism is unclear (Seitz et al. 1981, Cannon & Nedergaard 2004).

Cortisol, ACTH and aldosterone. Adrenocorticotropic hormone and cortisol are usually not secreted in response to cold exposure in humans (Wilson et al. 1970), but their secretion increases if the exposure is experienced as stressful (Leppäluoto et al. 1982). In a short-term exposure to cold increased secretion of cortisol may have a positive effect by increasing the blood glucose level. Hiramatsu et al. (1984) found that a short-term cold exposure increased the plasma aldosterone concentration, which was mediated by ACTH. A greater secretion of aldosterone increases the amount of extracellular fluid and the concentration of sodium in the blood, which tends to raise the blood pressure.

Growth hormone, prolactin, testosterone and LH. Growth hormone (GH) and prolactin are potentially thermogenic hormones due to their ability to increase the metabolism, but their secretion, especially that of prolactin, is suppressed during cold exposure (Mills & Robertshaw 1981, Leppäluoto et al. 1982, Weeke & Gundersen 1983, O’Malley et al. 1984). However in some studies no change in serum GH as a response to cold exposure has been observed (Berg et al. 1966, Galbo et al. 1979). Mild or moderate cold exposure has no effects or inhibitory effects on gonadotrophins, testosterone or estrogens (Wilson et al. 1970).


2.4 Effects of local cooling on blood pressure and heart rate

Different types of local cooling are divided by Holmer (2001) into extremity cooling, wind cooling (skin), contact cooling (contact of skin with cold materials) and respiratory cooling (breathing cold air). Local cold stress may occur, although overall whole-body heat balance is being maintained. By measuring the skin temperature in a finger Holmer (1999) has presented criteria for evaluation of strain of the local cold exposure on the extremity. In his study skin temperature 24–16 ºC is classified as none/light, skin temperature 15–8 ºC as medium, and skin temperatures 7 ºC or under as high/severe strain exposure (Holmer, 1999).
Respiratory cooling occurs typically during winter sports. In situations when the only exposure to cold occurs via breathing cold air the stroke volume of the heart increases but the heart rate and peripheral resistance do not change (Leon et al. 1970).

In the investigations of the reactivity of blood vessels to local cooling, a common method is the cold pressor test, developed as early as 1932 by Hines & Brown. In their test one hand was immersed up to the wrist in ice water for 1 min and values of blood pressure measured from the other hand and heart rate were registered at the end of the exposure. The original purpose of this test was to find individuals who are at risk of developing hypertension. In this test the blood pressure as well as the heart rate rises. The usual increase in heart rate is about 10–15%. The subjects can be divided into three categories according to the magnitude of the systolic BP rise at the exposure: hyporeactives, when the increase in systolic blood pressure is under 10 mmHg, normoreactives, when the systolic blood pressure rises 10–20 mmHg and hyperreactives, when the change in systolic blood pressure is over 20 mmHg. Wood et al. (1984) have suggested that 20% or less of the normoreactive subjects in this test can get hypertension, whereas among hyperreactives the amount of hypertensive individuals may reach 70%. The important reason for the rise in blood pressure is vasoconstriction. Vasoconstriction and increased heart rate are due to greater sympathetic nervous activity. In a cold pressor test, catecholamine secretion is activated, but other factors affecting a rise in blood pressure are also noted (Roy et al. 1987, Cummings et al. 1983). Cold pressor test leads to a perception of pain and experiencing of pain can also be an important factor causing higher blood pressure values in this test (Wolf 1951).

In modifications of cold pressor test cold exposures of the foot and face have also been used (Durel et al. 1993, Saab et al. 1993, Peckerman et al. 1994, Stancák et al. 1996, Peckerman et al. 1998, Khurana & Wu 2006). The cold face test evokes reflex bradycardia and pressor responses. Bradycardia has been used to assess vagal function in this test (Khurana & Wu 2006). In cold pressor test of the foot systolic blood pressure rises are accompanied by tachycardia (Durel et al. 1993), resembling the results of the cold pressor test of the hand (Komulainen 2007).
2.5 Adaptation to cold

After long-term or repeated exposure to cold, several adaptive physiological reactions can develop in the human body. Such adaptive reactions are related to the intensity of cold stress and individual factors, such as physical fitness, body fat and diet (van Marken Lichtenbelt et al. 2002). If the adaptation is produced artificially for example in laboratory conditions this reaction is called acclimation, which is described by the Commission for Thermal Physiology of IUPS (1987) as a physiological change, occurring within the lifetime of an organism, which reduces the strain caused by experimentally induced stressful changes in particular climatic factors. Acclimatization is described as a physiological change, occurring within the lifetime of an organism, which reduces the strain caused by stressful changes in the natural climate (e.g., seasonal or geographical) and habituation as reduction of responses to or perception of repeated stimulus.

Human adaptive mechanisms to whole-body cold exposure have been found to develop via hypothermic, insulative or hypermetabolic reactions (Bittel 1992). A mixture of these types has also been noted in the form of insulative-hypothermic or metabolic-insulative responses. In a hypothermic reaction, the body allows the core temperature to fall under cold exposure to a lower level than normally before the heat-producing mechanisms are activated. This reaction type can also include strong lowering of the skin temperature, which increases body insulation (Hammel 1964, Hensel 1981). Bittel (1992, 1998), Jansky (1997, 1998), Leblanc (1992) and Young (1996) have reviewed detailed aspects of human adaptation, acclimation and acclimatization to cold.

Studies regarding human cold adaptation have mainly been carried out among indigenous people living in cold districts (e.g. Hammel 1964), during Arctic or Antarctic exploring expeditions (e.g., Purkayastha et al. 1992, Savoureay et al. 1992, Rintamäki et al. 1993, Livingstone et al. 1996) or by exposing volunteers to various degrees of cold stress (e.g. Hurley et al. 1964, Raven et al. 1975, Muza et al. 1988, Tikuisis et al. 1991, Hesslink et al. 1992, Mäkinen et al. 2006). The hypothermic cold adaptation mechanism among indigenous people has been reported in aboriginals in the Kalahari desert (Hammel 1964) and in Korean scuba divers (Hong 1963). Bodey (1978) also found such mechanisms among members of an Arctic expedition group. The hypermetabolic adaptation to cold was noted e.g. by Scholander (1958) in individuals who lived in high latitudes with active physical training at the same time. In the hypermetabolic adaptation,
the rate of blood flow, basal metabolism and deep body temperature increases after cold exposure compared to individuals who are not adapted to cold.

Standardized cold exposure tests have shown that physiological reactions to cold stimulus are altered in different seasons. Girling (1967) found the most marked physiological changes in these reactions in spring. In wintertime darkness is also associated with the effects of cold (Leppäluoto et al. 2005). In studies classifying the deaths of humans in different seasons increased morbidity in winter months has been reported (Healy 2002, Näyhä 2005).

Repeated mild exposures to cold air have been found to lead to habituation responses such as delayed onset of shivering and reduced VO₂ response (e.g. Hesslink et al. 1992). No changes in rectal or skin temperatures were seen in a similar type of cold exposure by Mäkinen et al. (2006), but in their study the thermal sensations became less intense. Weakened thermal sensations in response to repeated cold exposure were also reported by Hurley et al. (1964), Muza et al. (1988) and Raven et al. (1975)

Long-term or repeated severe exposure to cold has been found to lead to hypothermic acclimation including reduced rectal temperature (Brück et al. 1976, Davis 1961, Marino et al. 1998). Insulative-hypothermic acclimation was reported e.g. by Young (1986) and was noted as decreasing rectal and skin temperatures. Bittel et al. (1987) found a metabolic acclimation reaction, which included increased metabolism together with decreasing rectal and skin temperatures.

Hormonal acclimation, such as decreased noradrenaline secretion in response to cold after repeated whole-body exposure has been found, indicating habituation of the autonomic nervous system. Radomski & Boutelier (1982) reported that subjects who swam in cold water on nine successive days had a lowered response in their noradrenaline secretion in a standardized cold exposure test to cold air compared to subjects who were not acclimatized to cold to the same extent. However, Young et al. (1986) found increased plasma NA concentrations after repeated immersions into cold water.

Local acclimatization is typically developed in the hands. Well acclimatized subjects have better circulation in their hands because cold-induced vasoconstriction has become weaker than in subjects without cold acclimatization. They develop so-called “fisherman’s hands”: heat loss from the hands is high, but manual performance remains good (Leblanc 1962, Rintamäki 2001).
2.6 Gaps in the knowledge

According to earlier studies interindividual differences in the thermal, hormonal and especially cardiovascular reactions to cold exposure can be great. The type of the exposure also seems to play an important role. Several earlier studies have concentrated on a single response to cold in laboratory conditions and the number of subjects tested has usually been limited. A larger group of subjects obviously help to minimize the effects of different individual responses. New aspects in thermal responses can also be found by measuring different types of responses in similar carefully controlled experimental conditions.

Habituation to cold has been produced by many kinds of repeated exposures to cold. However, the extent to which a mild repeated exposure to cold is sufficient to produce physiological changes and improved performance in cold conditions has remained unclear.

The mechanisms affecting cardiovascular responses to cold also seem to be different depending on the type of the cold exposure (local or whole-body). Useful information could thus be obtained by using homogenous populations in different types of cold exposure.
3 Aims of this study

The aims of this study were to find out the simultaneous thermal, hormonal and cardiovascular responses to whole-body and local cold exposure and to compare the effects of different types of exposure. The specific aims were:

1. To determine the effects of single whole-body cold exposure on thermal, hormonal and cardiovascular responses.
2. To determine and compare the effects of repeated 1-h and 2-h whole-body cold exposures on thermal, hormonal and cardiovascular responses. The hypothesis is that the responses are attenuated by repeated cold exposure.
3. To compare the effects of local and whole-body cold exposure on cardiovascular responses by using the same test subjects. The hypothesis is that individual sensitivity to local and whole-body cold exposure are associated with each other.
4 Materials and methods

4.1 Single 2-h whole-body cold exposure to 10 ºC

Twenty healthy male Caucasian volunteers (mean age 25 ± 3 yrs) gave their informed consent to participate in this study after examination by a physician. They were permanent personnel in the Finnish Defence Forces and can be classified as outdoor workers. The experimental protocol was accepted by the Ethics Review Board of the Medical Faculty, University of Oulu. The mean body weight of the study population was 76 ± 8 kg, mean skin area 1.9 ± 0.1 m² and mean body fat % 18.7 ± 5.6% (Table 1 of Study I). The experiments were carried out in June. Physical training or intake of alcohol was not allowed for two days prior to the tests. In order to avoid physical exercise before the test, the test subjects were transported by car to the study site at the Department of Physiology, University of Oulu. Supper was eaten at 5–6 pm on the preceding evening. On the test day the subjects woke up at 7 am, had a light breakfast and arrived at the laboratory at 9 am. After undressing, twelve skin and one rectal thermistors (YSI Instr., Yellow Springs Ohio USA) were fixed in place and each subject, clad in shorts, was taken into a room with a temperature of 28 ºC for 30 min. The HR was recorded continuously by radiotelemetry (MEDINIK), using EKG electrodes (S&W, Healthcare Corporation Brooksville USA). Skin and rectal temperatures as well as blood pressure readings were taken every 15 min. The mean skin temperature was calculated according to the method of Ramanathan (1964) and body heat content according to O‘Hanlon & Horvath (1970).

At 25-min time-point the oxygen consumption and CO₂ production were recorded by a breath gas analyzer (Pulmostar, Dr Fenyves & Gut Basel Switzerland). The metabolic rate was then calculated according to Consolazio et al. (1963) and presented in W/m². A venous blood sample was taken at the end of the 30-min stay. Thereafter, the subjects were taken into a room with a temperature of 10°C (range 9.5–11.2°C), air velocity less than 0.2 m/s and humidity 2–4 g/m³, where they sat for 120 min on a netted chair. The skin and rectal temperatures was registered every 15 min. Blood pressure was measured at time points 10, 60 and 120 min. At 120 min O₂ consumption and CO₂ production were measured.

A venous blood sample was taken immediately after the subjects left the cold chamber. An aliquot of the serum sample (1ml) was stored at −80 ºC in the
presence of 50 μl 1M Na₂S₂O₂ for measurements of serum adrenalin and noradrenaline by HPLC and electrochemical detection (Taylor et al. 1983). Serum LH, cortisol, T3 and T4 were measured using the radioimmunoassay (RIA) kits from Farmos (Turku, Finland), TSH using a RIA kit from Corning (MA, USA), prolactin using a RIA kit from DPC (CA, USA) and GH using a kit from Pharmacia (Sweden). The details of the radioimmunoassays are reported in Leppäluoto et al. (1986). Serum Na, Ca, FFA, cholesterol and triglycerides were measured by autoanalyzer (Technicon, MA, USA) and proteins by a biuret method.

The statistical significance between the values taken before the cold exposure and those during and at the end of the cold exposure were calculated by means of analysis of variance and the Bonferroni method (two or more simultaneous comparisons) or by paired t-test (one comparison).

4.2 Repeated 1-h and 2-h whole-body exposures to 10 ºC

Six healthy male Caucasian volunteers who were performing their military services gave their informed consent for the repeated cold exposures (1-h and 2-h). The subjects in these two different tests were not the same but similar experimental conditions were followed as described below. The physical characteristics of the volunteers are given in Table 1.

The experiments were carried out between June and August at the Department of Physiology University of Oulu. All subjects gave their informed consents and the experimental protocol was approved by the Ethical Committee of the Medical Faculty, University of Oulu. The subjects were familiarized with the experimental procedures (cold chamber, insertion of thermistors and blood sampling) before the tests. The subjects were transported by car to the study site. The study consisted of 11 repeated 2-h cold exposures. Ten of the exposures were carried out on successive days. The first (day 0) and last (day 11) cold exposure was the same (2-h) to both of these exposure groups.

During the cold exposures, the subjects were dressed in shorts and sat on a netted chair. Physical training, sauna baths, tobacco smoking or intake of alcohol was not allowed during the days when the study was carried out or 2 days prior to it. The subjects woke up at 6 a.m., had a light breakfast and arrived by car at the Department of Physiology at 8 a.m. Eighteen skin thermistors and one rectal thermistor (YSI, Yellow Springs Instruments, Ohio USA) were fixed and the subjects were taken into a room with a thermoneutral temperature (range 27–
28 °C) for 30 min. A physician measured their blood pressure every 15 minutes. The heart rate was recorded continuously by radiotelemetry (Hewlet Packard 9000/216 data logger). At time point 25 min the oxygen consumption was measured by a breath gas analyzer (Morgan Oxylog) and at the end of the stay a venous blood sample was taken in thermoneutral temperature. The temperature sensations were asked at time points 5 and 25 min. in the following locations: general, hands, feet and face according to the following scale: 1 = cold, 2 = cool, 3 = slightly cool, 4 = neutral, 5 = slightly warm, 6 = warm, 7 = hot (ISO 10551).

Thereafter the subjects (two at a same time) were taken into the same cold chamber described in chapter 2.1 with a temperature of 10 °C. The air velocity and humidity were also the same as presented in chapter 2.1. HR was registered continuously by the same method as in thermoneutral ambient temperature. Blood pressure and oxygen consumption were measured at time points 15, 30, 60, and 120 min.

At time points 5, 10 and 15 minutes and thereafter every 30 minutes the subjects were asked about their temperature sensations. A venous blood sample was taken immediately after the subjects left the cold chamber on the first, fifth and last test day. The methods in measurements of serum NA, A, TSH, T3, T4, Cortisol and FFA concentrations are presented in chapter 4.1. In measurements of serum A and NA there was an interassay coefficient of variation < 5% (Erikson & Persson, 1982) and in other analyses each was assayed in one assay with an interassay coefficient of variation < 8%.

The arithmetic mean ± SE was calculated for all data. The effects of cold exposures on the measured variables were analyzed separately through a two-way analysis of variance for repeated measures (BMD P2V) with the day of the exposure (days 0–10) and time of exposure in minutes as factors 1 and 2 respectively. Here Day 0 means here the first exposure day, when the time of the cold exposure was same 2-h for the both cold exposure groups (1-h and 2-h). Comparisons of each exposure time against the respective Day 0 values for the successive exposure days 1–10 were carried out with the method using contrast trials (differences).
Table 1. Physical characteristics of the subjects in repeated 2-h (Study II) and 1-h (Study III) whole-body cold exposures expressed as means ± SE (n = 6 for both studies, all males). Body fat was assessed from skinfolds according to Durnin & Womersley (1974).

<table>
<thead>
<tr>
<th>Exposure length</th>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>Body height (cm)</th>
<th>Body fat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-h</td>
<td>21 ± 0.2*</td>
<td>66 ± 3</td>
<td>174 ± 2</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>1-h</td>
<td>25 ± 0.8*</td>
<td>69 ± 10</td>
<td>176 ± 2</td>
<td>19 ± 1</td>
</tr>
</tbody>
</table>

*p < 0.001

4.3 Cold pressor tests

Twenty healthy males gave their informed consent to participate in this study. The volunteers were same persons as in the single 2-h whole-body cold exposure. Physical characteristics of the subjects are presented in Table 1 in chapter 2.1. On the test day the subjects woke up at 7 a.m., had a light breakfast and arrived by car at the laboratory at 9 a.m. The subjects were then exposed to two different cold pressor tests (arm and leg), both performed on the same day. The tests were carried out on June. During the test procedure the subjects were dressed in shorts and lay in supine position on an examination bed.

The resting values for systolic and diastolic blood pressure, heart rate and skin temperature of middle finger and big toe were measured before the cold exposure. In the hand cold pressor test, both hands up to the wrists and in the foot cold pressor test both feet up to the ankles were immersed in ice-water (temperature 2 °C) for 1 min. Blood pressure, heart rate and skin temperature readings were recorded at the end of the immersions. After the exposures the same measurements were performed again at 2, 4, 8 min. Blood pressure and heart rate were always registered by the same physician. Skin temperature of both middle fingers (1 cm distally from the nail) and big toes (1 cm distally from the nail) were recorded using YSI thermistors (YSI, Yellow Springs, Ohio, USA), which were held in place with adhesive tape.

The paired t-test was used in comparing the resting values (values after 10 min in rest before the ice-water exposure) and the values at the end of the ice-water exposure as well as after the exposure. To control for multiple comparisons, the observed p-values were adjusted using the Bonferroni method. Pearson correlation analyses were conducted to examine the association in the measured variables between the different types of cold exposures (whole-body cold room...
exposure versus local cold exposures). The rate of changes in the parameters were obtained between the last values before and at the end of the cold exposures.
5 Results

5.1 Single 2-h whole-body cold exposure in 10 °C

5.1.1 Rectal and skin temperatures, heat production and body heat content

The mean values of rectal and mean skin temperatures before and during the cold exposure are presented in Table 2 in Study I. The rectal temperature decreased 0.5 ± 0.3 °C (mean ± SD) after 120 min exposure to cold compared to the last values in thermoneutral temperature (p < 0.01). At the same time the mean skin temperature decreased 7.3 ± 1.3 °C (p < 0.01). During the first 30–60 min the rectal temperature did not change, whereas the mean skin temperature fell clearly.

The forehead skin temperature was reduced by 5.5 ± 2.4 °C (p < 0.001) and ear skin temperature by 10.3 ± 2.4 °C (p < 0.001) at the end of the cold exposure from the values measured in thermonutral temperature. The respective decreases in palm and middle finger skin temperatures were 13.3 ± 2.0 °C (p < 0.001) and 18.4 ± 2.8 °C (p < 0.001). The skin temperature of the foot diminished at the same time by 12.0 ± 2.2 °C (p < 0.001) and big toe skin temperature by 14.9 ± 3.2 °C (p < 0.001).

The heat production of the body increased from 39.0 ± 1.9 to 54.7 ± 2.6 W/m² (p < 0.01), while the heat content of the body was markedly decreased at the same time (Study I, Table 2). Table 2 summarizes the thermal responses in the single whole-body cold exposure.

Table 2. Thermal responses in single whole-body cold exposure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature</td>
<td>Decreased</td>
</tr>
<tr>
<td>Mean skin temperature</td>
<td>Decreased</td>
</tr>
<tr>
<td>Metabolic heat production</td>
<td>Increased</td>
</tr>
<tr>
<td>Body heat storage</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
5.1.2 Serum TSH, thyroid hormones, adrenalin, noradrenaline, cortisol, GH, prolactin, testosterone, LH, total proteins, FFA, triglycerides and cholesterol

The serum levels of TSH, T4, T3 and adrenalin did not show any significant changes between values measured before the cold exposure and those after the 120 min cold exposure (Study I, Table 4). Instead the serum noradrenaline content increased at the same time from 4.5 to 6.3 nmol/l (Study I, Table 4). The serum cortisol level decreased from 0.49 to 0.34 nmol/l (p < 0.01) after 120 min in the cold (Study I, Table 4). At the same time serum GH and prolactin exhibited a significant fall (Study I, Table 4). The serum levels of LH and testosterone were unchanged (Study I, Table 4). Table 3 summarizes the hormonal responses to single whole-body cold exposure.

Table 3. Hormonal responses to single 2-h whole-body cold exposure.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid stimulating hormone</td>
<td>No change</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>No change</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>No change</td>
</tr>
<tr>
<td>Adrenalin</td>
<td>No change</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Increased</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Decreased</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Decreased</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Testosterone</td>
<td>No change</td>
</tr>
<tr>
<td>Luteotrophic hormone</td>
<td>No change</td>
</tr>
</tbody>
</table>

The mean serum total protein concentration increased after the 120 min in the cold from 77 to 82g/l (p < 0.01), FFA from 0.34 to 0.44 mmol/l (p < 0.01) and cholesterol from 5.2 to 5.7 mmol/l (p < 0.05), but triglycerides did not change significantly (Study I, Table 3). Table 4 summarizes the biochemical responses to single whole-body cold exposure.

Table 4. Biochemical responses to single 2-h whole-body cold exposure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free fatty acids</td>
<td>Increased</td>
</tr>
<tr>
<td>Total proteins</td>
<td>Increased</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>No change</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Increased</td>
</tr>
</tbody>
</table>
5.2 Repeated 2-h and 1-h whole-body exposures in 10 ºC

5.2.1 Rectal and skin temperatures, metabolic rate, heat debt, systolic and diastolic blood pressures in 2-h exposures

The mean rectal temperature prior the cold exposure on Day 0 was 37.1 ± 0.1 ºC (mean ± SE) and it decreased on average by 0.5 ºC after the 120-min cold exposure (p < 0.001). At the end of the repeated cold exposures the decrease was similar. This indicates that no habituation process in deep body temperature was observed. The mean skin temperature decreased after 120 min from 33.1 ± 0.1 ºC (pre-exposure value) to 23.4 ± 0.2 ºC (p < 0.001) on Day 0. On the last test day the decrease was similar. However, on Day 5 this decrease was on average 0.8 ºC smaller compared to Day 0 (Study II, Fig 1). As for local skin temperatures, the forearm skin temperature became similarly 1.5–2.0 ºC warmer on Days 5–8 compared with Day 0 (Study II, Fig 1). The skin temperature of the chest decreased rapidly on each day and no significant changes were seen between Day 0 and the other days (Study II, Fig 1).

The metabolic rate increased significantly at the 30–120 min time points from the pre-exposure levels and these increases were essentially similar during the whole test period (Study II, Fig 3). The heat debt of the body showed at the same time similar decreases in the cold during the test period (Study II, Fig 3). The increases in systolic and diastolic blood pressure were the same during the repeated 2-h cold exposure period except for Days 4 and 6, when the increase in systolic blood pressure was significantly reduced at 60 min (Study II Fig 3).

5.2.2 Thermal sensations in 2-h exposures

The thermal sensations were estimated according to a subjective scale in which 5 = slightly warm, 4 = neutral, 3 = slightly cool, 2 = cool and 1 = cold. The results showed that the cold sensations became milder on certain days and time points during the repeated cold exposures. The general thermal sensation was 4.2 ± 0.2 on Day 0 before the cold air exposure and reached the minimum in 115 min cold exposure (Study II, Fig 2). During the next days, the general thermal sensations became significantly less intensive at time point 35 min on Days 1–3, 5–6 and 8, at 65 min on Days 3–5, 7 and 9–10 as well as at 115 min on Days 4–10.

On Day 0 the thermal sensation of the hands decreased from 4.2 ± 0.2 to 1.4 ± 0.2 (p < 0.001) during the 120-min cold exposure. The cold sensation of the
hands was significantly reduced on Days 1 and 4–10 at time point 115 min, on
Days 2–4 and 8–9 at time point 35 min, as well as on Days 5 and 7–9 at 65 min
(Study II, Fig 2).

The thermal sensations of the feet fell to a minimum (1) on Day 0 during the
120 min exposure to cold and the decrease was significantly reduced at 35 min on
Days 1, 2, 4 and 8–10 and at 65 min on Days 3–5 and 7–10 (Study II, Fig 2).
Thermal sensation of the face decreased less on Day 0 than that of hand or foot,
from 4.2 ± 0.2 to 2.8 ± 0.3 (p < 0.01). The decrease was significantly reduced at
35 min on Days 2 and 4–10 as well as at 65 min on Days 5 and 8–10 (Study II,
Fig 2).

5.2.3 Serum TSH, thyroxine, T3, cortisol, adrenalin, noradrenaline,
FFA and total proteins in 2-h and 1-h exposures

No significant changes in the levels of serum thyroxine, triiodothyronine, TSH,
cortisol and adrenalin were observed in response to the 120-min cold exposure
during the test period (Study II, Table 2). This result was the same in repeated 1-h
cold exposures too (Study III, Table 1). Serum prolactin concentration was
measured in the 2-h exposure group and it decreased in the cold on Days 0, 5 and
10. No significant change in this decrease was seen between these days (Study II,
Table 2). Serum noradrenaline concentration increased in the 2-h-exposure group
significantly from 473 to 1329 ng/ml on Day 0 and the increase was significantly
reduced on Days 5 and 10 (Study II, Table 2). In the 1-h exposure group this
increase in serum noradrenaline content was not reduced on Days 5 and 10 (Study
III, Table 1).

Blood FFA and total proteins were measured from the 2-h cold exposure
group and the serum FFA concentration increased significantly on Days 0
(p < 0.01), 5 (p < 0.05) and 10 (p < 0.05). This increase on Day 10 was
significantly smaller than on day 0 (p < 0.05) (Study II, Table 2). At the same
time serum total proteins tended to increase in response to cold (NS), but on Day
10 this response was smaller so that there was a statistically significant (p < 0.05)
difference compared to Day 0 (Study II, Table 2).
5.3 Comparison of heart rate and blood pressure responses between hand and foot cold pressor tests and single 2-h whole-body cold exposure test

In the arm cold pressor test, the systolic blood pressure increased from 135 to 158 mmHg ($p < 0.01$) (Study IV, Table I) and the diastolic blood pressure from 85 to 110 mmHg ($p < 0.01$) (Study IV, Table I). The mean increases of these values were $24 \pm 11$ and $25 \pm 11$ mmHg respectively. At the same time the mean values of heart rate tended to increase from 63 to 71 beats/min, but the increase was not significant (Study IV, Table I). In the leg cold pressor test the systolic blood pressure increased from 130 to 156 mmHg ($p < 0.01$) (Study IV, Table II) and the mean increase was $25 \pm 13.3$. The respective change in diastolic blood pressure was from 79 to 102 mmHg ($p < 0.01$) (Study IV, Table II) and the mean increase was $23 \pm 13.0$ mmHg. The heart rate increased at the same time from 58 to 73 beats/min ($p < 0.01$) (Study IV, Table II).

Both cold pressor tests caused a significant change in rate pressure product (systolic blood pressure x heart rate, $p < 0.05$ for arm cold pressor test and $p < 0.01$ for leg cold pressor test (Study IV, Tables I and II). There were no statistically significant differences in blood pressures between the both cold pressor tests. The mean decrease in skin temperature of the big toe was at the end of the ice-water exposure $9 \pm 2.6 ^\circ C$ and in the middle finger $14 \pm 3.2 ^\circ C$ ($p < 0.01$ for both values) (Study IV, Tables I and II).

At 28 °C, before the whole-body cold exposure test, the mean resting values of the systolic and diastolic blood pressures were 126 mmHg and 83 mmHg. After 120 min at 10 °C the values were increased to 145 and 100 mmHg respectively ($p < 0.01$ for both values) (Study IV, Table III). The heart rate decreased at the same time from 72 to 59 beats/min ($p < 0.05$) and the rate pressure product from 9400 to 8520 ($p < 0.05$) (Study IV, Table III). The increases in the systolic and diastolic blood pressure were significant after 10 min and the decrease in the heart rate after 60 min in the cold (Study IV, Fig 1). There was no statistically significant correlation between the rate of changes in blood pressure in the cold pressor tests and whole-body cold exposure. At the end of the cold air exposure skin temperature of the middle finger was decreased by $18 \pm 2.8 ^\circ C$ and that of the big toe by $15 \pm 3.2 ^\circ C$ ($p < 0.001$) (Study IV, Table III).
6 Discussion

6.1 Thermal responses

In the single whole-body cold exposure the responses in skin and rectal temperatures were consistent with earlier studies e.g. Hurley et al. (1964) (2 h in 10 °C), O’Hanlon & Horvath (1970) (2 h in 8 °C) and Raven & Horvath (1970) (2 h in 5 °C). The lowest skin temperatures were registered in peripheral skin areas (big toe, finger), where the cold-induced vasoconstriction is most effective. The highest skin temperature was detected in the forehead, which may be due to minor cold-induced vasoconstriction compared to other skin areas (Edwards & Burton 1960). The amount of the increase in heat production of the body in response to cold in this study is in line with earlier studies, where men were exposed to cold air for a short period (Girling 1966, O’Hanlon & Horvath 1970, Schwarz et al. 1977, Tanaka 1978, Futusoka & Veda 1982). The rapid increase in heat production in response to cold is important due to the fact that vasoconstriction of skin vessels alone is not sufficient to protect against the heat debt in the body. Despite increased heat production and enhanced vasoconstriction the heat content of body decreased markedly in this study resembling the results of earlier similar studies (e.g. O’Hanlon & Horvath 1970). According to the responses of skin and rectal temperatures as well as heat content of the body the whole-body cold exposures used in this study could be classified as moderate cold stress (Lloyd, 1986). In the cold pressor tests the effectiveness (fast change in skin temperatures) of the cold exposures caused sensations of pain. Thus the cold pressor tests used in this study could be classified as pain producing cold exposures, in line with earlier similar studies (e.g. Wolf 1951).

By exposing subjects to repeated daily cold air exposure it was found that significant decreases in mean skin temperature vanished after Day 5 and those in the forearm after Day 8. The reduced responses of mean skin and forearm skin temperatures to daily cold exposures show here transient habituation processes. In earlier studies it has been found that long-term cold-air exposures have resulted in increased skin temperatures in toe, arch and calf, but no changes were seen in chest, hand, forearm or finger (Kreider et al. 1959, Keatinge 1961). These differences in the results are probably explained by the different experimental settings. Mäkinen et al. (2005) measured in their repeated 2-h exposure to 10 °C significantly warmer mean skin temperatures on Days 6 and 10.
During the daily exposures no differences in responses to cold were found in rectal temperatures, indicating no habituation of deep body temperature during the experiment. Similar results during repeated daily cold exposures have been noted in the studies of Hesslink et al. (1992) and Mäkinen et al. (2005). Hesslink and coworkers (1992) used a 30-min cold exposure, which was repeated on 80 successive days, while Mäkinen and coworkers (2005) used repeated 2-h exposures during ten days. On the other hand, significant decreases in the responses of rectal temperature to cold have been observed in studies where the exposure times have been longer than the 2 h (Kreider et al. 1959, Keatinge 1961). Repeated exposures to cold in this study produced similar changes in metabolic heat production and heat debt of the body as seen in the studies above. In some previous studies, repeated cold air exposures have led to decreased metabolic responses after acclimation, but in those studies the durations of the cold acclimation processes were longer (Davis 1961, Keatinge 1961, Hesslink et al. 1992).

In this study the cold sensations first became habituated and the significant changes lasted to the end of the exposure period. The unpleasant nature of the cold sensation may explain its strong habituation. The habituation in skin temperature but not in cold sensations vanished after Days 5-8 and it may be related to the low intensity of the cold air stimulus used in this study. In repeated 10-day exposure to 10 °C Mäkinen et al. (2005) found also that the significant change in general thermal sensation lasted to the end of the exposure period, but this did not happen in the thermal sensation of the hands. In this study the thermal sensations of the hands was marked at certain single time points during the cold exposure, probably indicating the effect of the low intensity of the cold stimulus.

6.2 Hormonal and biochemical responses

6.2.1 Single whole-body cold exposure

Exposing lightly clothed subjects to a cold room with an ambient temperature of 10 °C for a 2-h period did not result in any changes in TSH or thyroid hormone serum concentrations. Previous studies have shown partly controversial results in the secretion of thyroid hormones in responses to nonhypothermic exposure to cold. A short exposure to low ambient temperature has been found to result in either unchanged (Hershman et al. 1970, Nagata et al. 1976) or increased
(Goldstein-Golaire et al. 1970, O’Malley et al. 1984) serum TSH and thyroid hormone levels in adult man. In studies where the subjects took icy drinks or crushed ice, no changes in serum TSH level were found (Berg et al. 1966, Weeke & Gundersen 1983). A more intense body cooling has however been observed to result in an increase in serum TSH levels (Tuomisto et al. 1976, Leppälumo et al. 1982). In the study of Leppälumo et al. (1982) the subjects spent 10 min in cold water (12 °C) followed by 20 min in 28 °C. This decreased the tympanic temperature by 1 °C. In the present study the mean decrease in rectal temperature was 0.5 °C. Thus it seems obvious that the cold air exposure here was not severe enough to produce an increase in thyroid hormone secretion.

In previous studies performed in laboratory conditions unaltered (O’Malley et al. 1984, Scriven et al. 1984, Šramek et al. 2000) or increased (Wilkerson et al. 1974, Galbo et al. 1979) serum or urine adrenalin levels have been reported in human subjects as a response to a single cold exposure. In the present study no increase in blood adrenalin level was found. It seems that the cold exposure used in this study was not sufficient to produce the activation of the adrenal medulla. The serum noradrenaline level showed at the same time a significant increase. This is in accordance with several previous studies, which demonstrate that the serum levels of noradrenaline increase in human subjects in response to cold exposure that is not severe (Wilkerson et al. 1974, Hiramatsu et al. 1984, O’Malley et al. 1984, Scriven et al. 1984, Weiss et al. 1988). It is likely that most of the increased blood noradrenaline was released from nerve endings, indicating activation of the sympathetic nervous system. The rapid increase in noradrenaline secretion is useful for the prevention of heat loss from the body, because it causes vasoconstriction of the skin vessels and thus lowers the temperature gradient between the skin and the environment. The increased noradrenaline secretion also causes lipolysis and generation of free fatty acids, which further stimulates the chemical heat production (Cannon & Nedergaard 2004). A joint occurrence of increased noradrenaline and FFA concentrations in the blood was also found in the present study.

Serum cortisol level decreased as a response to cold in this study. This decrease evidently relates to the diurnal secretion of cortisol with decreasing levels after early morning (Hellman et al. 1970). Opposite results have been reported by Okada (1970), Wilson et al. (1970) and Wilkerson (1974), who measured in their cold exposures elevated serum or urine cortisol concentrations. Leppälumo et al. (1982) found that if the intensity of the cold exposure is severe, as in the case of exposure to cold water, both ACTH and cortisol are secreted well
above the pre-exposure levels. Obviously, the individual characteristics and the strength of the cold stimulus appear to determine the amount of cortisol secreted in response to a cold stimulus.

Consistent to previous studies GH and prolactin appear to be suppressed after exposure to cold (Goldstein-Golaire et al. 1970, Leppäläuto et al. 1982, Mills & Robertshaw 1981, O’Malley et al. 1984). This decrease in the secretion of GH and prolactin that occurred during the cold exposure could be mediated by hypothalamic inhibitory mechanisms such as increases in dopamine or somatostatin secretion. As to GH a decrease in growth hormone releasing hormone is also possible.

During the present cold exposure there was an 11% hemoconcentration as judged from the measurements of serum total proteins. This hemoconcentration, however, did not lead to significantly increased levels of protein-bound hormones (T3, T4, cortisol and testosterone) or protein hormones (TSH, LH, GH and prolactin) and there were no significant correlation between the cold-induced increments of serum protein and those of TSH or thyroid hormone levels (Study I). Similarly in a previous study the position of body-induced increments of serum albumin did not correlate with those of selected plasma enzymes (Hyltoft Petersen et al. 1980). This means that some hormones or enzymes may extravasate (leakage of fluid from plasma to the interstitium) during the hemoconcentration.

### 6.2.2 Repeated whole-body cold exposure

After repeated 2-h cold air exposures the serum FFA response was attenuated, as was the noradrenaline response. This finding also supports a significant association between noradrenaline and serum fatty acid concentrations. The increase in the number of blood cells and in the concentration of serum proteins is due to hemoconcentration caused by cold-induced peripheral vasoconstriction that leads to extravasation of plasma water (Donaldson et al. 1997, Keatinge et al. 1984). However, on Day 10 serum proteins no longer became concentrated in response to cold. The possible mechanism to this reaction is reduced vasoconstriction in response to repeated cold stimuli. The repeated 2-h cold exposure caused habituation in serum noradrenaline, FFA and total protein concentrations. This happened to noradrenaline and FFA from Day 5 and to serum proteins on the last test day. Other hormones (GH, prolactin) showed no habituation. In the repeated 1-h cold exposure there was no habituation in serum
noradrenaline concentration. With the exception of age, the physical characteristics of the subjects did not differ markedly between the test groups. Therefore it appears that a 1-h stay lightly clothed in a cold room at 10 °C lightly clothed is not sufficient to reduce an increased sympathetic response to the cold, whereas a 2-h stay is. This could be a useful piece of information when planning experiments utilizing long-term repeated cold-air exposures. In a study regarding the effects of cold water immersions Leppäluoto et al. (2008) found during regular winterswimming (12 weeks, 20 seconds three times in a week) sustained cold induced stimulation of noradrenaline, which was remarkably similar between exposures.

6.3 Comparison of cardiovascular responses in local and whole-body cold exposures

Cardiovascular responses in lightly clothed men exposed to cold air have previously been extensively studied (Hurley et al. 1964, Budd & Warhaft 1966, Raven & Horvath 1970, Raven et al. 1970), as have the effects of local cold exposure (Hines & Brown 1932, Wolf 1951, Wood et al. 1984, Rodger et al. 1984). In this study, both local and whole-body cooling tests were carried out with the same individuals. This makes it possible to compare the cardiovascular effects of these different test types. In order to minimize the effects of individual variation 20 volunteers were recruited for this study.

Increased blood pressure results in a higher work load on the heart, but this is dampened by a decrease in the heart rate, which was seen in this study after 60 min exposure to cold air. This well-known bradycardia mechanism is mediated by baroreceptors. Decreases in HR (Hurley et al. 1964, Budd & Warhaft 1966, Raven & Horvath 1970) have also been observed in some earlier similar studies, while in others no such changes during cold air exposure have been reported (O’Hanlon & Horvath 1970, Raven et al. 1970). Cold as a stressor increases the sympathetic nervous activity, which has a strong stimulatory effect on the heart rate, possibly leading to these latter responses. The individual characteristics of the subjects especially when the number of the volunteers is small, also play a role in explaining these results. Leblanc et al. (1975) reported that especially cooling of the facial skin has an effect on the bradycardia reaction. The lowered heart rate response observed in this study led to a diminished rate pressure product (systolic blood pressure x heart rate), which is generally accepted as an indicator of the work load of the heart. In both cold pressor tests a significant rise
in systolic and diastolic blood pressures was found at the end of ice-water exposure. In the hand cold pressor test the systolic BP increased by an average of 24 mmHg, which is greater than the increase observed in normoreactive subjects during a one-hand cold pressor test (10–20 mmHg) (Wood et al. 1984). This result is probably due to the larger cold exposure area and thus to a more intensive activation of the sympathetic nervous system and vasoconstriction. There was no significant difference between these two different cold pressor tests in reactions of the systolic and diastolic blood pressures. The increase in HR was significant only in the cold pressor test of the foot. However, both cold pressor tests caused a significant enhancement in the rate pressure product, which indicates higher oxygen consumption in the muscle of the heart.

In the present study no statistically significant correlations were observed when comparing the rate of changes in systolic and diastolic blood pressure during the cold pressor tests and at the end of the whole-body cold air exposures. Some individuals had a greater rise in their blood pressure in the cold room test than in the cold pressor tests, whereas others had a greater increase in their BP in the cold pressor tests. In these different types of exposures, the mechanisms mediating the increase in blood pressure are partly the same: greater sympathetic nervous activity and vasoconstriction. This is also seen in increases in noradrenaline secretion, which was found in Study I and Study II. In the present cold pressor tests NA concentrations were not measured, but in previous studies increased catecholamine secretion in response to a cold pressor test has been found (Cummings et al. 1983).

The genetic association between blood pressure at rest and during the cold pressor test is not well characterized. However Choh et al. (2005) found that measures of blood pressure at rest and during cold immersions are significantly influenced by additive genetic effects.

Endothelin is a bioactive peptide, that has a vasoconstrictive effect, thus increasing blood pressure. Fyhrqvist et al. (1990) investigated plasma endothelin concentration during a cold pressor test and found an increase. In a cold room test like the one used in this study Hassi et al. (1991) noted no increase in blood endothelin concentration. This may be due to lesser local cold and pain during whole-body cold exposures.

During the cold pressor tests most of the subjects had sensations of pain, which was not observed or observed only to a minor extent in the cold air exposures (not measured, subjective observation). The heart rate response was significant in the foot cold pressor test but not in the hand cold pressor test. This
can probably be explained by the effects of skin temperature. In the foot test the skin temperature of the big toe decreased to 9 °C and in the hand test the finger skin temperature to 14 °C. The lower skin temperature in ice-water exposure of feet compared to hands could have lead to a severe sensation of pain, which tends to increase the heart rate. The values at the end of the cold air exposure were 16 °C for finger skin and 14 °C for big toe.

The cold receptors became rapidly adapted when the temperature was kept constant (Hensel 1981). The intensity of the cold stimulus was much greater and the time of the changes in skin temperatures much shorter in the cold pressor tests than in the cold air exposure. Both these factors have an influence on the pain reaction. It is well known that there are considerable inter-individual differences in how people experience pain which is a strong stimulus for raising the blood pressure. Peckerman et al. (1998) observed that in foot cold pressor test in normotensive subjects the increases in systolic blood pressure were greater during sessions in which pain was reported than in those sessions in which there was no pain. The role of cold-induced pain might partly explain the different individual reactions in blood pressure between these different types of cold exposures. The increased rate pressure product found in cold pressor tests indicates that a sudden local exposure to cold, especially when it also causes pain at the same time, seems to be more stressful for the heart in terms of workload than a longer mild cold exposure, even when the latter is applied to the whole body. Further studies are needed to qualify the role of cold-induced pain on blood pressure and heart rate.

The systolic and diastolic blood pressure did not show any habituation process after repeated whole-body exposure to cold despite a dampened vasoconstriction, which was seen in the increasing skin temperatures during the exposure period. The minor rate and transient habituation process in skin temperatures have obviously led to this result.
7 Conclusions

A 2-h whole-body cold air exposure at 10 °C decreased rectal and skin temperatures as well as body heat content but the metabolic rate increased. At the same time no significant changes were found in serum concentrations of adrenalin, TSH, triiodothyronine, thyroxine, testosterone or LH, whereas serum noradrenaline and free fatty acid levels increased, indicating a general activation of the sympathetic nervous system. Serum cortisol, GH and prolactin content fell in the cold. Serum total proteins increased due to cold-induced hemoconcentration. Thus a short-term whole-body cold air exposure of adult man does not have any effect on the pituitary-thyroid and pituitary-testis axis or adrenal medulla. Due to increased sympathetic nervous activity the systolic and diastolic blood pressure increased, but the pulse rate fell, which is probably mediated by a baroreflex mechanisms.

In the repeated 2-h whole-body cold air exposures to 10 °C a markedly smaller increase in serum noradrenaline concentration was found after the fifth day of exposure. At the same time hemoconcentration and cold sensations became habituated. When using a repeated 1-h exposure-time to 10 °C, the increase in serum noradrenaline concentration remained unchanged, indicating that a 1-h cold air exposure to 10 °C is not sufficiently intensive to reduce the cold-induced sympathetic response.

The cold pressor tests to hands and feet caused significant increases in systolic and diastolic blood pressures as did the 2-h whole-body cold air exposure. There were no significant differences in blood pressure between these types of cold pressor tests. The heart rate tended to increase in both cold pressor tests, but this increase was marked in the foot cold pressor test. In the cold air exposure the pulse rate fell causing a reduction in rate pressure product. In both cold pressor tests the rate pressure product increased. No significant correlations were seen when comparing the changes in blood pressure between the cold pressor tests for the hand and foot and the whole-body cold air exposure. Thus some individuals had a greater increase in their blood pressure in the whole-body cold air exposure, whereas others had a greater blood pressure increase in the cold pressor tests. Factors affecting the increase in blood pressure are partly the same in these different types of cold exposure tests: increased sympathetic nervous activity and vasoconstriction. However, cold-induced pain is a strong stimulus to increase the blood pressure. Pain is often experienced in cold pressor tests and there is great variation between individuals in how they experience pain. The cold
pressor tests caused an increase in rate pressure product while the whole-body cold air exposure test did not. Thus a sudden local exposure to cold, when it causes pain at the same time, seems to be more stressful for the workload of the heart than a longer-lasting mild exposure to cold, even when involving the whole body.

One practical application of the results presented here is that the 2-h whole-body cold air exposure to 10 °C with light clothing is adequate to produce general activation of the sympathetic nervous system, which can become habituated by repeating the test this effect can be seen after the fifth day of exposure. The habituation is seen especially in cold sensations and noradrenaline response and in attenuation of hemoconcentration. The 1-h cold air exposure to 10 °C does not seem not to be sufficiently intensive to reduce the cold-induced sympathetic response. Further studies are needed to assess the role of cold-induced pain on blood pressure and heart rate responses.
References


Original publications


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Original publications are not included in the electronic version of the dissertation.

Errata

There is an error in table 1 in the article III. The blood samples on day 0 were collected after 120 min stay in cold and not after 1-h stay as it is mentioned in the text.
980. Palosaari, Kari (2008) Quantitative and semiquantitative imaging techniques in detecting joint inflammation in patients with rheumatoid arthritis. Phase-shift water-fat MRI method for fat suppression at 0.23 T, contrast-enhanced dynamic and static MRI, and quantitative 99mTc-nanocolloid scintigraphy
981. Perkiömäki, Marja Riitta (2008) Craniofacial shape and dimensions as indicators of orofacial clefting and palatal form. A study on cleft lip and palate and Turner syndrome families
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THERMAL, HORMONAL AND CARDIOVASCULAR RESPONSES TO SINGLE AND REPEATED NONHYPOTHERMIC COLD EXPOSURES IN MAN

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