Heidi Hintsala

CARDIOVASCULAR RESPONSES TO COLD EXPOSURE IN UNTREATED HYPERTENSION
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UNIVERSITY OF OULU, OULU 2018
Cold weather associates with higher cardiovascular morbidity and mortality in various climates. It is also known that exposure to a cold environment instantly activates sympathetic nervous system and elevates blood pressure (BP) in healthy individuals. Hypertension can increase sympathetic reactivity and arterial stiffness, and could therefore exaggerate these cold-related changes. We implemented an experimental study to assess cardiovascular responses to habitual type of cold exposure among subjects with untreated hypertension.

We selected a random sample of middle-aged men in the city of Oulu, Finland. The recruitment included home BP measurements. 51 untreated hypertensive men and 32 men without hypertension (controls) underwent 15 minutes whole-body cold exposure (temperature -10°C, wind speed 3m/s, winter clothing, standing). Brachial, central aortic, and continuous BP, as well as electrocardiography (ECG) were measured before (15 min), during (15 min), and after (20 min) the exposure. Skin temperature and thermal sensations were also assessed.

The employed exposure increased central and brachial systolic (ca. 25 mmHg) and diastolic (ca. 10 mmHg) BP in both test groups. One fourth of men with mild to moderate hypertension had systolic BP exceeding 200 mmHg while exposed to cold. Small heart rate (HR) reduction was not enough to compensate for the elevated BP, and cardiac workload increased during cold exposure. Cardiac repolarization showed modest arrhythmogenic changes and frequency of ventricular ectopic beats increased slightly in cold conditions. Cold exposure also increased cardiac vagal baroreflex sensitivity in both test groups, whereas an estimate of vascular sympathetic activity increased only among controls. We also found an elevated systolic home BP variability to associate with higher cardiac workload and BP responses to cold.

Moderate cold air exposure substantially increased BP but also activated cardiac vagal regulation among untreated hypertensive and non-hypertensive men. The BP level reached in cold conditions was considerably high in those with hypertension, and especially in those with both hypertension and higher home BP variability. These results are important to health care professionals who treat hypertensive patients. The importance of year-round BP control and proper protection from cold should not be underestimated.

**Keywords:** blood pressure, cold temperature, electrocardiography, hypertension
Hintsala, Heidi, Verenkiertoelimistön vasteet kylmäaltistukseen hoitamatonta kohonnutta verenpaineetta sairastavilla.
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Tiivistelmä

Tutkimus analysoi Oulun väestöstä satunnaisesti valittuja keski-ikäisiä miehiä, joita määritettiin verenpaine kotimittauksilla. 51 hoitamatonta hypertensionta sairastava miestä ja 32 miestä, joilla ei ollut hypertensiota (virekot), altistettiin 15 minuutin ajan kylmälle (lämpötila -10 °C, tuuli 3 m/s, talvivaatteet, seisten). Verenpainetta mitattiin olkavarresta, epäsuorasti sydämestä ja jatkuvana signaalina ennen altistusta (15 min), sen aikana (15 min) ja jälkeen (20 min). Samalla seurattiin sydämen sähköistä toimintaa, iholämpötiloja ja lämpötuntemuksia.

Kylmäaltistus kohotti sekä sydämen että olkavarren ylä- (noin 25 mmHg) ja alapainetta (noin 10 mmHg) molemmissa tutkimusryhmissä. Neljäosalla lievää tai kohotettua hypertensiota sairastavista miehiä yläpaino kohosi yli 200 mmHg tasolle. Sykseen lasku ei riittänyt tasapainotamaan kohonnutta verenpainetta ja sydämen työmäärää nousi. Sydämen rytmihäiriöherkkyys ja vastaavasti kammioilsälöytäni esintymistihheyts olivat myös hieman kohollaa altistukseen aikana. Kylmäaltistus kasvattaa sydämen vagaalista barorefleksihäirkkyyttä molemmissa ryhmissä. Verisuonitten sympaattinen verenpaineteho kasvoi vain verrokeilla. Sydämen työmäärä ja verenpaine kohosivat kylmässä emännän heillä, joiden verenpaineen vaihtelu kotona oli korkeampi.
Tavanomaista talvipäivässä vastaava kylmälaitistes kohottii verenpainetta voimakkaasti, mutta myös aktiivoin sydämen suojautuvan saäteilyä sekä hoitamatonta hypertensiota sairastavilla että verrokeilla. Kylmässä saavutettu verenpainetaso oli merkittävä heillä, joilla oli hypertensio, ja erityisesti heillä, joilla oli sidottua hypertensioa, ja suurempi kotiverenpaineteho. Tämä tutkimustieto on tärkeää hypertensioopitoilille sekä heitä hoitaville terveydenhuollon ammattilaisille. Tulokset korostavat ympäri vuotisesen verenpainekontrollin ja kylmältä suojaautumisen tärkeyttä.

Asiakas: EKG, kohonnut verenpaine, kylmys, verenpaine
Dedicated to my beloved mother Hilkka
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17.6.2018

Heidi Hintsala
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BRS</td>
<td>baroreflex sensitivity</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>FFT</td>
<td>fast Fourier transform</td>
</tr>
<tr>
<td>HF</td>
<td>high frequency</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>IREQ</td>
<td>required clothing insulation index</td>
</tr>
<tr>
<td>LF</td>
<td>low frequency</td>
</tr>
<tr>
<td>MSNA</td>
<td>muscle sympathetic nerve activity</td>
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<tr>
<td>RANOVA</td>
<td>repeated measures analysis of variance</td>
</tr>
<tr>
<td>RAS</td>
<td>renin angiotensin system</td>
</tr>
<tr>
<td>RPP</td>
<td>rate-pressure product</td>
</tr>
<tr>
<td>SSNA</td>
<td>skin sympathetic nerve activity</td>
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<tr>
<td>UTCI</td>
<td>universal thermal climate index</td>
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Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


Contributions in research for publication: for publications I-IV, I participated in the planning and design of the study as a member of the research group. I had the main responsibility for the practical implementation of recruitment process and experiments, i.e. in data collection. For publications I and IV, I carried out the necessary signal processing, e.g. BP variability computations. For publication III, I participated in signal processing. I performed the statistical assessments for publications I-IV, with advice from statisticians (II, IV). I had a significant role in drafting the manuscript of publications I-IV.
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1 Introduction

Millions of people live in arctic and subarctic areas, regularly exposing themselves to cold temperature in wintertime during occupational and leisure time activities (1). Habitual cold exposure is usually moderate or mild (2), during which the whole body is exposed but the trunk and sometimes the head and extremities are protected by clothing. Not surprisingly, a recent study combining data from nearly 400 locations worldwide found moderate temperature exposures to have the greatest effect to human health, whereas more rare extreme temperatures contributed substantially less (2). In addition, this study detected multifold effects due to cold compared to heat, and which occurred in different climates in Europe, America, Asia, and Australia. In the future, climate change is expected to cause larger variance of temperatures, with more common weather extremes, such as heat and cold waves, snow storms, heavy rainfalls, flooding, and coastal cyclones (3-5), during which humans are more intensively exposed to non-optimal weather conditions. The adverse health effects of temperature rarely associate with hypo-or hyperthermia, but instead relate to worsening of chronic conditions, such as cardiovascular diseases.

The Global Burden of Disease Study 2015 ranked cardiovascular diseases as the leading cause of deaths (6), and high blood pressure (BP) as the largest contributor to global disability-adjusted life-years (7). The global age-standardized prevalence of hypertension is 20-24% (8), and approx. 40% among 35-70 years old have hypertension (9). It should be noted that less than half of those with hypertension are aware of their condition. In addition, unfortunately, among those treated for hypertension only a third reach the target levels. Further increase in burden of disease associated to cardiovascular diseases and hypertension are projected in the coming decades due the global population growth and aging (10, 11).

1°C fall in temperature below optimal level has been associated to up to few percentage increases in mortality, great majority of which occurs for respiratory and cardiovascular causes (12-15). In addition, 1-5°C decrease from the average or threshold temperature associated with increased risk of 2-9% for ischemic stroke, 1.6-6% for acute coronary syndrome, 0.6-12% for myocardial infarction (16). The risk of emergency admissions due the cerebrovascular and hypertensive diseases increased 56-78% with a temperature decrease of 12°C (16). A focal cardiovascular risk factor, BP, remains few mmHg higher during cold season (17), and 1°C fall in outdoor or indoor temperature associates with 0.26 or 0.38 mmHg increase in
systolic BP, correspondingly (18). The detected cold-related increase in cardiovascular events in epidemiological studies is likely multifactorial, as seasonal variation in temperature occurs in parallel with other seasonal variation, from daylight to life habits (19, 20), and other environmental exposures, such as air pollution, may vary according to temperature or season (19, 21). However, the effects of cold temperature should not be underestimated.

Short-term exposure to cold temperature activates autonomic thermoregulatory reflexes to reduce heat loss from the body to the environment (22, 23). However, these protective mechanisms also induce multiple changes in the circulatory system (24-27) that may involve a higher risk of cardiovascular events (28, 29). Cold exposure increases the activity of sympathetic nervous system (30-33) and elevates BP by 5-30 mmHg, (e.g. (34-36). Cardiac workload is augmented while exposed to cold (29, 36), and in certain populations coronary blood flow compared to workload restricted (36). In addition, exposure to cold temperature induces hemoconcentration and accelerates blood coagulation (34, 37-40). These physiological responses may act as a trigger to adverse health events and partly explain the cold-related morbidity reported in epidemiological studies. Most previous experimental research has been conducted among healthy subjects. However, from a public health perspective it would be important to know the temperature related responses among those with predisposing conditions, such as people with hypertension. Hypertension involves altered circulatory regulation and vascular and cardiac remodeling, which could modify cold-related cardiovascular responses, but the research related to this is lacking. With this in mind, we conducted a controlled experimental study to assess the effects of moderate short-term whole body cold exposure to cardiovascular function in untreated hypertensive men.
2 Review of the literature

2.1 Body heat balance

Humans are warm-blooded tropical mammals with core temperature that is maintained at approximately 37°C (23, 41, 42). Temperature of the extremities and skin, instead, varies in different environmental temperatures, partly as a result of thermoregulation aiming to homeothermy of the inner body (23, 25, 42).

Maintaining approximately constant internal temperature requires heat balance between the body and its environment. Therefore, metabolic heat production (M), external work (W), and heat loss by conduction (K), convection (C), radiation (R), and evaporation (E), should result in zero heat storage (S). This can be illustrated with the conceptual heat balance equation (41, 43, 44):

\[ S = M - W - K - C - R - E \]

If there is a net heat gain (S>0), body temperature will rise, and if there is a net heat loss (S<0), body temperature will fall. Although body temperature varies over time, heat balance (S=0) is reached over a longer time period. However, during cold or heat exposures, net heat loss or gain may occur. Even without changes in core temperature, local thermal imbalance can occur, e.g. cooling of hands, feet or respiratory tract.

Body heat balance is maintained by both physiological and behavioral thermoregulation. Physiological thermoregulation involves autonomic control of heat production (metabolic heat) and heat loss (vasocontrol and evaporation). Often, physiological thermoregulation maintains the thermal balance mainly by regulating vasodilation and vasoconstriction. This ambient temperature range is called the thermoneutral zone (Fig. 1) (43, 45, 46). Below this range, (i.e. below the lower critical ambient temperature), heat production mechanisms, namely shivering and non-shivering thermogenesis, must activate to maintain thermal balance (43). Above the thermoneutral zone, (i.e. the higher critical ambient temperature), sweating is required to maintain thermal balance (43). When heat loss or heat gain exceeds compensative physiological mechanisms, core temperature decreases or increases (below 36°C or above 38°C) (41, 47). Some studies have provided estimates of thermoneutral zone for healthy resting naked adult, and presented lower and upper critical temperatures of e.g. 26°C and 33°C (47). The thermoneutral zone depends on several factors, such as insulation (clothing), posture, and basal metabolic rate (43).
In addition to the (rather limited) physiological mechanisms, behavioral thermoregulation is an efficient means of maintaining thermal homeostasis and enables survival of human in various climates (41, 48, 49). Behavioral thermoregulation involves control of microclimate and macroclimate surrounding the body e.g. by seeking shelter, heating or cooling of the houses and vehicles, using protective clothing, increasing the metabolic rate through physical activity, as well as adopting a body posture that minimizes heat loss (41, 48, 49).

### 2.2 Human thermal exposure

The basic environmental variables characterizing thermal exposure to human are temperature and movement of the surrounding gas or liquid (air or water), radiant temperature, and contacts with solid materials (41). These involve different heat transfer mechanisms, which are discussed in chapter 2.3.3. Combined with the environmental parameters, metabolic heat generated by physical activity and clothing provides a way to determine the human thermal exposure (Fig. 2).
2.2.1 Environment

The environment exposes people to varying air temperatures, wind and humidity. In addition, rain or snow can wet the surface of the skin or clothing and accelerate heat exchange between the body and environment. Radiation from the sun warms the body compared to cloudy weather. Direct contact with cool or warm materials, such as when handling objects, or while sitting and lying on surfaces, provide a part of the thermal exposure. In addition to air exposure, exposure can occur in water. Thermal exposure to each thermal environment can be short or long, and the exposure may vary for different parts of the body, e.g. during head-out water immersion or when handling tools.

Assessments of cold exposure can be conducted in the form of indexes combining different components of thermal exposure. For example, the wind-chill index or wind chill equivalent temperature describe the combined effect of air temperature and wind to heat loss from the body (50). The required clothing insulation index (IREQ), on the other hand, determines the clothing insulation required for heat balance and thermal comfort by considering air and radiant temperature, wind, humidity, and metabolic rate of the body (41). A more recently developed index, the Universal Thermal Climate Index (UTCI), gives an equivalent temperature for a given combination of air and radiant temperature, wind, and
humidity, determined as the air temperature in the reference condition, which produces the same physiological responses, and is applicable for both heat and cold stress (51).

2.2.2 Clothing

Clothing provides thermal resistance between the body and the environment and can be adjusted to maintain thermal equilibrium (41, 48). The thermal function of clothes is affected by multiple factors, such as posture, compression caused by e.g. heavy wind, wetness caused by rain or sweating, as well as pumping effects of a moving body (41, 52). In steady state conditions, the thermal properties of clothes can be specified with thermal insulation and evaporative resistance, or simply as dry thermal insulation (41, 52). Dry thermal insulation depends on surface area, temperature gradient, and thermal conductivity. It can be expressed with as m² °CW⁻¹, or as a clo unit (41, 52). Clo is a relative thermal insulation unit, and 1 clo corresponds to the insulation value of thermoneutral clothing of a sedentary person in normal indoor environment (21°C, air velocity of 0.1m/s, relative humidity<50%), i.e. 1 clo = 0.155m² °CW⁻¹ (41, 52, 53). Dry thermal insulation values have been experimentally specified for individual clothing garments as well as for representative clothing ensembles (52). In addition, the insulation of a clothing ensemble can be estimated as the sum of the insulation values of each individual garment included in the ensemble (52).

2.2.3 Physical activity

Physical activity can increase metabolic rate temporarily up to ten-fold the basic metabolic rate among general population, or up to twenty-fold the basic metabolic rate among well-trained human athletes during maximal exercise (54). Already walking or light cycling can triple the resting metabolic rate (44). Body releases most of the consumed energy as heat and the proportion of energy converted to mechanical work is often negligible. For example, when walking on a flat surface, metabolic energy expenditure and heat production are nearly equivalent (44), and even during cycling or rowing ≤25% of the total metabolic rate is converted to mechanical work (44). Indeed, exercise can be helpful to maintain core temperature in cold environments.

In addition to augmenting metabolic heat production, exercise increases blood flow to skin and skeletal muscles, and therefore, heat loss from the body to the
environment (55). Heat loss is further enhanced due to the exercise related movements (convection), and through sweating (evaporation) together with the increased convective heat loss of the wet skin (41). In post-exercising conditions at rest, heat loss can remain augmented and predispose a person to a greater decline in core temperature than what it would be without prior exercise (56). In addition, exercise in a cold environment can involve simultaneous heat strain in torso or core temperature and local cooling of hands, feet, or face (57).

2.3 Physiological thermoregulation

2.3.1 Thermoregulatory system

Human body temperature is controlled with a thermoregulatory system consisting of temperature sensitive receptors, thermoregulatory centers in central nervous system, thermoeffectors, and the afferent and efferent neural pathways signaling between the central nervous system and the other parts of the system (41, 58, 59).

Temperature sensitive receptors

The temperature sensitive receptors are free nerve endings that have heat or cold sensitive ion channels. They include receptors exhibiting thermal response to noxious or non-noxious cold or heat. Cutaneous thermoreception to noxious cold has a thermal threshold at around 20-10°C, whereas sensing of noxious heat activates at temperatures above 43°C, with a peak discharge occurring at temperatures between 45 and 53°C (60). Non-noxious reception of cold is active at temperatures of around 37-20°C, with discharge increasing towards cooling and decreasing towards warming, and showing maximal activation between 30 and 20°C (60). Non-noxious sensing of warm exhibits similar operating profile on higher but overlapping temperatures, and reaching maximum activation at 40-43°C (60). The heat or cold receptors innervate both the skin (41, 58, 61), as well as the inner parts of the body (e.g. brain, spinal cord, and abdominal cavity). Face and torso have higher number of temperature sensitive receptors than limbs, and there are more cutaneous cold than warm receptors (41, 42, 61-64).
Central control of body temperature

Detailed descriptions of neural thermoregulatory pathways have mostly been derived from animal experiments, and conclusions from those should be cautiously translated to humans (58, 63). Afferent neural pathways convey the sensory information via slower non-myelinated C fibers (mainly warm stimulus) and fast myelinated A fibers (primary for cold stimulus) from the cutaneous temperature sensitive receptors to dorsal root ganglia neurons (primary sensory neurons). The generated signals are further conveyed to the spinal or medullary (trigeminal) dorsal horn (second-order sensory neurons) (58, 63) and after that to the lateral parabrachial nucleus (third-order sensory neurons), and further to the hypothalamus. The afferent thermosensory signals are processed in the hypothalamus, and especially its preoptic area. Neural afferent signals are conveyed from the hypothalamus to the sympathetic and somatic neurons controlling the thermoeffector responses in heat production, sweating, and vasomotor action (vasoconstriction and dilation) (58, 59). Based on the same afferent information on the thermal state of the body, effector responses are controlled independently of each other with different thresholds and gains (59, 63).

The thermoregulation system has traditionally been specified as a closed loop negative feedback system, which simply responds to an increase in body temperature by augmenting heat loss, and opposite. However, a more recent view consists of a main feedback control loop (core temperature, the controlled variable) and a supplementary feedback from “auxiliary” variable (skin temperature) (59, 63, 65). The auxiliary control loop allows adjustments of thermoeffectors also already before changes in the controlled variable occur (65). This system involves both negative and positive feedback, i.e. when core or skin temperature decreases, thermoeffectors are adjusted to reduce heat loss and increase heat production in central parts of the body (negative feedback to core temperature) and to diminish heat transfer to the periphery (positive feedback to skin temperature) (59, 65). Some researchers suggest that body temperature is controlled according to a set point, i.e. to reduce heat loss and increase heat production when body temperature is below, and to increase heat loss while being above a certain temperature threshold (66). Other researchers argue that the term set point is misleading in thermoregulation, in which only proportional control is used allowing deviation in the controlled variable (59).

In addition to autonomic thermoregulation occurring through the hypothalamus, there is a parallel afferent pathway for perception of temperature.
Similarly as for autonomic thermoregulation, cutaneous temperature sensitive receptors convey signals to spinal and trigeminal ganglia. Instead of hypothalamus, temperature information is directed to thalamus (60, 61), and thereafter to different areas of cerebral cortex in which the perception of temperature is formed (61).

**Thermoeffectors**

The somatic nervous system can increase body heat production through shivering of the skeletal muscles (58). The sympathetic nervous system, on the other hand, controls for heat loss through evaporation of sweat glands (23, 41), non-shivering thermogenesis of brown adipose tissue (41, 58), and cutaneous vasoconstriction and vasodilation (23, 25, 41, 58). In addition to the whole-body thermoregulatory reflex responses, cooling or heating also induce local responses, which further interact with each other (23).

In addition to the autonomic effectors, human thermoregulation involves behavioral effectors. Those involve both responses to current circumstances and preventive actions preceding exposure to cold or heat.

**Thermal sensations**

Thermal sensation is simultaneously a sensory experience related to a stimulus from afferent sensory signals to cortex and a psychological phenomenon, affected by individual characteristics (41, 67). It describes how a person feels at a specific moment and may be assessed separately for the whole body or for different areas, such as face or hands (67).

A thermal sensation depends on the exposure temperature, the location and size of the exposed area, the adaptation temperature, as well as the rate of temperature change (41, 68, 69). Overall, the body surface is more sensitive to cold than warm (64). Thermal sensitivity is high in the face, low for the extremities, and intermediate for other body areas (64). When the stimulated area is large, thermal sensitivity is higher and a more intense thermal sensation occurs (41). Furthermore, the same stimulus can be sensed as cool in warm and as warm in a cool environment (41), or a local stimulus can be sensed as colder when the whole-body thermal state is warmer, and vice versa (68). A rapid temperature change involves a more intense thermal sensation and lower thresholds for both warm and cold, than a slower change (41, 68).
Individual characteristics modify thermal sensations. Repeated mild or severe, whole-body or local cold exposures diminish cold sensation (48). This is due to habituation and decreased reactivity of the autonomic nervous system to repeated stimuli and can occur already after one or two exposures (70). In addition, thermal sensitivity declines gradually with age, particularly in the extremities (62, 64). This may relate to decreased density of temperature sensitive receptors of the skin or progressive decrements of nerve conduction velocity and amplitudes of neural action potentials (62). Chronic diseases or disabilities can also alter thermal sensations. For example, diabetic neuropathy decreases thermal sensitivity among type I and II diabetics (71), increasing both cold and warm thresholds.

2.3.2 Heat production

An average basic metabolic rate of adults expressed as energy consumption is around 2100-2300 kcal/day in men and 1700-1800 kcal/day in women (72). Most of the consumed energy is released as heat. Estimates of resting metabolic rate for sleeping (38 W/m²), sitting (44 W/m²), and standing (51 W/m²) have been provided (44).

In cold environments, the body can increase heat production by shivering and non-shivering thermogenesis. Cooling of the surface areas leads progressively to increased skeletal muscle tonus without visible shivering. If body cooling continues, asynchronous muscle contractions initiate to increase metabolic heat production by shivering (41). Shivering can increase heat production five or two times of resting levels for shorter and longer durations, respectively (41, 73, 74). Non-shivering thermogenesis occurs in brown adipose tissue through specific uncoupling proteins (primarily UCP1) that uncouple mitochondrial energy substrate oxidation from adenosine triphosphate production to dissipate energy as heat (75). Earlier, brown adipose tissue was considered to be relevant only among infants and those exposed to cold for substantial amounts, e.g. outdoor workers (30). However, recent studies found cold exposure to activate this tissue also among the general adult population (75, 76). Brown adipose tissue activation is stronger among leaner subjects (75) and repeated cold exposures further augment both non-shivering thermogenesis and activity of brown-adipose tissue (77). However, the heat production by non-shivering thermogenesis is small compared to shivering. For example, Ooijen et al. (78) reported increases from 45 W/m² to 53 W/m² among lean and from 45 W/m² to 48 W/m² among overweight men when resting for one hour in cold conditions.
2.3.3 Heat loss

Heat transfer between the body and its environment occurs through conduction, convection, radiation, and evaporation (41, 43, 44). Conduction occurs by a direct contact to stationary cold or warm materials (41, 43, 44). It is driven by temperature difference, at a rate that depends on thermal conductivity of the material and contact area (43, 44). For example, skin temperature falls rapidly when touching surface of cold metal, having high thermal conductivity (e.g. aluminum 180 WmK⁻¹) (79). Also, heat transfer by conduction between the body and still air is small because of low thermal conductivity of air (from 2.4 to 3.0 Wm⁻¹K⁻¹ with temperatures between 0°C and 80°C) (41). Heat transfer between the body and moving gas or fluid is called convection (43). In still cool air, natural convection occurs from movement of the warmed air away from the skin (44). Moving air (wind), or water, and moving of body during physical activities cause forced convection (43) and augment heat transfer between the body and environment considerably. As for stationary surrounding materials, the convective heat loss occurs according the temperature gradients, with an intensity that depends on thermal conductivity of the materials. For example, convective heat loss for a resting person caused by air or water at a temperature of 26°C (skin temperature of 32°C) and flow of 0.75 m/s are 36 and 474 W/m², respectively (44). Heat transfer by electromagnetic radiation to (or from) the body occurs as solar radiation and radiation from surrounding surfaces (43, 44). It is driven by temperature differences, as conduction and convection, but does not need intervening medium, i.e. it can occur through a vacuum. Typical values for radiant heat flux in indoor with temperatures of 25 and 42°C are around -25W/m² and 25W/m², and directly and diffuse from sun <1000W/m² and <200W/m², respectively (44). Evaporative heat transfer describes evaporation from or condensation to the skin and respiratory tract (43). The rate of evaporation depends on the water vapor concentrations of the surface and the air, in such a way, that higher air humidity suppresses evaporation from the surface. Human skin evaporation i.e. sweating (and respiratory evaporative heat loss) is the only physiological form to remove heat from the body to the environment when the surrounding temperatures are higher than the temperature of the body.

Cutaneous circulation in thermoregulation

Cutaneous circulation provides autonomic control for human thermoregulation by adjusting the heat loss between human body and environment (23, 25, 80). It is
based on thermal gradients between a) the body and the surrounding environment, and b) inner and outer parts of the body (41). When skin blood flow is restricted in cool environment, the thermal gradient between skin and environment is diminished and therefore conductive and convective heat transfer between body and environment is suppressed. Simultaneously, less heat is distributed through the circulation from central to peripheral parts of the body, which helps to maintain core temperature.

Under normothermic conditions at rest, skin blood flow is relatively low, estimates in the range of 0.25 to 0.5 L/min have been provided (23, 80). While exposed to cold, cutaneous circulation markedly reduces, and during severe cold exposure it is nearly zero (23, 80). On the other hand, as a response to heat stress, vasodilation increases skin blood flow almost up to 8 L/min during maximal tolerable heat stress (80, 81). Thermal insulation can be three to four times greater in maximally vasoconstricted compared to maximally vasodilated tissue (41). Regulation of cutaneous circulation includes whole body reflex and local control mechanisms, which further interact with each other (23, 80). The reflex innervation of skin vasculature occurs via sympathetic noradrenergic and cholinergic nerves, which mediate cutaneous vasoconstriction and active vasodilatation, respectively (23).

While exposed to cold, decreased skin and/or core temperature stimulates the thermoregulatory reflexes to conserve body heat. Sympathetic activity is increased causing arteriolar vasoconstriction, reducing skin blood flow, therefore diminishing heat loss from the body to the environment (23, 80). This cutaneous vasoconstrictor system is based on sympathetic noradrenergic mechanism involving release of norepinephrine, which activates α–receptors (mainly α2), and contribution of cotransmitters neuropeptide Y, and possible adenosine triphosphate (23).

Parts of extremities establish repeated cycles of cutaneous vasoconstriction and vasodilation in response to cold exposure (41, 82, 83). This process called “the hunting reaction” allows maintaining circulation e.g. in the hands while being exposed to cold (82). The major mechanism of this cold induced vasodilation is opening and closing of arterio-venous anastomoses (82). They are short vessel segments providing direct opening between small arteries and small veins, with an inner diameter of the vessel being adjustable from nearly complete closure to large opening (83). Arterio-venous anastomoses are found abundant in the nail beds of the fingers and toes and in the glabrous skin of the hands and feet (83).
Evaporative cooling

Ventilation of air from the respiratory tract causes dry convective heat transfer, but some heat is also lost when inhaled air is moistened in the lungs, i.e. by respiratory evaporation (41). More importantly for thermoregulatory purposes, evaporation occurs when eccrine glands secrete sweat to the skin surface to induce heat loss. The eccrine glands are distributed over the body surface, but more are found on the forehead, neck, trunk, back of the forearm and hand, and fewer on the thighs, soles of the feet, and palms (41). Eccrine glands are controlled by sudomotor impulses originating from preoptic area of hypothalamus, and presenting some activity even in cooler environments, with absence of visible sweating (84). Sweating occurs in physically active individuals even in cold circumstances and with low skin temperatures (57). When the body is exposed to heat, sweating is initiated more or less simultaneously with cutaneous active vasodilation (23, 84). With increased heat exposure, sweating provides the dominant physiological avenue for heat loss (41, 84).

2.4 Modifiers of physiological thermoregulation

Individual differences in physiological human thermoregulation have been linked to body composition (22, 23, 41), physical fitness (85-87), gender (22, 41), age (23, 31, 88-92), adaptation (48, 49), ethnicity (49, 93), and even to personality (94). Chronic diseases, such as those affecting to the autonomic nervous system and/or vascular function (e.g. diabetes and heart failure) (23, 71, 95), may also alter thermoregulation. Some of the most relevant to the current study are discussed below.

2.4.1 Anthropometry, body composition, and physical fitness

Anthropometry and body composition are important factors explaining the variation in thermoregulatory capability between individuals (41, 96). A higher body surface to mass ratio denotes larger area for heat exchange between human body and environment, and therefore increases the heat loss to the environment. The body surface area to mass ratio is larger for smaller body size, which partly explains why children or adolescents cool faster than adults, or women faster than men (22, 41). In addition, within an individual, peripheral parts have high surface
area to mass ratios, which accelerates local cooling compared to the central parts of the body.

Skin, adipose tissue, and vasoconstricted skeletal muscle together provide an insulating layer for the body (22, 41). The skin has an important role in thermoregulation and altering of cutaneous blood flow affects heat loss to the environment (23, 41). The adipose tissue has a high thermal resistance and low perfusion rates at different temperatures, and both at rest and when exercising (22, 41). Therefore, people with more fat mass have higher insulation of the body compared to leaner people. In addition, people with higher amount of adipose tissue have lower skin temperatures, which decreases thermal gradient and heat loss between the environment and body (22, 23). Adipose tissue and skin primarily accounts large part of the tissue insulation of torso (22). In contrast, resting skeletal muscle accounts most of the thermal insulation of limbs (22, 41). Furthermore, leaner people have a higher amount of brown-adipose tissue and higher non-shivering thermogenesis in cold conditions, which increases their cold-resistance (78).

Physical fitness associates to body composition, vascular functions, and heat production capacity, and therefore could affect to thermoregulation. Higher amounts of skeletal muscle increases the insulating layer at rest (22), as well as heat production capacity (87). In addition, improved or maintained vascular regulation, could enhance thermoregulation among fit subjects. Already in 1960, researchers suggested that higher physical fitness elevates heat production and skin temperature while exposed to cold (97). Later, Bittel et al. (85) found a direct relationship between maximal oxygen consumption and metabolic heat production, mean skin temperature, skin conductance, and onset of shivering in the cold. In a study by Ho et al. (86), young fit subjects showed higher cardiac output, skin blood flow, and total flow redirected from splanchnic and renal vascular beds during exercise at 36°C compared to their sedentary counterparts. They also found aging to modify the effects of physical fitness, and only part of the thermoregulatory improvements detected in young fit subjects were detected among older fit subjects (86).

### 2.4.2 Aging

Aging impairs physiological thermoregulation with blunted responsiveness of cutaneous circulation to cold (23, 31, 88, 89, 92, 98) and heat (23, 31, 88, 90). In addition, aging blunts sweating in warm (91), and heat production in a cold environment (92). Vasoconstriction is diminished among older people compared to
young even when subjects are matched for fitness and body size and composition (88). Impaired reflex cutaneous vasoconstriction associates with age-related decrease in skin sympathetic nerve activity (SSNA) response to cooling, probably originating from alterations in afferent signaling or central processing of thermoregulation (89). Also, neuropeptide Y, a co-transmitter released from sympathetic adrenergic nerves that contributes to cutaneous vasoconstriction in younger, does not mediate vasoconstriction in the elderly, (23, 96) Instead, vasoconstriction is more dependent on Rho kinase mediated pathways in older people (98). In addition, end organ responsiveness may be blunted by reduced noradrenaline bioavailability (23, 31, 89). During heating, the age-related impairments in both reflex vasodilation and local circulatory mechanisms blunt the vasodilation response (23, 90). The reduced evaporative response to heat among older people has been detected even when matched for anthropometric parameters and aerobic fitness (91). Aging also seems to decrease heat production in a cold environment, which partly relates to age-related changes in concurrent factors, such as body composition (e.g. decreased amount of skeletal muscle mass with ageing) and fitness level (88). Consistently, studies have found aging to associate with impaired ability to maintain stable core temperature during cold exposure (88). In addition to impairments related to healthy aging, elderly more often have chronic diseases and medications, which may further impair their capability to maintain thermal homeostasis.

2.4.3 Chronic diseases

Thermoregulation is altered in some clinical conditions (23, 31, 71, 95, 99). For example, type 2 diabetics show elevated threshold and attenuated response of vasodilatation (23, 71) as well as blunted sweating responses (71) while exposed to heat. Fewer studies have applied cold exposure (95), and some of those (71), but not all (100), suggest that also vasoconstrictive responses are blunted among diabetics. In addition, patients with heart failure have attenuated vasodilatation responses to heating, although their sweating response seems to be preserved (23). The detected changes among both diabetics and patients with heart failure restrict thermoregulatory responses, as also occurs with aging. This limits heat loss mechanisms in hot and/or heat preserving and heat productive mechanisms in a cold environment, and impairs an individuals' ability to maintain thermal balance.

Disease related changes in the vascular structure or regulation could modify thermal responses in populations having hypertension. Earlier studies assessing
exercise in warm environment found blunted forearm skin blood flow increases among unmedicated mild hypertensives (101, 102), without difference in core or mean skin temperatures, calculated heat exchange variables, or sweat rates (103). Some (104, 105), but not all (106), studies applying passive whole body heating have also found attenuated cutaneous vascular conductance increases among non-medicated hypertensives, likely related to blunted active vasodilator mechanisms (23, 95, 104). In addition, increase in cutaneous vascular conductance is blunted during local heating in essential hypertensives (23, 107).

Recently, Greaney et al. (99) found that whole-body cooling with water-perfused suit elicited greater cutaneous vasoconstriction among non-medicated hypertensive compared to normotensive subjects. This was likely attributable to enhanced increases in skin sympathetic nervous system activity and to a greater dependency on non-adrenergic sympathetic cotransmitters in mediating vasoconstrictor response to cooling in hypertensives. The augmented cutaneous vasoconstriction did not alter skin temperature, which decreased at a similar rate in both test groups. Another study found cutaneous vasoconstriction to be increasingly dependent upon Rho/Rho-kinase mediated mechanisms among hypertensives (108), an alteration that occurs also in healthy aging (98).

2.5 Essential hypertension

Essential (also called primary or idiopathic) hypertension is, by definition, a form of hypertension that has no clearly specified etiology (109-111). It accounts for more than 90% (109) of hypertensive cases. From a clinical perspective, it can be specified as a rise in BP of unknown cause that increases the risk of cerebral, cardiac, and renal events (110). The cut-off values for hypertension are ≥140 mmHg SBP and/or ≥90 mmHg DBP for office BP in Europe (112). For home or ambulatory BP recordings the cut-off values are slightly lower, ≥135 mmHg SBP and/or ≥85 mmHg DBP for the time being awake (112). However, the risk of adverse health events begins to increase already for BP values ≥ 115/75 mmHg (113), or even when systolic BP exceeds 110 mmHg (114). The detailed European classification for office BP values is presented in Table 1 (112). The Finnish national guidelines apply the same values (115).
Table 1. Classification of office blood pressure levels according to the recommendations of European Society of Hypertension (112).

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic Condition</th>
<th>Diastolic Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120 and &lt;80</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>120-129 and/or 80-84</td>
<td>80-84</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139 and/or 85-89</td>
<td>85-89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140-159 and/or 90-99</td>
<td>90-99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160-179 and/or 100-109</td>
<td></td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180 and/or ≥110</td>
<td></td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140 and &lt;90</td>
<td></td>
</tr>
</tbody>
</table>

2.5.1 Prevalence of hypertension and burden of disease

The Global Burden of Disease Study ranked high BP the largest contributor to global disability-adjusted life-years in 2015 (7). The study ranked cardiovascular diseases as the leading cause of death, and of which the ischemic heart disease and stroke together accounted 85% (6). In Finland, cardiovascular diseases accounted for 37% of the deaths and ischemic heart disease was the leading cause of death in 2015 (116). Worldwide, 55% of both ischemic heart and cerebrovascular disease deaths are attributable to systolic BP ≥110 mmHg (114).

The global age-standardized prevalence of hypertension in adults was estimated to be 24% among men and 20% among women in 2015 in a study pooling data from 1479 studies published from 1975 to 2015 (8). According to the same study, the age-standardized prevalence of hypertension in Finland was near the global mean value for men, and somewhat lower for women (8). On the other hand, at the same time the crude prevalence of hypertension among Finns above 30 years was 53% in men and 46% in women (117). In the past 40 years, the age-standardized prevalence of hypertension has decreased in high-income countries, such as Finland (117), and some middle-income countries, but remained the same elsewhere (8). However, at the same time the number of adults with hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) has doubled from 0.59 to 1.13 billion (8), due to population growth and aging. In addition, 3.5 billion adults are estimated to have systolic BP at least 110 or 115 mmHg in 2015, on a level, which already associates with a higher risk of multiple cardiovascular outcomes (114). Further increase in BP and cardiovascular disease related burden of disease are projected in the coming decades due to the global population growth and aging (10, 11).
In addition to being highly prevalent, hypertension remains often undetected. Also, a variable proportion of the patients with diagnosed hypertension receive treatment, and those of treated, many do not reach the target BP. A large multinational study, applying a cross-sectional sample collected between 2003 and 2009, found that less than half of adults with hypertension were aware of their condition (9). The majority of those aware received pharmacological treatment, nearly 90%, but only 33% of the treated patients achieved target BP of 140/90 mmHg. In 2007 in Finland, 68% of individuals with hypertension were aware of their condition, but only 52% of those aware were treated with antihypertensive drugs (118). The proportion of the drug-treated patients who achieved BP target of 140/90 mmHg was comparable to the global estimates, 37%. It was also found that according to cardiovascular disease risk stratification modified from 2007 ESH-ESC hypertension guidelines, 79% of the non-treated were in an immediate need for the initiation of antihypertensive drug treatment (118). Together these findings show that the proportion of hypertensive people not aware of their disease and those aware, but not treated is remarkable.

2.5.2 Pathophysiology of hypertension

Etiology

As mentioned, essential hypertension is, by definition, a form of hypertension that has no clearly specified etiology. However, many risk factors for the disease have been recognized. In societies of hunter-gatherers or forager-horticulturalists, hypertension is rare and age-related BP increase minimal (119-121). Parallel with the changes towards modern “western” lifestyle, the prevalence of hypertension has substantially increased. For example, obesity, sedentary lifestyle, high alcohol or salt intake, and stress increase the risk of hypertension (109-112). There are also unmodifiable risk factors of hypertension, such as aging and family history of hypertension (110, 112). In addition, there are multiple environmental risk factors for hypertension. For example, ambient air pollutants (122), cold temperature (18), and residence in high altitudes (123) increase BP, and long-term exposures to these could promote development of chronic hypertension (124).

There is tremendous amount of literature on research assessing pathophysiological mechanisms that would cause essential hypertension. Some researchers suggest that essential hypertension begins with a hyperkinetic state
involving heightened sympathetic activity and blunted parasympathetic activity, before changes in vascular structure are introduced. Indeed, elevated HR, cardiac output, plasma norepinephrine and epinephrine levels, muscle sympathetic nerve activity (MSNA), and ratio of sympathetic to parasympathetic HR variability have been detected already in early phases of hypertension (125-128). Sympathetic overactivity is also present in the later phases of hypertension (111, 127) and has been suggested to have a key role in the progression of the hypertensive state (127). Other studies suggest that chronic inflammatory processes and oxidative stress have important roles in the development of hypertension (129, 130). Oxidative stress is increased in patients with cardiovascular disease, such as hypertension. It is involved in inflammation, endothelial dysfunction (decreased nitric oxide bioavailability), fibrosis, and other factors that contribute to cardiovascular and renal remodeling in hypertension (129). It is also likely that impaired renal mechanisms play a major role in the pathogenesis and maintaining an elevated BP in hypertension (109, 131). Oparil et al. (109) and Johnson et al. (131) suggested that hypertension is initiated by agents causing systemic and intrarenal vasoconstriction. Over time intrarenal injury develops, leading to a balance favoring sodium retention, and increased BP. Eventually, there is a persistent rightward shift in the pressure-natriuresis curve, and therefore persistent hypertension. Interestingly, autonomic imbalance, oxidative stress, and renal dysfunction interact with each other (111, 127), but the causal pathways between these are ambiguous. To conclude, diverse individual, environmental, and demographic risk factors as well as multiple pathophysiological changes associating with hypertension have been recognized, but the exact mechanisms causing the essential hypertension remain to be established.

Vascular remodeling in hypertension

Vascular changes in hypertension are characterized by endothelial dysfunction and remodeling of the large and small arteries, which lead into reduced dilation capability and increased stiffness in resistance vessels (111, 132). The vascular endothelium is an active layer of cells located on the innermost side of vessels, which responds to mechanical forces (pressure) and receptor-mediated signaling (133). It releases vasoactive factors, most importantly vasodilative NO, to influence vascular smooth muscle function (133). In hypertension, the bioavailability of nitric oxide is reduced, and the capacity of arteries and arterioles to dilate attenuated (111, 134). In addition, hypertensive endothelial dysfunction involves endothelial
inflammatory activation, characterized by enhanced release of endothelial-derived constricting, proinflammatory, prothrombotic, and growth factors (111, 134). One of the principal mechanisms in endothelial dysfunction is the production of reactive oxygen species (ROS), which reduce bioavailability of nitric oxide and activate the signaling molecules of cell growth, fibrosis, and inflammation (111).

Over a time, multiple factors, e.g. endothelial cell dysfunction, neurohormonal activation, and elevated BP, cause remodeling of blood vessels (111). Vascular remodeling involves collagen deposition, smooth-muscle cell hypertrophy, and also thinning, fragmenting and fracture of elastin fibers in the media (109). Structural elasticity of arterial walls is diminished and media-lumen ratio increased, resulting in increased vascular resistance to pulsatile blood flow, and therefore, a further increase in BP. Small artery remodeling is initiated by vasoconstriction, of which a rearrangement of normal smooth muscle cells around a smaller lumen follows, without change in the amount of vessel wall material (111). Remodeling of larger arteries, instead, is typically characterized by the expression of hypertrophic genes that induce growth in medial thickness (111). This involves both growth of vascular smooth muscle cells and accumulation of extracellular matrix proteins, such as collagen (111). In addition, inflammatory changes of the arteries can lead to transformation to fibrolipid plaques, and eventually, into fibroatheroma in the vessel wall, which has a core of lipids covered on the luminal side by a fibrous cap (135). These atherosclerotic changes in the vessel wall reduce arterial elasticity and lumen diameter, cause turbulent blood flow, and involve a risk of plaque rupture (111). Overall, the different changes in arterial structure in hypertension can lead to stenosis, aneurysm or dissection of aorta, to cerebrovascular impairments that pose higher risk of ischemic and hemorrhagic stroke, cognitive impairment and dementia, and also to atherosclerotic peripheral or coronary artery disease (111).

Cardiac remodeling in hypertension

Besides vascular changes, hypertension associates with cardiac remodeling (111, 136). In particular, left ventricular remodeling is frequent in hypertensives (111, 136). Increased pressure load of the heart is considered the major determinant of cardiac remodeling among hypertensives (111, 136, 137), although in some individuals increased blood volume may have greater attribution (136). When increased BP augments pressure load to the heart, the responses to this aim to normalize myocardial wall stress. The main mechanism involves hypertrophic
growth of cardiomyocytes (136). In addition, it has been suggested that hypertrophic growth is combined with hyperplasia, i.e. an increase in the amount of cells: cardiomyocytes and other cells (136). Importantly, in addition to cardiomyocyte hypertrophy or hyperplasia, cardiac remodeling involves several other alterations of the cardiomyocyte and the non-cardiomyocyte components, such as apoptosis, fibrosis and changes in the coronary circulation (136).

Cardiac remodeling and hypertrophy impair cardiac function. For example, the active relaxation time of the heart diminishes, which reduces blood flow to coronary arteries and increases the risk of myocardial ischemia (137). Changes in cardiac structure also cause heterogeneous cardiac conduction and increase the occurrence of electrical abnormalities, such as ventricular (137, 138) or atrial (111, 138, 139) arrhythmias, or altered cardiac repolarization patterns (137). Excessive left ventricular mass and other cardiac remodeling can translate to left ventricular dysfunction (reduced ejection fraction or filling abnormality), and eventually to heart failure (111).

2.6 Cardiovascular morbidity and mortality in cold weather

2.6.1 Excess mortality and morbidity in winter

Excess mortality and morbidity in winter is a well-established phenomenon. Most of it is attributed to respiratory and cardiovascular diseases and the effect is increased by advancing age. Researchers have found the wintertime peaks of mortality in the southern and northern hemisphere, and in both in temperate and cold climates (140). These seasonal differences are lowest near the equator (140) and highest in the countries located at a mid-distance from the equator, such as in the Mediterranean area (12, 140). For example, in 14 European countries between 1988 and 1997 excess winter mortality was lowest (10%) in Finland, having the coldest mean winter temperature, and highest in Portugal (28%), having the warmest mean winter temperature (141), and the same “latitude phenomenon” was confirmed in a more recent study assessing seasonal variation in mortality worldwide (140). This study by Marti-Soler et al. (140) combined data between 2000 and 2010 from 19 countries locating in Europe, Northern and Southern America, Africa, Asia, and Australia, amounting to over 54 million deaths. It found seasonal variation of all-cause mortality and mortality for cardiovascular disease with a peak in winter in all countries except in two that located close to Equator.
The seasonal variation (peak-nadir) in the ratio of observed to expected deaths was between 0.130 and 0.334, and for deaths caused by cardiovascular diseases, it was between 0.185 and 0.466.

Various cardiovascular events peak in wintertime, and often more so with advancing age (19). For example, mortality from acute myocardial infarctions was found to be higher in winter months at least 80 years ago (19), and new evidence supporting this is still published (142, 143). Sheth et al. (144) reported excess (winter vs. summer) acute myocardial infarction deaths of approx. 6% for people <65, 8% 65 to 74, 13.4% for 75 to 84 and 15.8% for >85 years. In addition, heart failure (19, 145, 146), deep venous and pulmonary thromboembolism (19, 147, 148), atrial fibrillation (149), and sudden cardiac deaths (150, 151) show excess winter incidence. Incidence of stroke (142, 144, 152, 153) and ruptures or dissection of aortic aneurysms (154) often peaks in winter, although some studies detected highest incidence during other seasons (19, 155). For ventricular arrhythmias, both winter (156-158) and summer (159) peak incidences have been suggested.

### 2.6.2 Seasonality in cardiovascular risk factors

Multiple cardiovascular risk factors show seasonal variation in parallel with changes in cardiovascular mortality and morbidity. For example, wintertime associates with higher levels of coagulation biomarkers. Fibrinogen peaks at winter (160-164), also among hypertensives (165), and with augmented variation among elderly (164). Similarly, platelet levels (162, 163, 166, 167), and plasma or whole blood viscosity (163) peak during winter. However, not all studies have found consistent results (168), or the variation has been modest for some variables (160, 167). A recent large study showed higher wintertime concentrations of total, LDL, and HDL cholesterol, with concurrent increases in BMI, waist circumference, and blood glucose (17). In addition, seasonal variation in autonomic nervous function may result in unfavorable changes in winter and increase the risk of adverse health effects. HR variability has been found to be lower (169), and HR level higher (160, 170-172) or comparable (169, 173), and MSNA higher (173) during the cold compared with warm season.

One of the most well recognized seasonal variation is that BP is elevated in winter and reduced in summer. A recent study combining data of 24 population-based studies from 15 countries detected this seasonality of BP in both the Northern and Southern hemisphere, and in countries with varying climates (17). The
difference between peak and nadir was approx. 3 mmHg and 1 mmHg for systolic and diastolic BP, correspondingly. In addition to office BP (e.g. (174-176), studies report winter time peaking in ambulatory (177, 178) and home BP (178-180). Stergiou et al. (178) measured BP in clinic, at home, and with 24h ambulatory ABP from the same hypertensive subjects, and found all BP parameters except night time ambulatory BP to be higher in winter than summer. As BP increases in winter, its control is impaired (181), hypertension becomes more prevalent (182), and hypertensive emergency hospitalizations more frequent (183, 184).

The increase in cardiovascular mortality, events, and risk factors in wintertime is probably caused by a complex combination of seasonal variation of direct and indirect effects of environmental exposures and seasonality of life habits (19-21). For example, dietary habits may be less healthy and physical activity may be lower in wintertime (19, 185). Cardiac deaths increase during Christmas time celebrations (186). Respiratory infections peak in winter (187, 188) and may trigger cardio- or cerebrovascular events (189, 190). Reduced daylight and vitamin D levels or higher particulate matter concentrations during winter may also play a role as cardiovascular risk factors (19). In conclusion, multiple cardiovascular risk factors exhibit seasonal variation, and provide potential explanations for the higher wintertime cardiovascular morbidity and mortality. The reasons behind this are likely multifactorial, although direct and indirect effects of cold temperature should not be underestimated (191).

2.6.3 Mortality, occurrence of cardiovascular events, and ambient temperature

The risk of mortality increases slowly and quite linearly for cold temperature, and by contrast, for high temperature the mortality increase is steeper and non-linear (2). The association between temperature and cardiovascular mortality can also be described as being U- V- or reversely J-shaped (28). The health effects of high temperature are immediate and occur within a few days, whereas the cold-related health events are delayed with couple days (192) and have a longer lag lasting up to 3 or 4 weeks (2). As for seasonal differences, the most of the temperature related excess mortality is attributed to respiratory and cardiovascular diseases (2, 15). The optimal temperature, i.e. the temperature demonstrating minimal mortality, is higher in warmer climate and lower in a colder climate. It has been estimated to be around 75th percentile of temperature (192). For example, minimal mortality is approx. at 14°C in Finland (193), at 19°C in Toronto, Canada, at 22°C in Rome,
Italy, and at 30°C in Bangkok, Thailand (2). A recent observational multi-country study combining data from 384 locations worldwide involving 74 million deaths found that nearly 8% of mortality was attributable to non-optimum temperature (2). Most temperature attributable deaths were caused by cold (7.29% vs. heat 0.42%), and by moderate non-optimal temperatures, which are far more common than extreme cold or hot periods.

A landmark study combining data from northern, middle, and southern Europe collected between 1988 and 1992, estimated an increase in mortality for each 1°C fall in temperature to vary between 0.27% in southern Finland to 2.15% in Athens, while e.g. in London it was 1.37% (12). A later study consisting of European data from 15 countries between 1990 and 2000 applied apparent temperature and showed comparable results (14). Another study (13) including 2.5 million deaths in 7 locations in US between 2004 and 2009 explored the seasonal mortality pattern and its association with climatic factors (temperature, dew point, precipitation, barometric pressure), influenza levels, air pollution levels, hours of daylight, and day of week. They found temperature to demonstrate consistently the strongest association with mortality. After adjusting for multiple covariates and potential confounders, there was a 0.49%, 0.56%, 0.32%, and 0.70% increase in all-cause, circulatory, coronary heart disease, and ST-elevation myocardial infarction death rate for every 1°C decrease in temperature.

Fewer studies have assessed temperature related burden of the disease with (quality- or disability adjusted) years of life lost due to disease. Yang et al. (194) found cumulative lagged cold effects to associate with an increase of around 4% and 5% in years of life lost for non-accidental and cardiovascular deaths in a Chinese study sample. An Australian study found a U-shaped association between temperature and years of life lost for cardiovascular deaths (195).

Temperature variability has additional effect to human health. Both inter and intra daily temperature variability seem to associate with higher mortality, independently of mean temperatures (196, 197). Also cold spells, i.e. unusually cold weather events, increase mortality for non-accidental causes and cardiovascular diseases with around 10% worldwide (198). Cold waves earlier in the cool season seem to be more dangerous, which may reflect lack of preparedness for those circumstances (behavioral adaptation) (28).

A recent study (15) reanalyzed meta-analyses to summarize the available evidence related to the association between ambient temperature on morbidity and found 1°C decrease in temperature to associate with an increase of about 1% in cardiovascular morbidity. Another review (16) described the following increases of
risk with 1°C decrease from the average or threshold temperature: 2% for ischemic stroke and 1.6–6% for acute coronary syndrome, and for each 1–5°C decrease 0.6-12% higher risk of myocardial infarction. The risk of emergency admissions due the cerebrovascular and hypertensive diseases increased by 56–78% with a temperature decrease of 12°C, and for cardiac arrest in elderly by 11–16% with a decrease of 5°C from threshold temperature (16). In addition to mortality and morbidity, few studies have reported cold-related cardiorespiratory symptoms, such as dyspnea, chest pain, and arrhythmias, to occur both in healthy and manifold among those with chronic diseases (199-201).

Adverse health effects of cold temperature intensify with advancing age (14, 15, 28). However, not all studies have confirmed this (28), and the association may differ for certain outcomes, such as sudden cardiac death (202). Elderly people have more predisposing conditions and impaired thermoregulation (88), which likely explains their vulnerability. Large studies in Europe (12, 14), US (203), and China (204) have found the association between cold temperature and mortality or morbidity to be stronger in warmer countries and weaker in countries with colder climate, although recent global meta-analyses have given inconsistent results (16, 205). This effect variation in different latitudes has been associated with behavioral coping with thermal exposures, such as better heating or insulation in houses (12, 203, 204), or more commonly wearing cold protective clothes (12). Some studies have found higher cold-related mortality among illiterate, individuals with lower education level, or population residing in rural areas (28). In addition, out-of-hospital mortality may involve a higher cold-associated risk than in-hospital mortality (28, 204, 206), which has been suggested to associate with higher exposure to cold. Interestingly, a recent study (202) found usage of aspirin, beta-blockers and/or nitrates to decrease the risk of ischemic sudden cardiac death during cold spells, opening new lines of research in mitigating the adverse temperature related health effects.

Some studies have suggested stronger associations between cold temperature and adverse health outcomes in people with chronic diseases (28). For example, the effect of cold on emergency room visits was stronger in individuals with a comorbid cardiac disease, and risk of cold-related cardiovascular deaths higher among those with hyperglycemia (28). Qiu et al. (207) compared mortality during extreme cold periods to milder conditions and found hypertensive diseases as cause of death to exhibit greatest vulnerability to extreme cold exposure. Wang et al. (208) found decline in temperature to increase risk of hemorrhagic stroke in hypertensives but not in those without hypertension. Cold-related cardiovascular
symptoms are particularly high in people with coronary heart disease or cardiac insufficiency (199), and cold-related cardiorespiratory symptoms are more common among those having diabetes (201) or hypertension in combination with another cardiovascular disease (200). On the other hand, effect modification by hypertension was not detected for cold-related mortality and hospital admission for heart failure (209), or all-cause mortality (210). Nevertheless, as the risk of cardiovascular events and deaths is generally remarkably higher among hypertensives and people with other cardiovascular diseases than the healthy ones, they are also important populations when examining the association between low temperature and cardiovascular outcomes.

2.6.4 Cardiovascular biomarkers and cold temperature

Studies have found cold temperature to associate with higher levels of fibrinogen in general populations (211-213), coronary heart disease patients (214) and type 2 diabetics (215, 216). In addition, increases in other coagulation factors (212, 215), such as platelet count (211, 214), alpha-2 macroglobulin that inhibits fibrinolysis (211), and coagulation factor VII (212) associated with a decline in temperature. Contradictory results for cholesterol have been reported, with either increases (213) or decreases (211) in HDL, possible increases in triglycerides (213) and total cholesterol (212), and no change in LDL (213), with declining temperature. Yeh et al. (212) and Wu et al. (217) studied the association between temperature and multiple coagulation factors (212) or a sum index for coagulation formed from individual biomarkers (217) and found accelerated coagulation with declining temperature.

Studies reporting association between ambient temperature and inflammatory markers have given less consistent results. C-reactive proteins have been reported to increase (215, 218), decrease (214, 216, 219), or show no change (213, 214) with decreasing temperature. Interleukins increased with declining temperature in selected patient samples (215, 216) or in the general population of elderly men (218). Halonen et al. (218) found cumulative exposure to decreased temperature to associate with elevated plasma concentrations of soluble Intercellular Adhesion Molecule-1 and Vascular Cell Adhesion Molecule-1 but unaltered white blood cell count in elderly men. Wu et al. (217) applied indices combining information from multiple individual biomarkers and found a 10°C decrease in 2-day average daily temperature to associate with increased systemic inflammation, systemic oxidative stress, and antioxidant activity in a small study sample.
There is some evidence of elevated sympathetic autonomic function with low outdoor temperature. Kruse et al. (220) found outdoor temperature to positively correlate with endothelin-1 and angiotensin II levels but negatively correlate with plasma epinephrine and norepinephrine among 10 healthy subjects assessed at monthly intervals during 13 consecutive months. Several studies report no association between HR and outdoor temperature (221-223), although a large Chinese study detected V-shaped association between those (224). Number of studies have consistently found an inverse association between ambient temperature and BP (chapter 2.6.5), providing likely the strongest evidence supporting sympathetic activation in a cold environment.

### 2.6.5 Blood pressure and temperature

BP has an inverse association with ambient temperature (18, 225). A recent meta-analysis (18), including data from Europe, North America, and Asia, found 1°C decrease in mean daily outdoor and indoor temperature to associate with 0.26 mmHg (95% CI: 0.18–0.33) and 0.38 mmHg (95% CI: 0.18–0.58) increase in systolic BP. Diastolic BP increased 0.13 mmHg (95% CI: 0.11–0.16) per 1°C decrease in mean daily outdoor temperature. Association was weaker between BP and maximum or minimum than for mean temperature. Cross-sectional and longitudinal (with repeated BP measurement) studies gave comparable results.

Studies examining the association between temperature and BP have applied different temperature estimates, such as apparent temperature, dew point, or ambient temperature, and different induction times, from immediate effect to few weeks lag. Halonen et al. (226) found the strongest association between BP and apparent temperature (considering both air temperature and water vapor content), however quite comparable to the results obtained when only ambient (air) temperature was considered. The closer the measured temperature is to the temperature that the individual is exposed, the stronger is the association with BP (227). For example, ambulatory BP had stronger association with in- than outdoor temperature, except when being outdoors (227, 228). In addition, temperature recorded in bed related more to BP than room temperature in nighttime (227, 228). Few studies have applied personal temperature monitors, providing further evidence on the association between temperature and BP (229-231). Immediate, lagged (0-7 days), and cumulative temperature effects on BP have been reported (18, 226, 230), some studies suggesting strongest association with cumulative...
temperature exposure from previous days (226) and others diminished association with increasing time lag (230).

The majority of studies assessing temperature dependency of BP have applied office or clinic BP measurements (18, 225). In addition, studies report an inverse association between home or ambulatory daytime BP and outdoor temperature (223, 232) and ambulatory daytime BP and personal-level temperature (229). Conversely, higher nighttime ambulatory BP associated with increased ambient temperature among treated elderly (223) and in another study population with a wider age range (233). The opposite relation between night and daytime BP with temperature resulted to higher morning BP surge on coldest compared to warmest day (233). The direct association between nighttime BP and temperature may relate to the down titration of antihypertensive medication with warm weather (223) or increased daylight hours instead of temperature (229). In addition to BP level, some (234, 235), but not all (233), studies report increasing 24 hours ambulatory BP variability with decreasing temperature.

In addition to brachial BP, few epidemiological studies evaluated the association between environmental temperature and central hemodynamics. Adamopoulos et al. (236) evaluated the association between several environmental variables (air pollution, temperature, relative humidity, atmospheric pressure) and central hemodynamics and found 24-h mean temperature to independently associate with increased and brachial systolic BP and aortic pulse pressure, and decreased subendocardial viability ratio. They did not find any association between temperature and carotid-femoral pulse wave velocity, an index of arterial stiffness, consistent with a more recent study by Di Pilla et al. (237).

The inverse association between temperature and BP is stronger among the aging population (18, 172, 174, 224). Contradictory results of the effect modification by BMI or gender have been reported. Stronger association between temperature and BP have been found in both lean (224) and obese (226, 238) people, and in men (239) or women (225, 238), whereas other studies report no association (174). Some studies suggest stronger association between temperature and BP in those with lower socioeconomic status (238), which could associate to poorer housing conditions (240). Increase in BP has been found to be higher (241), lower (239), or comparable (224) in people with hypertension compared to normotensive. On the other hand, the usage of antihypertensive drugs have been found to reduce (238, 242) or have no effect (174, 222, 226) to the temperature related BP changes. Hypertension and antihypertensive medication may associate with temperature in
opposite ways, and should therefore both be considered when evaluating their effects.

The inverse association between BP and temperature in epidemiological studies likely reflects physiological thermoregulation: vasoconstriction and increased peripheral resistance in cold conditions and vasodilatation and reduced peripheral resistance in warm environment. When repeatedly exposed, there might be additional regulatory mechanisms involved, as BP remains at a higher level during cold season even when assessed indoors with a stable ambient temperature.

2.7 Cardiovascular responses to experimental cold exposures among healthy and in hypertension

In addition to the long-term exposure, a short-term cold exposure alters circulatory functions. Exposure to cold temperature activates the autonomic nervous and renin angiotensin system (RAS), increases BP, induces hemoconcentration, and accelerates blood coagulation. The changes result from physiological thermoregulation, reducing heat loss to the environment by sympathetic activation and peripheral vasoconstriction. However, it simultaneously possess additional strain to the cardio- and cerebrovascular system.

2.7.1 Systems regulating cardiovascular responses

Thermoreceptors sensing cold stimulate the autonomic nervous system, resulting in augmented sympathetic activation (22, 23, 28). Consistent with this, increases in norepinephrine, HR variability, MSNA, and SSNA occur in a cold environment.

Norepinephrine mediates the cold protective cutaneous vasoconstriction, and therefore increases in plasma norepinephrine with cooling can be expected (22, 23, 28). For example, increased plasma norepinephrine was detected with 0.5-3h cold air exposure (30), 1h cold water immersion (30), skin surface cooling (243) or by invasive core cooling (243). With 2h exposure to 10°C air among lightly clothed subjects (33) or 10 min skin surface cooling by water (16°C) perfusion suit (243) plasma norepinephrine concentrations doubled, and after core cooling by intravenous cold fluid four fold concentrations were reported (244).

Increased activity of autonomic nervous system in cold conditions can be detected as elevated HR variability, reported with whole-body (33), facial (245), and skin surface cooling without cooling of the head (246). Skin cooling can increase HR and low frequency/high frequency (LF/HF) ratio of HR variability (29,
48

247), reflecting a change towards sympathetic cardiac regulation. However, if cold exposure involves facial cooling, either as a cold face test (26, 248, 249) or as part of a whole body cold exposure (33, 247), stimulation of trigeminal nerve simultaneously increases vagal activity, and a decrease in HR and LF/HF ratio may occur.

Augmented MSNA has been detected with facial (32, 248) or whole body cold exposure (250), and already during cold air inhalation (32). Contradictory, skin cooling without cooling of the head may not alter MSNA (31). More consistently, SSNA enhances with different types of cold exposures, as increased efferent SSNA elicits peripheral cutaneous vasoconstriction (31).

Cold also activates the renin-angiotensin system (RAS), which can be observed as elevated angiotensin-II (28, 251) or aldosterone (252) levels in plasma, although not all studies have confirmed this (253). In animal studies, blockade of RAS prevents or attenuates cold-induced chronic hypertension (254). Zhang et al. (251) suggested that augmented RAS activity in humans is secondary to the elevated SNS activation in a cold environment. It is likely that SNS and RAS interact with each other and jointly contribute to the elevated BP while exposed to cold (251, 254).

Activation of autonomic nervous system and RAS leads to multiple changes affecting circulatory system, such as elevated brachial and central BP, increase in cardiac workload, hemoconcentration, and accelerated blood coagulation.

2.7.2 Hematological changes and immune system

Hematological changes occurring while exposed to cold temperature involve multiple signs of hemoconcentration and accelerated blood coagulation. For example, cold-related increases in platelets (34), red cells (34, 40), fibrinogen (37), erythrocyte count (37, 39), hematocrit (39), cholesterol (34, 37), and viscosity (34) have been reported, although not with full consistency between the studies. In addition, some studies found cold-related increase in thromboxane B2 and beta-thromboglobulin, reflecting platelet activation and aggregation (38). A shift in blood platelet subpopulations to those favoring aggregation has also been detected (38).

Acute cold exposure may also stimulate the immune system, as the observed increase in leukocyte counts suggests (39, 255, 256), but research on this topic has given equivocal results (257). In addition, cortisol is secreted in response to stress and therefore augmented serum cortisol levels could be expected during cold
exposure. However, the results from studies are contradictory, studies reporting increased, decreased or unchanged levels (253, 257).

### 2.7.3 Blood pressure and central hemodynamics

**Brachial blood pressure**

Short-term exposure to cold environment induces sympathetic activation and peripheral vasoconstriction to maintain the core temperature, but simultaneously causing a fast and substantial increase in BP. Acute cold-related BP elevation has been studied with whole-body (34, 35, 92, 252, 258), facial (26, 245, 259) and local cooling (35, 260), as well as with whole-body cooling without cooling of the head (36, 261, 262) (Appendix 1 Table 12). BP increase has been induced with water-perfused skin suit (36, 261, 262), or by applying an ice-bag on the skin (26, 245, 259), with cold air chamber exposure (34, 35, 92, 258), cool water (247, 263), local ice water immersion (35), or even with cryotherapy (264) and cold air inhalation (265). Study populations have involved healthy adolescents (260), young (35, 92), middle-aged (266) and elderly adults (92, 267). Experimental research among patient populations is sparse, but cold-related BP increases have been studied at least among hypertensives (99, 268, 269) and cardiac patients (29).

Exposure to cold environment increases systolic, diastolic, mean, and pulse BP. BP begins to rise almost immediately after the beginning of the exposure (26, 266, 270, 271). During cold chamber exposures, the increasing trend of BP continues for the first 5-10 minutes, after which BP stabilizes to the increased level (266, 272) and some studies applying water perfusion suit to cooling of skin reported comparable profile of BP increase (261, 271). With cold face test, peak value has been reported to occur already after 40s from the beginning of the exposure (26), although other studies reported continuous increase in BP during 60s cold stimulus (270) or longer duration (32).

Comparable average increases of 5-30 mmHg in systolic and 5-20 mmHg in diastolic BP have been reported with quite a variety of cold exposures (Appendix 1, Table 12). However, BP increase has dependency related to exposure intensity, exposure area, and its duration. An increase of BP with 10-15 mmHg (systolic) and 10 mmHg (diastolic) occurred already with an exposure of lightly clothed young and older subjects to 17°C for 1h (272). Among older subjects, the systolic BP increase was stronger (15 vs. 20 mmHg) when exposed to 12°C for 1h (272). A
study by Gavhed et al. (258) found few mmHg higher systolic BP increase with wind of 5 m/s compared to 0 or 1 m/s in winter clothed subjects exposed to -10°C for 30 min. Already exposure to 24°C increased BP by 12 mmHg (systolic) and 18 mmHg (diastolic) when combined with wind of 10 m/s in lightly clothed subjects (34). In addition, a cryotherapy study applying a very short and intense exposure reported higher systolic BP responses to -110°C than -60°C or -10°C (approx. 24 vs. 15 mmHg) (264). Wearing a hat reduced systolic BP response with a few mmHg to 15 min cold (-5°C) air exposure by in winter-clothed subjects and accelerated the recovery during rewarming (266). Another reduction in systolic BP with a few mmHg was reported by wearing a heat and moisture exchange mask (vs. no mask) in a study assessing winter clothed hypertensive subjects during 1h cold (-5°C) air exposure (269).

With exposure corresponding to subarctic winter conditions (-15°C, wind of 3.5 m/s, winter-clothed subjects, 15 min) increases of 20-25 mmHg (systolic) and 10-15 mmHg (diastolic) have been reported (268, 273). Studies applying cold face test report comparable, 10-20% increases in BP (26, 245, 259, 270, 274). In addition, cooling with water-perfused suit has been reported to increase BP with 5-25 mmHg (systolic) and 5-10 mmHg (diastolic) (36, 261, 262, 275).

There are fewer reports from the recovery of BP after cessation of cold exposure, but it seems to depend on type and duration of the exposure. BP returned to baseline level fast, within 10 minutes after cryotherapy, which applied very intense but short exposure (276). Instead, after mild but longer exposure, 1h to 20°C in lightly clothed subjects, BP remained augmented compared to baseline levels even after 1h rewarming period (267). BP recovery after cold exposure likely depends on heat debt and BP recovers to normal levels after heat balance is achieved.

In summary, thermal effects of BP can be expected beyond the thermoneutral state. The more intense (temperature, air or water, wind, clothing) or the longer the exposure is, the stronger the BP responses and the longer the BP recovery time are. However, BP responses to cold can reflect, in addition to heat loss reductive mechanisms, sympathetic activation from other reasons (e.g. pain), and the activation of heat production to reduce the need for heat preservation.

Central aortic hemodynamics

Only a few studies performed with healthy subjects have assessed effects of cold to central aortic BP (Table 2). Those have found cold exposure to increase non-
invasively assessed central aortic BP with either comparable (261) or higher (277-279) responses than peripheral BP. One study applying an invasive measurement also found an increase in the BP in ascending aorta among young healthy subjects (280). The previous studies assessing central BP have applied either facial (261, 278), superficial skin cooling (261), or whole-body cold exposure (277, 279, 280). Contradictory to the other studies, King et al. (27) did not detect increased brachial or central BP during a mild whole-body cold exposure.

The studies assessing central hemodynamics have also reported a substantial increase in augmentation index, an index of arterial stiffness and wave reflection (Table 2), and shorter time to the wave reflection. In addition, pulse wave velocity, another index of arterial stiffness, has been reported to increase (261, 278), although with more modest changes (278), or only among older subjects (261). One study assessed subendocardial viability ratio, an index of myocardial oxygen supply/demand relation, and found no cold-related changes among healthy young subjects (278). This is consistent with increased coronary blood flow during cold exposure in healthy subjects (29).
Table 2. Studies assessing the effect of cold exposure on central aortic blood pressure (BP) in healthy people. Changes in parameters from baseline to cold exposure presented. MAP, SBP, DBP, mean, systolic, diastolic BP; PWV, pulse wave velocity.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cold exposure</th>
<th>Subjects</th>
<th>Central BP, mmHg</th>
<th>Central vs. brachial</th>
<th>Augmentation index, %</th>
<th>PWV, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alterhög et al.</td>
<td>Closed hypothermic operating table, cold air 15°C, wind 0.5m/s, 60min, vs. (before cold) room T, 15min, naked, supine</td>
<td>8 water-loaded males, age 27 years</td>
<td>MAP (mean±SD)</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Edwards et al.</td>
<td>Whole-body cold air, 4°C, wind 6.1m/s, 30min, vs. (randomized) 24°C, 30min, seated</td>
<td>12 males, age 28±2 years</td>
<td>SBP 112±3 → 125±3</td>
<td>+</td>
<td>3.4±3.3 (mean±SD)</td>
<td>na</td>
</tr>
<tr>
<td>Edwards et al.</td>
<td>Cold face test, a cold gel pack (0°C), on forehead for 7min, vs. (randomized) no cooling, supine</td>
<td>12 (6 males), age 23±3 years</td>
<td>SBP 94±3 → 116±4</td>
<td>+</td>
<td>-1.4±3.8 5.6±0.2</td>
<td>6.2±0.2</td>
</tr>
<tr>
<td>Hess et al.</td>
<td>Skin cooling with water perfused suit, 15-18°C water, 20min, vs. (randomized) 35°C water, 20min, supine</td>
<td>12 older (55–75 years, 6 males), 12 younger (18–35 years, 6 males)</td>
<td>SBP increased by ca. 25 (older) and 10 (younger), and DBP by ca. 8 (both) No change in control</td>
<td>+/- 5 15 in younger older, no change in control</td>
<td>Ca. 9 11 in control</td>
<td>na</td>
</tr>
<tr>
<td>King et al.</td>
<td>Whole-body cold air, 12°C, RH 40%, 60min, light clothing vs. (randomized) 21°C, RH 40%, 60min, light clothing, supine</td>
<td>16 (10 males), age 43±19 years</td>
<td>SBP 109±18 → 113±19</td>
<td>na</td>
<td>15±15 → 21±15 No change in control</td>
<td>na</td>
</tr>
<tr>
<td>Koutnik et al.</td>
<td>Whole-body cold air, 4°C, RH 60%, 41min, shorts and t-shirt vs. (randomized) 24°C, RH 60%, 41min, shorts and t-shirt, supine</td>
<td>20 males, age 18–35 years</td>
<td>SBP, Cold 109±2 &gt; Control 95±3</td>
<td>+</td>
<td>Cold 11±3 na</td>
<td>na</td>
</tr>
</tbody>
</table>
Modifiers of blood pressure responses

Few factors modifying BP responses to cold exposure have been reported. Importantly, cold increases BP more among older than younger people (261, 262, 272, 275). This age related augmentation in BP responses has been associated with higher arterial stiffness (261), pronounced cold-related MSNA increases (262), increased left ventricular preload (275), and to blunted thermogenesis (267). In addition to aging, body composition could modify the cold-related BP responses. As mentioned earlier, a higher fat percentage increases the insulating layer of the body (22) and, could therefore result in blunted BP responses towards cold exposure. Consistent with this, Kingma et al. (267) found a negative association between fat percentage and post exposure BP changes among older subjects. On the other hand, overweight associates with impaired cardiovascular health, such as increased arterial stiffness (281), and could therefore (indirectly) augment BP response. Higher physical fitness, involving higher muscle mass, could give a better capacity to heat production while exposed to cold, and therefore reduce the need for BP responses related to improving insulation. The existing evidence is contradictory, however (22, 272, 282). In addition, cold habituation may lower sympathetic responsiveness (33).

Cardiovascular reactivity and blood pressure variability

In addition to thermoregulation, generally altered cardiovascular regulation could modify BP response to cold exposure. For example, the changes resulting in cardiovascular instability shown as higher BP variability in office, ambulatory, or home measurements could associate with pronounced vascular reactivity to everyday stressors, including cold exposure. Notable is, that BP variability has an independent association to cardiac and vascular damage and to increased risk of cardiovascular events (283). Studies have also found individuals who exhibit greater stressor evoked CV reactions to have elevated risk of clinical and preclinical endpoints of CV disease (284, 285). Temperature sensitivity of BP seems to associate with poor health outcomes (221). To date, the studies assessing the relation between ambulatory or home BP variability or reactivity and cardiovascular reactivity towards varying laboratory stressors (e.g. cold pressor test, handgrip, or psychological stress tests) have yielded diverse results, where some studies have detected (286-288) an association and others not (289-291). Research examining the association between BP variability and cardiovascular reactivity has
typically applied ambulatory measurements, which involves confounding from changes in BP occurring during daily activities. In contrast, the home BP measurement protocol includes assessment performed under standardized circumstances diminishing this type of confounding. However, research on the association between home BP variability and CV reactivity to physical or physiological stress is lacking.

### 2.7.4 Heart rate

Cooling of the skin activates the sympathetic nervous system, which can, in addition of increasing BP, increase HR as well (29). Correspondingly, some studies have reported modest cold-related increases in HR, of 5-10 bpm (29). On the other hand, facial cooling or cooling of the forehead activates parasympathetic nervous system via stimulation of trigeminal nerve, which reduces HR through a diving reflex (26). Consistent with this, experimental studies applying facial cooling usually report a reduction in HR, changes varying from few bpm (245, 270) to over 20 bpm (26, 259). With whole body cold exposure involving facial exposure HR is typically decreased (34, 267) or unaltered (292), but has also been found to increase (293). HR decreases are modest, from few up to ten bpm (35, 266, 267). However, also skin surface cooling without exposure of the head either has no effect on HR (261, 262, 271) or reduces it (246, 275). In addition to the direct vagal activation via stimulation of trigeminal nerve (26), baroreflexes can suppress HR secondary to augmented BP, a mechanism that does not require facial exposure (24). In conclusion, non-hypothermic cold-related changes in HR are often modest or negligible, and reflect increased autonomic nervous system activity, either separate sympathetic, or co-activation of both sympathetic and vagal regulation.

### 2.7.5 Cardiac electrical function

At present, the effects of short-term cold exposure with only superficial cooling on cardiac electrical function are not well known. Previous studies based on accidental (294) or therapeutic (295) hypothermia in human, or applying pronounced whole-body cooling in dogs (296) have detected multiple electrocardiographic (ECG) manifestations such as the J (Osborne) waves, interval prolongation, T-wave abnormalities, and atrial and ventricular arrhythmias. Among cardiac patients exercising in a cold environment shortened the time to onset of ST-depression (297),
or increased the frequency of ventricular ectopic beats (298). In healthy subjects, cold impaired post exercise cardiovagal regulation (292).

Sympathetic activation alone can alter cardiac function and involve a higher risk of arrhythmias and cardiac events (299). On the other hand, facial cooling (26), and possible cooling without facial exposure (246), simultaneously increases vagal tone. This “diving reflex” phenomenon may protect heart by limiting the increase in cardiac workload (35) and lead to more efficient cardiac function by combination of longer time for ventricular filling and stronger contraction of myocardium (300). However, it also causes conflicting inotropic and chronotropic drives to the heart (247, 300) (autonomic conflict), which may have an arrhythmogenic effect in addition to the sympathetic activation alone (247). Consistent with this, cardiac arrhythmias have been reported after cold-water submersion in healthy subjects (247). Already facial cold-water immersion can be enough to induce arrhythmias. For example, a study assessing adolescents detected supraventricular ectopic beats in 60%, ventricular beats in 20%, atrioventricular block in 30%, and junctional rhythm in 60% of subjects during immersion of face in cool water (301). Another study found facial cold exposure without breath hold to cause alteration in fractal HR dynamics towards more random pattern that has been found to precede the onset of ventricular tachyarrhythmias and atrial fibrillation (248). Also, an in vitro study with isolated rat heart showed that superimposing parasympathetic stimulant on a background of augmented sympathetic drive induced wide range of arrhythmias, such as extrasystoles and atrioventricular block (247).

Sympathetic activation increases dispersion of cardiac repolarization (proarrhythmic) (299), and therefore changes in repolarization could occur while exposed to cold, but research on non-hypothermic exposures is lacking. Among the very few observations, a mismatch in QT interval – HR relation during short facial cold-water immersion has been reported (247). Researchers detected that strong bradycardia observed with diving reflex was not accompanied by a prolongation of the QT interval. They speculated that change in QT interval might need longer time than the applied about 30 s stimulus. Alternatively, facial immersion may have some unique effects differing from pacing or exercise induced changes. However, they also stated this observation as a possible arrhythmogenic change (247).

2.7.6 Baroreflex sensitivity and blood pressure variability

Baroreflex is the dominant short-term control mechanism for adjusting BP (302). It alters the activation level of vagal cardio-inhibitory neurons and sympathetic
neurons to both the heart and peripheral vessels to buffer changes in BP (302).

Previous studies show an increase in cardiac baroreflex sensitivity (BRS) among healthy individuals during the cold face test (245, 270, 303) as well as during cold exposure without cooling of the face (246, 304) (Table 3). The detected augmentation of BRS in cold conditions probably originates from central vagal activation (245, 246, 303).

BP variability increases proportionally with BP level, and it has an independent association with cardiac and vascular damage and higher risk of cardiovascular events (283). LF BP variability enhances during sympathetic simulation and is coupled with efferent synchronous oscillations and thus considered as a surrogate measure of vascular sympathetic activity (305). Short-term cold exposure induces vascular sympathetic activation (23, 25), and therefore augmented BP variability could be expected to occur in a cold environment. However, the few previous experimental studies have reported contradictory results (245, 304, 306, 307).
Table 3. Studies assessing the effect of cold exposure on cardiac baroreflex sensitivity in healthy people.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cold exposure</th>
<th>Subjects</th>
<th>Method for BRS</th>
<th>BRs</th>
<th>LF BPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckberg et al.</td>
<td>Face immersion in cold (ca. 5°C) water, breathing through snorkel, supine, vs. baseline</td>
<td>9 males, 22-27 years</td>
<td>Stimulation of carotid baroreceptors with neck suction</td>
<td>+ Baroreflex bradycardia and sinus arrhythmia were augmented during cooling</td>
<td>na</td>
</tr>
<tr>
<td>1984 (303)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hilz et al. 1999</td>
<td>Cold face test, cold compresses (0-1°C) on forehead and maxillary region for 60s, regular breathing, supine, vs. baseline</td>
<td>15 (6 males), 25±10 years</td>
<td>LF transfer function gain of BP and HR</td>
<td>+ Increased in healthy subjects during cooling</td>
<td>na</td>
</tr>
<tr>
<td>(270)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinugasa et al.</td>
<td>Cold air chamber, head outside, t-shirt and trunks, T of 18°C, 24°C, 48°C, and 60°C, each 20 min, randomized order, supine</td>
<td>11, 21-26 years</td>
<td>Sequence method</td>
<td>(+) Tended higher in cool compared to hot T, ns</td>
<td>- Decreased from hot to cool</td>
</tr>
<tr>
<td>1999 (307)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamazaki et al.</td>
<td>Skin cooling (10°C) vs. (randomized) heating (45°C) with water perfused suit (head not exposed), exposed until skin T stabilized, supine</td>
<td>15 males, 22±1 years</td>
<td>Sequence method, before, during, and after 5min 70° head-up tilt</td>
<td>+ Increased during cooling, no change during heating</td>
<td>na</td>
</tr>
<tr>
<td>2000 (246)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamazaki et al.</td>
<td>Identical to Yamazaki et al. 2000</td>
<td>11 males, 21±1 years</td>
<td>Sequence method</td>
<td>+ Increased during cooling, no change during heating</td>
<td>- Decreased during cooling</td>
</tr>
<tr>
<td>2001 (306)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stemper et al.</td>
<td>Cold face test, cold compresses (0-1°C) on forehead and maxillary region for 60s, regular and paced breathing, supine, vs. baseline</td>
<td>10 (5 males), 22-35 years</td>
<td>LF transfer function gain of BP and HR</td>
<td>+ Increased during cooling, independently of breathing protocol</td>
<td>+/- Unaltered</td>
</tr>
<tr>
<td>2002 (245)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mourot et al.</td>
<td>Cold (26-27°C) vs. neutral (35-36°C) head-out water immersion and no immersion, 20+20min each, supine</td>
<td>10 male students, 26±1 years</td>
<td>Sequence method, before and during a 20min 60° head-up tilt</td>
<td>+ Increased in upright but not supine posture with cold water immersion.</td>
<td>+/- Unaltered</td>
</tr>
<tr>
<td>2007 (304)</td>
<td></td>
<td></td>
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</table>

Age presented with mean and standard deviation, mean and standard error of the mean, or range. Hilz et al. assessed also patient population but those results are not included here. BRS, baroreflex sensitivity; LF, low frequency; BPV, blood pressure variability; BP, blood pressure; HR, heart rate; T, temperature.
2.7.7 Cardiovascular changes in cold conditions among hypertensives

Hypertension involves altered structure and function of the circulatory system, which could modify cold-related cardiovascular responses. First, hypertension increases arterial stiffness (109, 111), which has been associated in pronounced BP responses in the aging population (261). Secondly, autonomic sympathovagal regulation is impaired in hypertension (111, 125), which could modify cold-related cardiac and vascular responses in various ways. However, there are only few previous experimental studies assessing the effect of cold exposure on cardiovascular function among hypertensives (Table 4).

In the beginning of 2000, Komulainen et al. (268, 308, 309) studied the effects of antihypertensive medication (carvedilol, metoprolol, and hydrochlorothiazide) on BP responses to cold air chamber exposure among young hypertensive subjects. They found that antihypertensive medication reduced BP level before and during cold exposure without an effect to the magnitude of the cold-related BP increase. One of these studies (268) involved also normotensive subjects but did not detect differences in the cold-related BP responses between the hypertensive and normotensive participants. Later, two studies applied cryostimulation to assess its effect on BP among normotensive and hypertensive subjects (276, 311). Zalewski et al. (276) reported a decrease in systolic BP in hypertensive and no changes in normotensive at around 10 minutes post exposure from basal levels. In contrast, Missmann et al. (311) detected cold-related increases in both systolic and diastolic BP when measured immediately after the cryostimulation. They did not report differences in the BP responses between hypertensive and normotensive, in their study population consisting of rheumatic patients.
<table>
<thead>
<tr>
<th>Author</th>
<th>Cold exposure</th>
<th>Subjects</th>
<th>Treated</th>
<th>F/M</th>
<th>Age</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>HR, bmp</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Komulainen et al. 2000 (268)</td>
<td>Whole-body cold air, −15°C, RH 50%, wind 3.5 m/s, 15 min, winter clothing, seated</td>
<td>10 HT</td>
<td>Placebo</td>
<td>2/8</td>
<td>27±8</td>
<td>132±4 → 152±7</td>
<td>85±5 → 101±7</td>
<td>75 → 68</td>
<td>BP responses did not differ between HT and NT.</td>
</tr>
<tr>
<td>Komulainen et al. 2004a (308)</td>
<td>-II-</td>
<td>7 HT</td>
<td>Placebo</td>
<td>4/3</td>
<td>30±9</td>
<td>129±9 → 152±6</td>
<td>86±7 → 103±4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Komulainen et al. 2004b (309)</td>
<td>-II-</td>
<td>6 HT</td>
<td>Placebo</td>
<td>4/2</td>
<td>22±3</td>
<td>133±3 → 152±4</td>
<td>91±3 → 104±2</td>
<td>77 → 65</td>
<td></td>
</tr>
<tr>
<td>Seifert et al. 2013 (269)</td>
<td>Whole-body cold air, −5°C, 1 h, winter clothing, a) and b) with or c) without face mask</td>
<td>53 HT</td>
<td>Treated</td>
<td>30/23</td>
<td>57±13</td>
<td>a)127±17 → 138±18</td>
<td>b)128±18 → 146±19</td>
<td>c)131±20 → 147±18</td>
<td>Increased - Mask reduced BP responses, especially in older subjects.</td>
</tr>
<tr>
<td>Zalewski et al. 2014 (276)</td>
<td>Cryostimulation, T between -115 and -125°C, 3 min, supine</td>
<td>13 HT</td>
<td>Untreated</td>
<td>0/26</td>
<td>-</td>
<td>139±7 → 133±6, post exposure</td>
<td>No change, post exposure</td>
<td>No change</td>
<td>BP was not elevated ca. 10 min post exposure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 NT</td>
<td></td>
<td></td>
<td></td>
<td>No change, post exposure</td>
<td></td>
<td>61 → 55</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Cold exposure</td>
<td>Subjects</td>
<td>Treated</td>
<td>F/M</td>
<td>Age</td>
<td>Systolic BP, mmHg</td>
<td>Diastolic BP, mmHg</td>
<td>HR, bpm</td>
<td>Conclusions</td>
</tr>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Prodel et al.</td>
<td>Facial cooling, cold compresses (0°C) on forehead and cheeks, 3 min, supine</td>
<td>9 HT</td>
<td>Treatment discontinued</td>
<td>0/9</td>
<td>51±4</td>
<td>139±4 → 197±7 (brachial)</td>
<td>89±4 → 111±4 (brachial)</td>
<td>No change</td>
<td>Peripheral and central BP increased with simultaneous increase in MSNA.</td>
</tr>
<tr>
<td>Missman et al.</td>
<td>Cryostimulation, -110°C, wearing swimsuit, shoes, gloves, headband, and a facemask, 3 min</td>
<td>10 HT, 13 NT treated</td>
<td>8/15 53±10</td>
<td>120±13 → 125±14 (immediate post exposure in all subjects)</td>
<td>76±9 → 78±8 (immediate post exposure in all subjects)</td>
<td>129±5 → 170±21 in (central aortic)</td>
<td>No change</td>
<td>Cryostimulation increased BP when assessed immediately after exposure.</td>
<td></td>
</tr>
<tr>
<td>Greaney et al.</td>
<td>Skin cooling with water (ca. 16°C) perfused suit from 34 to 30.5°C in ca. 30 min, supine</td>
<td>14 HT</td>
<td>Treatment discontinued</td>
<td>8/6 55±2</td>
<td>132±4 → 145±4</td>
<td>85±3 → 91±3</td>
<td>No change</td>
<td>HT had greater increases in SSNA than NT.</td>
<td></td>
</tr>
<tr>
<td>Greaney et al.</td>
<td>Identical to Greaney et al. 2017a</td>
<td>13 HT</td>
<td>Treatment discontinued</td>
<td>6/7 58±2</td>
<td>130±3 → 149±4</td>
<td>81±2 → 88±2</td>
<td>No change</td>
<td>BP and MSNA but not HR responses were exaggerated in HT.</td>
<td></td>
</tr>
<tr>
<td>Greaney et al.</td>
<td></td>
<td>10 NT</td>
<td>4/6 53±3</td>
<td>121±3 → 130±5</td>
<td>76±2 → 80±3</td>
<td>No change</td>
<td>BP and MSNA but not HR responses were exaggerated in HT.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP and age are presented as mean values and standard deviations and HR as mean values, when available. Treated, treated with antihypertensive drugs; F, female; M, male; BP, blood pressure; HR, heart rate; RH, relative air humidity; T, temperature; HT, hypertensive; NT, normotensive SSNA, skin sympathetic nerve activity; MSNA, muscle sympathetic nerve activity.
Recently, Greaney et al. (99, 312) published results from two experiments applying a superficial skin cooling suit in hypertensive and normotensive subjects, and of which one found no significant difference (99), and other exaggerated (312) BP responses in hypertensives compared to normotensives (Table 4). They also found elevated peripheral cutaneous vasoconstrictor response (99) and greater increases in MSNA (312) in subjects with hypertension. Two studies by other research groups assessed cold-related BP responses among hypertensives without a normotensive control group, and reported increased systolic and diastolic BP during cold chamber (269) and facial cooling (310) exposures. Also, experimental animal studies comparing the effects of acute cold exposure between hypertensive and non-hypertensive rats have given contradictory results, others showing pronounced and others blunted responses (28).

In addition to the studies listed in Table 4, there are several studies assessing BP responses to the cold pressor test among hypertensive subjects. Some studies have detected pronounced BP responses to cold pressor test that predict future hypertension (e.g. (313), but other studies have challenged this (e.g. (314). However, the cold pressor test, which is performed by inserting a hand or foot in ice-cold water for 1 to 2 minutes, represents a painful stimulus (35) and reflects high cardiac sympathetic but no vagal activation (248). Furthermore, it induces different cardiovascular responses that deviate from those observed with moderate whole body cold exposure (35).

Altered circulatory regulation or structure could modify the central aortic hemodynamics in cold conditions among hypertensive subjects, but studies assessing this are lacking. Recently, Prodel et al. (310) reported increased peripheral and central BP, augmentation index, and MSNS activity while exposed to cold among nine hypertensive subjects. The reported mean increases were around 40 and 15 mmHg for central systolic and diastolic BP and around 60 and 20 mmHg for brachial systolic and diastolic BP, which are somewhat higher than reported in studies involving healthy subjects. However, they did not include a control group without hypertension, which hinders the evaluation of the contribution of the disease to the reported responses.

Cold-related activation of the autonomic nervous system can either increase, decrease, or have no effect on HR. Hypertension, involving impaired sympathovagal regulation could alter HR changes, but results of the few studies are contradictory. Komulainen et al. (268) found cold chamber exposure to reduce HR in hypertensive but not in normotensive. Three other studies found no cold-related
HR response in hypertensive or normotensive after cryostimulation (276) or at the end of skin surface cooling exposure without facial cooling (99, 312).

Cold-induced arrhythmias could be more frequent or severe in patients with hypertension, among which sympathetic nervous system is overactive (315), and the risk of both atrial and ventricular arrhythmias augmented (138). Hypertension associates also with cardiac and vascular remodeling, such as left ventricular hypertrophy (111, 137, 138) and altered cardiac repolarization patterns, which could modify cardiac function in cold conditions. Hence, in a cold environment, the augmented sympathetic drive, conflicting inotropic and chronotropic drives during intense co-activation of vagal and sympathetic autonomic nervous system, combined with increased pressure load and cardiac work, could further aggravate the course of hypertension and increase the risk of electrical anomalies in cardiac function.

Cardiovascular diseases, such as hypertension, associate with decreased cardiac BRS (302). The impaired cardiac BRS could alter BP regulation during physiological challenges, such as short-term cold exposure. In addition, reported increase in cardiac BRS among healthy subjects while exposed to cold has been suggested to result from central vagal activation. This response could be altered in hypertension, in which sympathovagal balance is commonly impaired (315). Interestingly, Greaney et al. detected an association between MSNA and diastolic BP, an estimate of sympathetic vascular BRS, to increase while exposed to cold in hypertensive but not in normotensive participants. However, this does not reveal whether there are alterations in cold-related responses of cardiac vagal BRS that does not correlate with sympathetic vascular BRS (316), is impaired in hypertension, unlike sympathetic vascular BRS (317), and increases while exposed to cold in healthy individuals (Table 3). In addition to altered cardiac BRS, hypertension associates with elevated BP variability (283), which could modify cold-related changes in LF BP variability, a surrogate measure of sympathetic activity (305).

### 2.8 Gaps in the knowledge

It is well recognized, that acute cold exposure induces sympathetic activation and increases BP, and this has been suggested as one mechanism explaining the excess cold-related cardiovascular morbidity and mortality. Hypertension involves functional and structural circulatory changes, such as increased arterial stiffness and impaired autonomic regulation that could alter the cold-related BP responses,
but the experimental studies on the topic are lacking. There are very few studies assessing the BP responses to short-term whole-body cold exposure in hypertensive subjects. In addition, those were designed to assess the effects of antihypertensive medication onto cold-related BP responses (268) or did not include a normotensive control group (269, 308, 309). The few later studies applying other types of cold exposures have given contradictory results (99, 276, 311, 312).

In addition to brachial BP, hemodynamics in more central parts of the circulation are of interest, such as estimated BP in the aorta. The few previous studies assessing central hemodynamics in cold conditions involved healthy subjects (27, 261, 277, 278, 280), or did not include a control group without hypertension (310). Contradictory, others reported comparable (261) and others augmented (277, 278) central BP compared to brachial BP changes in the cold environment. In addition, a notable increase in central wave reflection was reported (27, 261, 277, 278, 310). Myocardial oxygen supply/demand ratio was maintained in healthy young subjects (278). Hypertension could result in pronounced central aortic BP and wave reflection responses, as well as impairments in myocardial oxygen supply/demand ratio, while exposed to cold. However, no previous studies have assessed this.

Previous studies involving pronounced whole-body cooling and hypothermia have detected ECG manifestations such as the J (Osborne) waves, interval prolongation, T-wave abnormalities, and atrial and ventricular arrhythmias (247, 294). At present, the effects of mild cold exposure involving only superficial cooling on cardiac electrical function are not established. It is possible that cold-related increase in sympathetic or simultaneous increase in sympathetic and vagal autonomic nervous activity induces ECG anomalies, such as higher repolarization heterogeneity or a risk of arrhythmias. Moreover, these effects could be altered in hypertension, which associates with cardiac and vascular remodeling (109, 137) and impaired sympathovagal regulation (125, 315). However, to our knowledge, this has not been studied before.

Research among healthy individuals has shown an increased cardiac vagal BRS while exposed to cold (245, 246, 270, 303, 304). Hypertension, on the other hand, associates with impaired BRS that could disturb BP regulation during short-term cold exposure. In addition, short-term cold exposure related sympathetic activation could result in increased beat to beat BP variability, and estimate of sympathetic vascular activity, but results from previous experimental studies with healthy subjects are contradictory (245, 306). To our knowledge, no previous
experimental studies have assessed BP variability in cold conditions among hypertensive subjects.

BP variability is an independent cardiovascular risk marker beyond the average BP level (318). The changes resulting in cardiovascular instability shown as higher BP variability in office, ambulatory, or home measurements could lead to pronounced vascular reactivity to everyday stressors, and so, a greater BP level while facing everyday challenges, such as exposure to environmental cold temperature. However, the previous studies on the topic have yielded diverse results. To our knowledge, there is no previous research on association between BP variability and cardiovascular responses to cold exposure among hypertensives.

In conclusion, cold exposure induces cardiovascular responses in brachial BP, central hemodynamics, cardiac electrical function, and short-term BP control that hypertension could modify, but research on this is lacking.
3 Aims and hypotheses of the study

The general aim of the study was to assess cardiovascular function of untreated hypertensive men during moderate short-term cold exposure. Their responses were compared to the ones obtained from men without hypertension.

The specific aims of the study:

1. To assess how central hemodynamics, such as central BP and wave reflection, change during short-term cold exposure. (I)
2. To investigate cardiac electrical function, arrhythmias, and HR variability while exposed to cold. (II)
3. To examine the effect of cold exposure on spontaneous BRS and beat-to-beat BP variability. (III)
4. To assess the association between home BP variability and cardiac workload responses to short-term cold exposure. (IV)

The hypotheses of the study:

1. Cold exposure increases central aortic BP and wave reflection, and decreases myocardial oxygen demand/supply relation. These changes are exaggerated in hypertensives. (I)
2. Cold exposure induces autonomic co-activation and increases dispersion of repolarization and results to higher frequency of arrhythmias. The adverse changes are exaggerated in hypertensives. (II)
3. Cold exposure increases spontaneous BRS and beat-to-beat BP variability. The cardioprotective BRS increase is blunted and sympathetic beat-to-beat BP variability increase augmented by hypertension. (III)
4. Higher home BP variability is associated with higher cardiac workload responses to cold exposure. (IV)
4 Subjects and methods

4.1 Participants in the study

The source population consisted of men between the ages of 55 and 65 years living in the town of Oulu, Finland (65 °N, 25 °E). We conducted a population-based recruitment by randomly sampling 1000 of those men from the Finnish Population Register in 2011. Information letter was sent to the participants, after which their eligibility for the study was confirmed with a telephone interview. The flow depicted in Fig. 3 describes the applied recruitment procedure.

Fig. 3. Recruitment procedure. BP, blood pressure. a Excluded for coronary heart disease, asthma, chronic obstructive pulmonary disease, or use of antihypertensive drugs. b Excluded before experiment for limited size of control group (n=74), inadequate home measurements (n=7), having BP ≥ 175/105 mmHg in home measurements and/or starting medication for hypertension before experiments (n=6), or for other medical condition preventing the experiments (n=8). c Excluded before data analyses for the usage of antihypertensive drugs (n=4, alpha blockers for prostatic hyperplasia, n=1 other) or inadequate data quality (n=1, frequent arrhythmias).

Eligible subjects willing to attend to the study performed home BP measurements according to the guidelines of European Society of Hypertension (319). For this purpose, they used a validated (320) automatic oscillometric device (HEM-7200-E; Omron Healthcare, Kyoto, Japan). The cuff size (HEM-CR24 or HEM-CL24)
was chosen based on arm circumference. We trained the participants to measure their BP after five minutes of rest in a sitting position and with the arm supported so that the cuff was approximately at the level of the heart. The participants were advised to abstain from eating, caffeine, exercise, smoking, and sauna for 30 minutes before the measurements, and from licorice for the entire week of the measurements. Otherwise, they were instructed to continue their everyday lives as normal. The participants measured their BP twice in the morning and twice in the evening for seven consecutive days. Systolic and diastolic home BP values were then computed as the arithmetic mean of all 28 measurement values. Measurements consisting of irregular heartbeats (deviation of two or more RR-intervals > 25% from an average RR-interval during the measurement), movement, or cuff misplacement were not included for computations, and a minimum of 16 successful measurements (319) was required. Based on home measurements the participants were classified either to a hypertensive group (systolic BP $\geq 135$ mmHg and/or diastolic BP $\geq 85$ mmHg) or to those without hypertension (BP $< 135/85$ mm Hg), i.e. control group. We referred men belonging to the hypertensive group to their health care center for further evaluation of their disease and for receiving treatment. Participants were excluded in the case BP medication was applied prior to the experimental study.

The aim was to have at 2:1 ratio of men with hypertension and men in the control group for the data analyses, respectively. We chose this to enable subgroup analyses in the group of hypertensive men. Therefore, all untreated subjects with mild to moderate hypertension according to the home BP measurements and one third of the men without hypertension were invited and attended to the experimental measurements (Fig. 3).

70 (38%) of 182 subjects who had adequate home BP data were hypertensive. None of the hypertensives were treated for high BP and 61 (87%) were not aware of having hypertension (current or previous). In a large Finnish study sample collected in 2007 the prevalence of unaware hypertension was around 20% in men between the ages of 25 and 64 (118). The higher prevalence of (unaware) hypertension in our study (34% of 182 subjects) likely reflects the higher age range (55–65 years).

The study protocol was approved by the ethics committee of Northern Ostrobothnia Hospital District (EETTMK: 111/2010), and all participants gave written informed consent. The study is registered in the international Clinical Trials registry (www.clinicaltrials.gov, ID:NCT02007031).
4.2 Experimental protocol

We performed the laboratory measurements during office hours from August to November in 2011. The participants were advised to abstain from alcohol and strenuous exercise a day before, and tobacco products, eating, exercise, and caffeine products two hours before the measurements. They were also advised to have a light meal about two hours before the reserved time, and avoid exercise when arriving to the climatic laboratory. The participants had filled in a questionnaire, which inquired of their health and lifestyle, and reported of their latest health events.

Fig. 4 depicts the applied systematic laboratory protocol and Fig. 5 the data collection of a phase (baseline, cold, or recovery). For the baseline and recovery measurements, the participants wore socks, short and long-legged underpants, a T-shirt and a thin long-sleeved sweater, over-trousers, winter shoes, and a winter coat (insulated) with an open coat zipper. For cold exposure, they additionally wore a warm winter cap and gloves, and the zipper of the winter coat was closed. The insulation values of baseline (same for recovery) and cold exposure clothing ensemble were about 1.6 clo and 2.0 clo (52), correspondingly. During the measurements, participants stood with arms supported at the level of the heart. While exposed to cold, they had their face towards the wind.
Fig. 4. Experimental protocol applied in the laboratory measurements. BP, blood pressure; ECG, electrocardiography.
Fig. 5. Measurement protocol presenting fifteen minutes data collection of a phase (baseline, cold exposure, recovery follow-up). For recovery phase, data collection was continued five minutes longer with same sample intervals. BP, blood pressure.

4.3 Measurements

4.3.1 Body composition, fitness, and health

Weight and body composition were assessed with bioelectrical impedance analysis (InBody 720 Biospace, Seoul, Korea). Maximal oxygen uptake was estimated based on resting HR variability measurements performed in quite room after few minutes rest in a supine position (321) (Polar S610; Polar, Kempele, Finland).

The health related questionnaire included questions concerning with the health status, life habits, cold sensitivity, and occupation. More specifically, we asked about possible chronic diseases during past year (e.g. diabetes, musculoskeletal or psychiatric diseases), health events during past 30 days (e.g. back pain or nausea), any medication (medicine and purpose of use), leisure time and work related physical activity, diet and sodium usage, as well as consumption of alcohol (past year) and tobacco products (current or previous). Cold-related questions were used to inquire of average weekly time exposed to cold conditions during previous
winter at work or during leisure time, cold-related symptoms (shortness of breath, cough, cardiac symptoms, and symptoms in finger circulation), and cold sensitiveness.

4.3.2 Skin temperature and thermal sensations

We assessed thermal sensations from the participants with a subjective 9-points two-pole rating scale (67) separately for the whole body and face (I-IV).

Skin temperature was recorded at 12-second intervals with an 8-channel data-logger (SmartReaderPlus; Acr Systems, Surrey, BC, Canada) (I-IV). The participants were equipped with thermistors (NTC DC95; Digi- Key, Thief River Falls, MN, USA) on the left side of their body at the following sites: calf, shoulder blade, chest, arm, back of the hand, middle finger, and cheek. Matlab software (MathWorks, Inc., Natick, MA, USA) was applied to downsample the data by taking every fifth sample for each channel of each individual, i.e. resulting a sampling interval of one minute.

4.3.3 Blood pressure and baroreflex sensitivity

Brachial systolic and diastolic BP was recorded with oscillometric sphygmomanometry from left arm (Schiller BP 200 Plus; Schiller, Baar, Switzerland) (I-IV). We supported the arm to place the cuff (for arm circumference of 25–35 cm) approximately at the level of the heart. Pulse pressure was computed as systolic–diastolic BP. Rate-pressure product (RPP) was computed as systolic BP x HR to estimate cardiac workload.

We applied radial artery applanation tonometry to assess central hemodynamics (I). It is a non-invasive method, which produces indirect estimates for central aortic BP, wave reflection, and myocardial oxygen demand/supply relation (322, 323). During the measurement, a tonometric pressure sensor (SPC-301, Millar Instruments, Houston, TX, USA) was placed over the radial artery of the right arm. The pressure signal was recorded digitally for at least 10 seconds and central hemodynamic parameters were computed by SphygmoCor software (SphygmoCor Px; AtCor Medical, Australia). We used a built-in quality index, namely the operator index, to ensure good quality of the data. It combines quality control indexes of beat-to-beat variation in diastolic BP (<5%), and shape (<4%) and amplitude (<5%) of the pulse pressure, and magnitude of pulse amplitude (>80mV). An operator index of at least 75% was required and an average operator
index was 93±6% (mean ±SD) in both test groups. BP level was calibrated according to arithmetic mean of three systolic and diastolic brachial BP.

The Sphygmocor software computes the central aortic pressure waveform by transforming the recorded radial artery pressure waveforms to aortic pressure waveforms by a validated (322) mathematical algorithm and averaging the resulted waveforms over a 10 second time window (Fig. 6). Systolic and diastolic BP were specified as the maximum and minimum values of the pressure curve. Central RPP and pulse pressure were computed as for brachial BP. An augmentation index is a measure of wave reflection and a surrogate estimate of arterial stiffness (323). Augmentation index was computed from difference of the first and second systolic BP peak (P2-P1, i.e. augmentation pressure) divided by height of the pressure curve, i.e. pulse pressure (323). Time to first (T1) and second (T2) systolic BP peak and estimate of ejection duration were specified from the BP waveforms (Fig. 6). Subendocardial viability ratio, known also as the Buckberg index, is an estimate of myocardial oxygen demand/supply relation (324). It has been shown to correlate with coronary flow reserve assessed with Doppler among people with untreated essential hypertension (325). Subendocardial viability ratio was computed as central aortic BP time integral ratio of diastolic and systolic phases (pressure time integral after/during the left ventricular ejection, Fig. 6).

![Fig. 6. Measured radial and estimated central aortic pressure waveform. ED, left ventricular ejection duration; SBP and DBP, systolic and diastolic central aortic blood pressure; P1 / P2 and T1 / T2 blood pressure and time from beginning of pressure wave at first / second SBP peak (at inflection point), respectively.](image-url)
We examined continuous arterial BP with a non-invasive method that applies the volume clamp principle (326) (Nexfin, BMEYE Medical systems, Netherlands) (III). The BP cuff (size according to measured finger circumference) was placed at the forefinger of the right hand, and the arm was supported approximately at the level of the heart. A height sensor was placed at the level of the heart to allow the Nexfin device to automatically correct for the hydrostatic pressure influences. We used the automatic Physiocal calibration method (327) for assessing the BP signal at least once in every 70 seconds to maintain the adequate level of continuous BP. Respiration was recorded with a piezo-electric belt (PneumoTrace, ADInstruments, Australia). Continuous BP, respiratory and ECG (lead I, II, or III, data collection described in chapter 4.2.5.) signals were connected to the lab top with an analog-to-digital-transformer with 1 kHz sampling frequency (Power Lab/8SP, ADInstruments, Australia) managed with Labchart software (v7.3.2, ADInstruments, Australia). We applied pre-defined criteria to ensure data quality also during cold exposure (Physiocal calibration > 2 times/min, no frequent arrhythmias or otherwise noisy signal), resulting in the exclusion of 42 participants from further data analyses. Recovery measurements were not included in the analyses because of the low quality of the post-exposure finger BP data.

We performed data analyses for the recorded continuous BP, respiratory and ECG data with a custom-made Matlab-based (MathWorks, Inc., Natick, MA, USA) software. Ectopic or anomalous beats were removed from the signals manually and replaced with local average. Data sequences missing for automatic calibration were replaced with a linear interpolation method (328). Time series of RR-interval and beat-to-beat systolic BP were extracted. We estimated total BP variability as a standard deviation of systolic BP. For the spectral analyses, very low frequencies (<0.04 Hz) were detrended by the Savitzky-Golay method. We then computed spectral estimates for stabilized periods of baseline and cold exposure (5 minutes from the end of both phases) on LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) bands of HR and BP variability by applying FFT (Welch’s method, sequence length 128, overlapping 50%). Spectral estimate of spontaneous BRS was computed on LF band with alpha method (329) as follows

\[
BRS = \sqrt{HRV_{LF}/BPV_{LF}},
\]

in which HRV\textsubscript{LF} and BPV\textsubscript{LF} denote RR-interval variability and systolic BP variability on LF band. The method presumes a high degree of linear correlation of RR-interval and systolic BP, and therefore analyses were done only if coherence
between HR and BP variability was >0.5. Respiration frequency was computed manually as the amount of respiration cycles/time.

4.3.4 Home blood pressure variability

The home BP data collection procedure is described in chapter 4.1. First, the measurements with arrhythmia, movement, or cuff misplacement were excluded from the collected BP data (IV). Then, the mean values of systolic and diastolic BP and HR were defined for each individual as arithmetic mean of all remaining home measurements. For daily variability analyses, measurement days including only morning or evening values were excluded, and after that a minimum of four days of successful measurements were required for calculations. Systolic BP variability was computed as within-subject standard deviation of daily mean values, and the coefficient of variation was defined as within-subject variability divided by arithmetic mean of the values applied in variability calculation (330). Subjects were divided in the groups of high and low BP variability (above and below the median daily systolic BP variability).

4.3.5 Electrocardiography

ECG was recorded with Medilog AR-12 (Huntleigh Healthcare, Austria) applying 16-bit amplitude resolution and 256 Hz sampling rate throughout the measurement phases (II). This data was used after different preprocessing procedures to assess a) ECG intervals, amplitudes and spatial QRS-T-angle, b) HR variability, and c) arrhythmias.

The data recorded using Medilog AR 12 was derived into 12-channel and vectorcardiographic (X,Y,Z) data (331, 332). Signal pre-processing and computation of ECG intervals, amplitudes and spatial QRS-T-angle was performed with custom-made Matlab-based (MathWorks, inc. Natick, MA, USA) software. Low-pass (40Hz) and cubic spline interpolation filters were applied to suppress baseline wander and high frequency noise. Ectopic (>20% difference from the last valid RR-interval) and abnormally shaped beats were removed from the data. Signal was resampled from 256 Hz to 512 Hz. Cardiac beats were aligned in each of the leads based on cross-correlation without changing the time alignment between the leads. Ten-beat-wide sliding window filter was applied to the aligned beats to produce representative median beats for each cardiac cycle with reduced noise. Three representative median beats were taken with five minutes interval for
each phase (baseline, cold, and recovery), resulting nine time points for the analyses. To ensure the accuracy of the interval measurements, the P wave onset, QRS boundaries, T-wave peak, and T-wave offset were manually identified on each of the 12 leads for each sample.

After the pre-processing procedures, PR, QRS, QT, and T-peak to T-end intervals were computed for leads II and V5. The nomogram method was applied to adjust QT interval according to HR (QTc) (333). Sokolow-Lyon voltage criteria was chosen for the estimation of left ventricular hypertrophy. Left ventricular hypertrophy was defined as the sum of S amplitude in lead V1 and R amplitude in lead V5 or V6 (lead with higher amplitude) >3.5 mV in baseline (334, 335). The maximum T-wave amplitude was computed from leads II and V5. If the amplitude in lead V5 was below 0.15 mV, lead V4 or V6 (lead with higher amplitude) was used instead. Orthogonal X, Y and Z leads were reconstructed from the 12-lead ECG samples with inverse-Dower matrix (331) to compute the spatial vectorcardiographic T-axes and QRS axes, and mean angle between these axes, i.e. spatial QRS-T angle.

HR variability was assessed in time and frequency domain as described previously (Hearts 8, Heart Signal Co., Oulu, Finland) (336). Ectopic beats and artifacts were replaced with the local average. Linear de-trending was performed to the measured RR-interval data. Subsequently, the power spectral densities of the RR-interval variability were computed by fast Fourier transform (FFT) for LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) bands. The ratio between LF and HF powers (LF/HF-ratio) was defined. These power spectral components of HR variability were computed in five-minute periods. Standard deviation of all normal RR-intervals in the time domain was computed for each 15 minutes phase to have an overall estimate of HR variability.

Ventricular and supraventricular ectopic beats were detected automatically (Medilog Darwin Holter Analysis software V1.13.4, TOM Medical Handels Gmbh, Austria) from baseline, cold exposure, and recovery ECG recordings by Medilog ADAPT algorithm (337). The threshold for the prematurity of a beat was defined as 15% difference compared to three normal preceding beats. The automatically detected ectopic beats were confirmed by visual inspection. The mean of ectopic beats per time was computed for all phases of the measurements.

ECG was also followed real-time with three-lead measurements (Cardiolife Tec-7100; Nihon Kohden, Tokyo, Japan). The analogous signal from lead I, II, or III (whichever had the highest R-peak in baseline measurements) was recorded with 1 kHz sampling frequency and operated with LabChart 7.3.2 (ADInstruments,
Sydney, Australia). The signal was used to assess HR variability in relation to simultaneously measured BP variability (described in detail in chapter 4.2.3.).

4.4 Statistical methods

The subjects were compared between the study groups (hypertensive vs. control group (I-III), high vs. low BP variability (IV), and the original study sample of experiments vs. the subjects included in the data analyses (III). The statistical significance for the differences between the groups was assessed by independent t-test for continuous variables and chi-square test for categorical variables. According to the sample size estimation and power analysis (G-Power 3.1.0) (power 0.9, type I error probability 0.05) 23 participants per test group were required to the smallest detectable difference of 20 mmHg.

Cardiovascular parameters with non-Gaussian distributions were transformed into natural logarithm for parametric statistical tests. The differences in the means between baseline and cold, and baseline and the recovery, as well as study groups (I-IV) and measurement method (central vs. brachial, I) were compared by two-way repeated measures analysis of variance (RANOVA) and contrast tests (simple). Sensitivity analyses were conducted by repeating the analyses without diabetic subjects (n=4). Results did not change, and therefore diabetics were not excluded.

Spearman (skewed variables) or Pearson correlation analyses were applied to assess relation between parameters showing significant group x time interaction. More closely, correlations were computed between the cold induced changes in LF BP variability and baseline BP variability, HR variability, and BRS (III) or between daily systolic home BP variability and cold induced changes in RPP, systolic BP, and HR (IV). Linear regression was calculated to evaluate the HR-dependency of T-wave amplitude change (II) and to estimate the percentage of variation in RPP and systolic BP changes explained by home BP variability (IV). Regression analyses (IV) were adjusted for home BP level, body fat, age, augmentation index, and smoking. For correlation and regression analyses assessing relation between home BP variability and cold-related responses, the responses were defined as area under RPP, systolic BP, and HR time curves (AUC) (IV).

The results are presented as means and their 95% confidence intervals or standard deviations for variables with Gaussian distribution and as medians and interquartile range (Q1, Q3) for skewed variables. Statistical analyses were performed with IBM SPSS for Windows versions 19-23 (IBM Corporation, New York, USA) and significance was set at p<0.05.
5 Results

5.1 Participants in the study

The study population consisted of 51 hypertensives and 32 controls (I-III) (Table 5). In addition to a higher BP level, the hypertensive men had higher weight, body mass index, and fat percentage than the controls, and four subjects in the hypertensive group and none in the control group had type 2 diabetes.

Table 5. Characteristics of the study groups (I-III) (modified from (II), CC-BY license).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive, n=51</th>
<th>Control group, n=32</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60±3</td>
<td>60±3</td>
<td>p = 0.90</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177±6</td>
<td>176±6</td>
<td>p = 0.89</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84±9</td>
<td>79±11</td>
<td>p = 0.02*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±3</td>
<td>25±3</td>
<td>p = 0.01*</td>
</tr>
<tr>
<td>BF, %</td>
<td>25±6</td>
<td>21±6</td>
<td>p = 0.01*</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>143±9</td>
<td>120±8</td>
<td>-</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>86±6</td>
<td>73±6</td>
<td>-</td>
</tr>
<tr>
<td>Sokolow-Lyon index, mV</td>
<td>1.8±0.6</td>
<td>1.9±0.6</td>
<td>p = 0.51</td>
</tr>
<tr>
<td>Estimated VO2max, ml/kg/min</td>
<td>37±6</td>
<td>38±7</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (8)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>28 (55)</td>
<td>20 (63)</td>
<td>p = 0.56</td>
</tr>
<tr>
<td>Alcohol consumption ≥ 1</td>
<td>35 (69)</td>
<td>25 (78)</td>
<td>p = 0.42</td>
</tr>
<tr>
<td>Retired, n (%)</td>
<td>20 (39)</td>
<td>12 (38)</td>
<td>p = 0.98</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean values ± standard deviation, categorical variables as number of cases (percentage). For studies I and III the participants included in the data analyses were subsamples of those that are presented here, but characteristics do not differ between the original and final study sample and are presented in the original publications. BMI, body mass index; BF, body fat percentage; SBP and DBP systolic and diastolic blood pressure in home measurements; and Sokolow-Lyon index, estimate of left ventricular hypertrophy; estimated VO2max, indirectly estimated maximal oxygen uptake. *p<0.05 controls vs. hypertensive (group), assessed with independent t–tests or chi-square tests.

We also divided the participants to groups with higher or lower systolic home BP variability, independently of their BP levels (IV) (Table 6). The participants with higher home BP variability had higher fat-percentage and three of them and none in the other group had type 2 diabetes. The amount of hypertensives was similar in both groups, although systolic BP levels were slightly but non-significantly higher.
in those with higher home BP variability. Otherwise, the groups did not differ from each other.

Table 6. Characteristics of the study groups divided according to home blood pressure variability (IV).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High variability, n=38</th>
<th>Low variability, n=38</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 (60 to 62)</td>
<td>60 (59 to 61)</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (26 to 28)</td>
<td>26 (25 to 27)</td>
<td>0.29</td>
</tr>
<tr>
<td>BF, %</td>
<td>25 (23 to 27)</td>
<td>23 (21 to 24)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Estimated VO₂max, ml/kg/min</td>
<td>36 (34 to 38)</td>
<td>38 (36 to 40)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (8)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>21 (55)</td>
<td>25 (66)</td>
<td>0.48</td>
</tr>
<tr>
<td>Alcohol consumption ≥ 1 time/month, n (%)</td>
<td>30 (81)</td>
<td>26 (68)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean values and 95% confidence intervals or medians and interquartile ranges (Q1, Q3), and categorical variables as number of cases and percentages. BMI, body mass index; BF, body fat percentage; estimated VO₂max, indirectly estimated maximal oxygen uptake; SBP and DBP, systolic and diastolic blood pressure; HR, heart rate; SBPV, systolic blood pressure variability; CV, coefficient of variation. * p<0.05 vs. high variability (group), assessed with independent t–tests and chi-square tests.

5.2 Skin temperature and thermal sensations

The applied cold exposure involved a rapid and substantial facial cooling (Fig. 7) (I-IV). Instead, superficial cooling of trunk was modest. Skin temperature remained lower at all the measurement sites during the recovery than in baseline, especially on peripheral body parts. Subjective thermal perceptions (median) of face and trunk were neutral in baseline, and recovered to neutral stage almost immediately (face) or within 10 minutes (trunk) after exposure to cold. Sensations of cooling increased from slightly cool in the beginning to cool or cold at the middle, and in the end of the 15 minutes exposure for both face and trunk. Skin temperature and thermal
perceptions did not differ between hypertensives or control subjects, or between those with lower or higher systolic home BP variability.

Fig. 7. Skin temperature of face and torso. Values are means and standard deviation, dashed line for control group and solid for hypertensives.

5.3 Blood pressure

5.3.1 Blood pressure, heart rate, and rate-pressure product during exposure to cold

The applied cold exposure increased systolic and diastolic brachial BP, decreased HR and increased RPP (Table 7, Fig. 8). Most of the change in BP occurred during first few minutes of the exposure to cold and BP reset at a higher level within 10 minutes (Fig. 8). BP recovered to baseline values 15 minutes after the cessation of cold exposure, whereas HR remained at a lower level until the end of recovery.

Systolic BP increased in all subjects, and diastolic BP in all but two. Peak values of systolic BP in cold conditions (mean and SD) were 185±19 mmHg, (range from 152 to 241 mmHg) and 160±16 mmHg (range from 130 to 200 mmHg) in hypertensives and in the control group, correspondingly. These resulted to maximal systolic BP increases of 38±15 and 33±14 in hypertensive and control group (mean and SD).
Table 7. Brachial blood pressure, heart rate, and rate-pressure product in cold conditions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n=51)</th>
<th>Controls (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Cold</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(144 to 151)</td>
<td>148</td>
<td>175</td>
</tr>
<tr>
<td>(14 to 179)*</td>
<td>(24 to 30)</td>
<td>(123 to 131)*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>92</td>
<td>104</td>
</tr>
<tr>
<td>(89 to 95)</td>
<td>(101 to 106)*</td>
<td>(10 to 13)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>(71, 89)</td>
<td>(66, 85)*</td>
<td>(-7, -1)</td>
</tr>
<tr>
<td>RPP, (mmHg x bpm)</td>
<td>11800</td>
<td>13600</td>
</tr>
<tr>
<td>(10100, 13200)</td>
<td>(11500, 14900)*</td>
<td>(500, 2300)</td>
</tr>
</tbody>
</table>

Values are means (95% confidence intervals) or medians and interquartile ranges (Q1, Q3). SBP and DBP, systolic and diastolic blood pressure; HR, heart rate; RPP, rate-pressure product. *p<0.01 vs. baseline (time), ** p<0.05 vs. hypertension (group), no significant differences in responses between groups (time x group interaction), assessed with 2-way RANOVA and contrast tests.

Fig. 8. Brachial systolic and diastolic blood pressure in hypertensive men and control group, presented with mean values (line) and confidence intervals (area).

Ten (20%) hypertensive men and one (3%) man in control group had systolic BP ≥ 200mmHg while exposed to cold (Fig. 9A) (I). Among 9-10% of both hypertensive and control subjects the maximal increase in systolic BP was higher than 60 mmHg
(Fig. 9B), and among 20% of hypertensive and 13% of men in the control it was higher than 50 mmHg. The cold-related changes in systolic and diastolic BP (an increase while exposed and recovery after the exposure) were comparable between hypertensive men and the control group.

**Fig. 9.** Plots of systolic blood pressure in individuals. Individuals with maximal blood pressure ≥ 200 mmHg (A) and blood pressure response ≥ 60 mmHg (B) plotted with solid lines.
5.3.2 Central hemodynamics in cold conditions

The increases in central aortic BP while exposed to cold were comparable to the changes in brachial BP (Fig. 10, Fig. 11, Table 8) (I). P1 and P2 increased by about 20 and 30 mmHg, respectively, resulting in almost a threefold augmentation pressure and twofold augmentation index in cold conditions compared to baseline. Wave reflection began faster (T1 decreased) and time to the peak of pressure (T2) increased. Increase of (T2-T1) was comparable to total prolongation of the ejection duration, about 20ms in cold conditions. The subendocardial viability ratio decreased by about 10% during exposure to cold. The detected changes in aortic hemodynamics did not recover to baseline level during about 10 minutes of follow-up in either test group, except T1 in hypertensives. Fig. 11 depicts two examples of measured central aortic pulse pressure wave before and during the exposure to cold.

![Figure 10](image-url)

**Fig. 10.** Central aortic blood pressure increased parallel with peripheral blood pressure. Changes from baseline to cold conditions depicted with box plots (n=61). SBP and DBP, systolic and diastolic blood pressure.
Central BP level (systolic, diastolic, P1, and P2) was higher among hypertensive men than in the control group (Table 8) (I). The ejection duration, T1, T2, and subendocardial viability ratio were lower in hypertensive compared to the control group. The augmentation index and pressure did not differ between the study groups.

The cold-related changes in aortic hemodynamics were comparable between the test groups (I), except for the cold-related decrease in T1, which was blunted among hypertensives (p=0.03 for time*group interaction).
Table 8. Central hemodynamics in cold conditions (modified from (I), published by permission of AJH).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (N=41)</th>
<th>Controls (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Cold</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>130</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>(126 to 133)</td>
<td>(155 to 167)*</td>
</tr>
<tr>
<td>Central</td>
<td>93</td>
<td>107</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>(91 to 96)</td>
<td>(104 to 110)*</td>
</tr>
<tr>
<td>Central AP, mmHg</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>AI, %</td>
<td>(3 to 7)</td>
<td>(11 to 17)*</td>
</tr>
<tr>
<td>AI75, %</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>P1, mmHg</td>
<td>(8 to 14)</td>
<td>(20 to 27)*</td>
</tr>
<tr>
<td>P2, mmHg</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(10 to 16)</td>
<td>(21 to 26)*</td>
</tr>
<tr>
<td>T1, ms</td>
<td>104</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>(122 to 128)</td>
<td>(144 to 152)</td>
</tr>
<tr>
<td>T2, ms</td>
<td>162</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>(126 to 134)</td>
<td>(156 to 168)</td>
</tr>
<tr>
<td>ED, ms</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>(101 to 107)</td>
<td>(96 to 102)*</td>
</tr>
<tr>
<td>SEVR, %</td>
<td>13</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td>(179 to 196)</td>
<td>(168 to 185)*</td>
</tr>
</tbody>
</table>

Values are means and 95% confidence intervals. SBP and DBP systolic and diastolic blood pressure; AP, augmented pressure; AI, unadjusted augmentation index; AI75, augmentation index adjusted to heart rate of 75 beats/min; P1 and P2 the first and second systolic pressure peaks; T1 and T2 time to first and second systolic pressure peaks; ED, ejection duration; SEVR, subendocardial viability ratio. *p<0.05 vs. baseline (time), **p<0.05 vs. hypertensive (group), #p<0.05 vs. response among hypertensive (time x group interaction), assessed with 2-way RANOVA and contrast tests.

5.3.3 Cold-related responses in blood pressure, heart rate, and rate-pressure product, and home blood pressure variability

Cold exposure increased RPP and systolic BP more among participants with high systolic home BP variability compared to those with low variability (Fig. 12, Table 9) (IV). The group difference in the responses was detectable already at the beginning and remained more or less the same throughout the exposure. No group difference was observed after 5 to 10 minutes of exposure.
Table 9. Cardiac workload in baseline and while exposed to cold (IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Cold</th>
<th>Difference</th>
<th>Baseline</th>
<th>Cold</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPP, (mmHg x bpm)*min</td>
<td>11200 (10300 to 12100)</td>
<td>13100 (12000 to 14100)*</td>
<td>1900 (1500 to 2160)*</td>
<td>10800 (10100 to 11400)</td>
<td>11700 (11000 to 12400)*</td>
<td>900 (600 to 1200) #</td>
</tr>
<tr>
<td>SBP, mmHg*min</td>
<td>142 (136 to 147)</td>
<td>173 (167 to 179)*</td>
<td>31 (28 to 35)</td>
<td>78 (132 to 142)</td>
<td>160 (154 to 166)***</td>
<td>23 (20 to 25)#</td>
</tr>
<tr>
<td>HR, bpm*min</td>
<td>78 (74 to 83)</td>
<td>75 (70 to 80)*</td>
<td>-3 (-5 to -2)</td>
<td>79 (74 to 83)</td>
<td>73 (69 to 78)*</td>
<td>-5 (-7 to -3)</td>
</tr>
</tbody>
</table>

Values are area under curve (AUC/min) group means and 95% confidence intervals. RPP, rate-pressure product; SBP, systolic blood pressure; HR, heart rate. *p<0.01 vs. baseline (time), **p<0.05 vs. high home systolic BP variability (group), #p<0.01 vs. cold-baseline difference among high variability group (time x group interaction), assessed with 2-way RANOVA and contrast tests.

Fig. 12. RPP, rate-pressure product; SBP, systolic blood pressure; HR, heart rate. # p<0.05 for time x group interaction (2-way RANOVA and contrast tests). (IV).
Systolic home BP variability correlated with RPP and SBP changes in cold conditions (Fig. 13) (IV). The regression models for RPP and systolic BP change from baseline to cold are presented in Table 13, Appendix 2. Home BP variability contributed 11% and 14% to the cold-related changes in RPP and systolic BP, correspondingly, and this change was independent from the home BP level. In the fully adjusted model, home BP variability and fat percentage contributed 16% to the cold-related changes in systolic BP, whereas the contribution to RPP responses was insignificant.

Fig. 13. Scatter plot and regression line with Spearman correlation ($r_s$) and crude $R^2$-squared between daily home blood pressure variability and changes from baseline to cold in (A) rate-pressure product (RPP) and (B) systolic blood pressure (BP). (IV).

$$r_s = 0.34, p=0.003$$

$$R^2 = 0.11, p=0.004$$

$$r_s = 0.38, p=0.001$$

$$R^2 = 0.14, p=0.001$$
Systolic BP (Fig. 14) was comparable in cold conditions among hypertensives having low home BP variability and those with high home BP variability but no hypertension (p=0.23 for difference), although a difference was observed during baseline (p=0.01) (IV). Among hypertensives with high home BP variability, systolic BP in cold was higher than among others (p<0.05).

Fig. 14. Systolic blood pressure in cold conditions among those with high / low blood pressure variability at home and hypertension / no hypertension. A) Group means and SD for baseline and each measurement during and after exposure. B) Mean values of all measurements in cold conditions depicted as boxplot. (IV).
5.4 Electrical function of the heart

5.4.1 Electrocardiographic morphology and arrhythmias in cold conditions

The maximum of T-wave amplitude increased by 20-30% in leads II and V5 during exposure to cold (Table 10) (II). T-peak to T-end interval increased during exposure to cold when computed from lead II but not from lead V5. QTc, but not QT, interval and QRS-T-angle decreased during exposure to cold. PR and QRS intervals were unaltered. Changes in T-wave and QT interval did not fully recover during the 15 minutes of follow up after the exposure to cold. The frequency of ventricular, but not atrial, ectopic beats increased during cold exposure (Table 10). The frequencies of detected arrhythmias did not differ between baseline and recovery follow-up. Overall, the amount of detected ectopic beats was low in both test groups throughout the measurements. Regression equation analyzing HR dependency of T-wave amplitude was estimated for lead V5: T-wave amplitude change = 48.370 + 0.426 * RR change (adjusted R2 = 0.296, p<0.001).

T-wave amplitude was about 0.05-0.1mV (30%) lower and HR approx. 7 beats higher among hypertensive men compared to the control group in all measurement phases (Table 10) (II). Otherwise, we found no differences in the analyzed ECG parameters or frequency of arrhythmias between the study groups. One participant in both test groups had left ventricular hypertrophy according to the Sokolow-Lyon voltage criteria.

Cold induced changes in ECG parameters and arrhythmias were comparable between hypertensive men and the control group. Hence, we found no time x group interaction (II).
Table 10. Electrocardiographic parameters presented for each experiment phase (modified from (II), licensed under CC-BY).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive, N=51</th>
<th>Controls, N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Cold</td>
</tr>
<tr>
<td>HR, bpm **</td>
<td>80±13</td>
<td>77±14*</td>
</tr>
<tr>
<td>T-peak (II), mV **</td>
<td>0.12±0.06</td>
<td>0.14±0.06*</td>
</tr>
<tr>
<td>TpTe (II), ms</td>
<td>67±14</td>
<td>72±16*</td>
</tr>
<tr>
<td>QT (II), ms **</td>
<td>368±27</td>
<td>366±30</td>
</tr>
<tr>
<td>QTc (II), ms</td>
<td>408±27</td>
<td>398±19*</td>
</tr>
<tr>
<td>PR (II), ms</td>
<td>153±17</td>
<td>154±20</td>
</tr>
<tr>
<td>QRS (II), ms **</td>
<td>97±12</td>
<td>96±13*</td>
</tr>
<tr>
<td>T-peak (V5), mV **</td>
<td>0.22±0.11</td>
<td>0.27±0.12*</td>
</tr>
<tr>
<td>TpTe (V5), ms</td>
<td>80±15</td>
<td>81±12</td>
</tr>
<tr>
<td>QT (V5), ms **</td>
<td>365±27</td>
<td>364±31</td>
</tr>
<tr>
<td>QTc (V5), ms</td>
<td>405±27</td>
<td>395±20*</td>
</tr>
<tr>
<td>PR (V5), ms</td>
<td>152±17</td>
<td>154±17</td>
</tr>
<tr>
<td>QRS (V5), ms</td>
<td>90±13</td>
<td>90±14</td>
</tr>
<tr>
<td>QRS-T angle, °</td>
<td>34 (21, 91)</td>
<td>27 (19, 67)*</td>
</tr>
<tr>
<td>VEB2, count/15min</td>
<td>2.3±5.2</td>
<td>3.2±5.3*</td>
</tr>
<tr>
<td>AEB2, count/15min</td>
<td>1.0±3.7</td>
<td>1.3±5.2</td>
</tr>
</tbody>
</table>

Levels in different phases and differences between cold and baseline presented with means ± standard deviations or medians and interquartile ranges (Q1, Q3). HR, heart rate; T-peak, T-wave amplitude; TpTe, T-peak to T-end interval; QT, QT-interval; QTc, QT adjusted to HR; PR, and QRS, corresponding intervals on ECG; QRS-T angle, spatial angle between QRS and T vectors; VEB2, ventricular and AEB2, atrial ectopic beats for those who had ectopic beats during the measurements (n=28 hypertensive and 13 controls). *p<0.05 vs. baseline (time), **p<0.05 vs. hypertensive (group), no significant differences in responses between groups (time x group interaction), assessed with 2-way RANOVA and contrast tests.
5.4.2 Heart rate variability during cold exposure

Both LF and HF components of HR variability substantially increased during exposure to cold, while LF/HF ratio and HR decreased (Fig. 15) (II). HR variability increased also when analyzed in time domain, as standard deviation of RR-intervals, from 31 (22, 40) (median (Q1, Q3)) and 33 (26, 38) ms at baseline to 37 (26, 47) and 40 (32, 48) ms in the cold among hypertensives and the control group, respectively. HR variability decreased and level of HR increased (i.e. changed towards to the levels before the exposure) during the recovery period following the cold exposure, but only the LH/HF ratio reached the baseline levels during the 20-minute follow-up.

![Graphs](image)

Fig. 15. Heart rate variability. HF and LF high and low frequency; HRV, heart rate variability. * p<0.05 vs. baseline (time), assessed with 2-way RANOVA and contrast tests.
5.5 Baroreflex sensitivity and blood pressure variability in cold conditions

Cold exposure increased BRS with approx. 15%, simultaneously with increasing HR variability (Table 11, Fig. 16) (III). HF BP variability also increased while exposed to cold. These changes did not differ between hypertensives and control group.

The respiration frequency did not change in cold conditions: 0.31 ±0.08 and 0.30 ±0.10 Hz in hypertensive men, 0.26 ±0.05 and 0.24 ±0.05 Hz in the control group during the baseline and cold measurements, respectively, p =0.2 (III).

LF BP variability increased only in the control group but not among hypertensive men (Table 11, Fig. 16, interaction, p = 0.012) (III). Correspondingly, the SD of systolic BP increased in the cold only among the control group. Otherwise, we found no time x group interaction on BRS and BP variability data.

Table 11. Baroreflex sensitivity and blood pressure variability before (baseline) and during cold exposure (modified from (III), licensed under CC-BY).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n=24)</th>
<th>Controls (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Cold</td>
</tr>
<tr>
<td>LF BRS, ms/mmHg</td>
<td>(2.0, 4.2)</td>
<td>(2.5, 5.1)*</td>
</tr>
<tr>
<td>LF BPV, mmHg²</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>(19, 39)</td>
<td>(19, 51)</td>
</tr>
<tr>
<td>LF RR, ms²</td>
<td>220</td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>(130, 470)</td>
<td>(170, 590)*</td>
</tr>
<tr>
<td>SBP SD, mmHg</td>
<td>8.8</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>(8.3, 9.8)</td>
<td>(7.2, 11.3)</td>
</tr>
<tr>
<td>HF BPV, mmHg²</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(4, 9)</td>
<td>(5, 21)*</td>
</tr>
</tbody>
</table>

Values are group medians and interquartile ranges (Q1, Q3), computed over five minutes phases in the end of baseline and cold exposure. LF, low frequency; BRS, baroreflex sensitivity; BPV, (systolic) blood pressure variability; RR, RR-interval; SBP, systolic blood pressure; SD, standard deviation. *p<0.05 vs. baseline (time), *p=0.05 vs. hypertensive (group), #p<0.05 vs. (cold-baseline) difference among hypertensive (time x group interaction), assessed with 2-way RANOVA and contrast tests.
Fig. 16. Baroreflex sensitivity (BRS) modestly increased in cold conditions. *p<0.05 vs. baseline. Heart rate (middle) and blood pressure variability spectra below. Modified from III, licensed under CC-BY.
6 Discussion

The current study assessed cold-related cardiovascular responses among 51 untreated hypertensive and 32 control subjects using a population-based recruitment and applying environmental conditions similar to every-day winter circumstances in a subarctic climate. According to our results, short-term cold air exposure substantially increased central aortic and brachial BP, both in hypertensive men and in the control group. Systolic BP in control group while standing still in the cold chamber was comparable to typical BP levels during moderate to vigorous exercise (338). In those with hypertension, BP level while exposed was substantially high (I) and reached values comparable to hypertensive crisis in normal resting conditions in every fourth. We also found an association between BP responses to cold and variability of systolic BP in home measurements that was independent of the BP level (IV). The observed HR reduction in cold conditions was insufficient to compensate for the increase in BP, resulting in augmented cardiac workload (I). Cold exposure resulted in autonomic co-activation and modest changes in cardiac repolarization towards an arrhythmogenic direction (II). Consistently, frequency of ventricular ectopic beats slightly increased while exposed to cold. When it comes to short-term BP regulation during exposure to cold, we detected an increase in spontaneous BRS, reflecting cardiac vagal activity, both among hypertensive and control subjects (III). However, LF BP variability, a surrogate estimate of vascular sympathetic activity, increased only in control subjects (III).

6.1 Blood pressure, heart rate, and cardiac workload changes in cold conditions

During cold exposure, we detected an increase of systolic and diastolic BP with approx. 30 and 10 mmHg, as a group average (I, IV). The magnitude of BP response is comparable (268, 273, 308, 309, 339) or a bit higher (258, 269) than in previous studies applying corresponding exposures. Elevation in BP was detectable at the very beginning of the exposure and after 5 to 10 minutes BP did not increase, but remained on a new, higher level. After the exposure, BP slowly returned to baseline level within 15 minutes. Although BP consistently increased among all subjects, there was a large inter-individual variation in the magnitude of the responses. Of note, cold exposure increased systolic BP momentarily above 200 mmHg in one quarter of men with mild to moderate hypertension. Our study also provided
evidence that despite a decline in HR, cardiac workload is elevated during exposure to cold, both in hypertensive men and in control subjects (I, II), consistent with previous studies involving healthy middle-aged subjects (261, 275).

The acute cold-induced increase in BP is caused by the activation of the autonomic nervous system. Cooling-related sympathetic response induces vasoconstriction in peripheral and possible visceral (271) arteries and subsequently increases BP and cardiac workload (24). Facial cooling, on the other hand, elicits a vagal response through trigeminal nerve stimulation (26) and may lower HR (resembling the diving reflex), which can be beneficial for limiting cardiac workload in the cold (35).

6.2 Central hemodynamics in cold conditions

The increase in BP did not only occur when measured peripherally, but we also detected comparable increases in central aortic BP (I). It provides an estimate of BP in ascending aorta, which better reflects the BP load of central organs than the peripheral BP estimates (340). There are only few controlled studies assessing central aortic BP responses in cold conditions. Those have involved healthy subjects (27, 261, 277-280), except a study published in 2016 (310), which involved only subjects with hypertension (no controls). Our results are consistent with previous studies that reported increased central aortic BP in cold conditions, either with comparable (261), higher (277-279), or lower (310) increase than in brachial BP. The magnitude of central aortic BP elevation in cold conditions resembled our results when facial cooling was applied (277), or the subjects were middle-aged (no hypertension) (261), and was lower with mild whole-body exposure to cold (27) or with young subjects (261, 277, 279, 280), and higher among hypertensive subjects during facial cooling (310).

We detected a substantial increase of augmentation index in cold conditions (I, Table 8), consistently with other studies involving healthy subjects (27, 261, 277-280) or hypertensives without a control group (310). The elevated augmentation index was associated with an increased peak amplitude of the reflection wave (P2) compared to forward pressure peak (P1), while timing of the peak reflection (T2) lengthened in parallel with prolonged ejection duration and RR-interval. The increased augmentation index in cold conditions is due to peripheral vasoconstriction that accelerates the pressure reflection from the arterial tree towards the heart. Among our middle-aged subjects, the peak reflection mostly occurred during systole, when augmented pressure reflection elevates cardiac
workload. Our study further showed a slight decrease in subendocardial viability ratio in both test groups while exposed to cold, reflecting a decrease in the myocardial oxygen supply/demand relation (1). In contrast with our results, a previous study involving healthy young subjects did not detect changes in subendocardial viability ratio in cold conditions (278). The contradictory results likely relate to aging, because older people have a higher cardiac workload (36, 261, 275) and lower myocardial oxygen supply (36) during exposure to cold compared to young people.

6.3 Effect of hypertension to blood pressure responses

Contrary to our hypothesis, BP increases were comparable among subjects with and without hypertension (1). The hypothesis predicting an augmented BP response to cold was based on the expectation that hypertension might have led to changes in the vascular structure (e.g. stiffening of arteries) or cardiovascular function, such as sympathetic overactivity, which would aggravate the BP response during exposure to cold, as has been detected among healthy aging population (261, 262). Indeed, we detected mildly elevated baseline levels in the estimates of cardiac (II) and vascular (III) sympathetic activity among hypertensive subjects. However, a comparable augmentation index among hypertensive and controls supported unaltered arterial stiffness (I). It could be, that our subjects with mild to moderate untreated hypertension represented the early hyperkinetic state of hypertension, in which heightened sympathetic activity elevates BP before the changes in arterial structure are introduced (125-128).

We can only speculate as to the reasons for unaltered BP responses in hypertensives. Comparable arterial stiffness would be consistent with the detected comparable responses to cold exposure, and could explain the results that were contrary to our hypothesis (1). However, hypertensive group had a slightly elevated cardiac (II) and vascular (III) sympathetic activity, but neither of these caused different BP responses. It could be that the elevation in sympathetic activity was too small to cause detectable differences. Another and perhaps more likely explanation is that chronically higher sympathetic activity might not represent sympathetic responsiveness. Indeed, an inverse association between tonic sympathetic activity and vascular sympathetic responsiveness has been reported in both healthy subjects (341) and those with cardiovascular diseases (342, 343). In our study, changes in the indirect estimates of sympathetic cardiac and vascular
activity in cold conditions were comparable (II) and blunted (III), correspondingly, among hypertensive compared to control group.

Although contrary to our hypothesis, the unaltered BP responses to cold among hypertensives are consistent with a previous study by Komulainen et al. (268). They also applied cold exposure inducing substantial facial cooling but negligible trunk cooling, although their study was designed to compare the intra-individual effects of antihypertensive drugs on BP responses. Interestingly, a recent study of Greaney et al. (312) found exaggerated BP responses in hypertensive subjects during cooling with water perfusion suit, parallel with higher MSNA responses, indicating augmented sympathetic responsiveness. In another recent study by Greaney et al. (99), the BP responses during skin surface cooling tended higher in hypertensive subjects, although statistical significance was not reached. The authors speculate that the different results may relate to the applied exposures.

The few studies comparing cold-related BP responses in those with or without hypertension (99, 268, 312), including ours (I), have all involved subjects with group BP levels corresponding to high normal BP or grade I hypertension (112). The studies assessing BP responses to cold conditions among only hypertensive without a control group have neither involved subjects having untreated group BP level that corresponds to more severe stage of hypertension (268, 309, 310). Therefore, it is not known whether more severe hypertension would cause stronger alterations in BP responses, caused for example by increased arterial stiffness.

However, both comparable and higher BP responses to cold in hypertensives results to higher BP level also while exposed to cold. For example, in our study the BP level of the control group in a cold environment corresponded to BP level of hypertensive group before exposed to cold, and BP of every fourth of men with mild to moderate hypertension reach a level that in normal resting conditions would be considered a hypertensive crisis and should be treated immediately (112, 115).

### 6.4 Blood pressure responses to cold and home blood pressure variability

Irrespective of hypertension, we found those with higher daily systolic BP variability in home measurements to exhibit elevated systolic BP and therefore elevated cardiac workload responses to cold (IV). These effects were independent of BP level. This could relate to an overall higher BP reactivity, and reflect exaggerated sympathetic responsiveness, causing higher BP variability both related to experimental stress, as well as home circumstances. Instead, there was no
association between home BP variability and HR response that represents predominantly vagal activation during facial cooling. Increased arterial stiffness could also mediate the association between BP reactivity to stress and home BP variability, but the augmentation index did not contribute to the cold-related responses and baseline levels of it were comparable in the test groups, which do not support this. However, we also observed that the contribution of home BP variability to the responses was modest, explaining less than one-fifth of the variation at its best. This is probably due to multiple mechanisms (e.g., humoral and behavioral) contributing to home BP variability, in addition to sympathetic reactivity and arterial stiffness (283, 344). We also found those individuals with combination of high home BP variability and hypertension to show the highest BP levels during experimental cold stress. Perhaps those individuals should receive a special attention as a possible high-risk population for stress related exaggerated cardiovascular load.

Previous studies have found inconsistent associations between BP variability and CV reactivity to stress (287, 290, 291, 345, 346). For example, the BP response to a cold pressor test (a sympathoexcitatory stimulus) did not to associate with daytime or 24h ambulatory BP variability among young people (290, 291) but showed a modest correlation in a study involving both young and middle-aged subjects (346). Instead a strong correlation was detected between daily systolic home BP variability and cold pressor test responses among middle-aged population (287). In addition, BP level during a stress test has been found to independently associate with ambulatory BP level measured at work or during perceived stress (347-349). The observed inconsistent results may be due to lack of controlling for important determinants of 24h BP variability, such as physical activity, posture, and caffeine consumption (346, 350). Therefore, adjusting for important covariates has provided stronger associations (286).

These results highlight the importance of standardized or adjusted conditions when evaluating out-of-lab BP variability. In addition to this, differences of the results may relate to variability of applied stress tests (e.g. cold pressor test, psychological, handgrip), definition of BP variability (measurement and calculation methods), and individual characteristics (age, diseases). From a clinical perspective, home BP measurements could be considered ideal to assess daily BP variability (351), as they are easy to perform, inexpensive, and well accepted for long term monitoring by hypertensive patients. Albeit, there is some variation regarding the applied indexes (351) (e.g. morning, daily, how many days, handling
of missing values), which, however, are currently assessed to be better standardized (344, 352).

6.5 Cardiac electrical function in cold conditions

We observed modest changes in the cardiac repolarization pattern during exposure to cold (II). This included both slightly prolonged duration and elevated amplitude of the T-wave, reflecting dispersion of repolarization, (353-355). This can predispose to ventricular arrhythmias (353-355), and correspondingly, we detected higher frequency of ventricular ectopic beats in cold conditions compared to baseline or recovery phases. However, the frequency of ectopic beats was in overall low among our study population. Previous studies assessing ECG have involved intense cold exposures, such as accidental (294, 356) or therapeutic (295) hypothermia or cold water immersion (247), or applied exercise in a cold environment (357). Those have reported several ECG anomalies, such as atrial (247, 294, 295) and ventricular (247, 356, 357) arrhythmias, T-wave abnormalities (294, 358), interval prolongation (294, 356, 358), and earlier signs of cardiac ischemia in exercising cardiac patients (357). In addition, a study applying facial cooling detected changes in HR dynamics known to predispose to arrhythmias (248). We also detected lack of prolongation in the QT interval although HR was decreased. This is consistent with a previous study applying facial cold-water immersion (247), in which QT interval remained unaltered with a considerable HR reduction by 40bpm. Our study provides further evidence of a QT–HR mismatch occurring also during moderate 15 minutes cold air exposure. This overrides one of the explanations suggested previously (247) that the mismatch would be caused by a short (30s) duration of facial exposure. Generally, the ECG changes that we detected did not return to baseline levels during the 15 minutes post-exposure follow-up period. None of the cold-related ECG changes differed between the test groups. Throughout the measurements, without differences in the responses, hypertensive subjects had augmented cardiac sympathetic activity, seen as elevated HR and LF/HF-ratio of HR variability.

The observed ECG changes (II) were likely caused by altered autonomic nervous system activity while exposed to cold (247, 248). The applied exposure to cold increased both sympathetic and vagal activity, observed as increased BP (I), and augmented HR variability with decreased HR (II). Sympathetic stimulation increases T-peak to T-end interval in limb leads (354, 355) and results either inverted or positive T-wave, depending on the stimulated area (359, 360).
Sympathetic activation alone (299), and with simultaneous intense stimulation of sympathetic and vagal activity (247, 300), involves a higher risk of arrhythmias. This type of response may occur during cold-water immersion (247) or a cold face test (248). We also suggest that the detected QT-HR mismatch relates to sympathetic vagal co-activation of autonomic nervous system, in which vagal activation reduces HR and sympathetic activation causes simultaneous relative QT-shortening (247, 300, 361, 362). We did not observe full post-exposure recovery of the ECG and HR variability changes, which may be explained by the sustained lower skin temperature, the source of physiological stimulus. In addition, autonomic nervous system regulation may not anyhow recover immediately after the cessation of the stimulus. Some of the detected changes in our study likely associate with decreased HR in cold conditions, reflecting rate-dependency instead of specific autonomic nervous system activation. According to linear regression model, most of the observed change in T-wave amplitude was not explained by HR reduction. The T-peak to T-end interval probably has only a minor or no connection to HR (363). In contrast, the association between QT interval and HR is indisputable (363). The detected parallel decrease in QRS-T angle and HR is consistent with a previous study assessing rate-dependency of the parameter (364).

6.6 Spontaneous baroreflex sensitivity and beat-to-beat blood pressure variability in cold conditions

We detected increased spontaneous cardiac BRS during whole-body cold exposure, similarly in hypertensive and control subjects (III). This is consistent with previous studies assessing healthy subjects, and applying the cold face test (245, 270, 303), water perfusion suit (246, 306), and cold water immersion (304). Previous studies have estimated cardiac BRS with neck suction (303), sequence method (246, 304, 306) or transfer function gain (245, 270). In contrast to cardiac BRS, sympathetic vascular BRS increases in hypertensive and does not change in healthy individuals during skin surface cooling (312, 365). The detected increase in cardiac BRS likely results from either direct central vagal activation (245), or as central interaction of signaling from baroreceptors and thermosensitive skin receptors (246, 303). The comparable increase in hypertensive subjects could be interpreted as a sign of functional normal cardioprotective vagal activation.

We observed increased LF BP variability in control subjects during cooling (III). In contrast to our results, LF BP variability was not affected by a cold face test (245), and decreased during superficial skin cooling not without facial exposure.
in healthy subjects. LF BP variability is a surrogate measure of peripheral vascular sympathetic modulation that generally augments with sympathetic stimulus (305) and BP variability also potentiates with higher BP level (283). Our observation of augmented LF BP variability is consistent with this theory. In contrast to control subjects, hypertensive men did not show elevation in LF BP variability while exposed to cold. Comparable results were found with total beat-to-beat BP variability. The blunted response of BP variability may associate with chronically augmented level of sympathetic activity in hypertension and indicate either saturation of sympathetic vascular oscillatory activity or downregulation of sympathetic responsiveness at central or vascular level. Previously, an inverse relation between tonic activity of sympathetic vasoconstrictor nerves and vascular adrenergic responsiveness was detected in healthy people (341). In hypertensive subjects, blunted LF BP variability response has previously been observed with postural tilt test (343). In contrast, direct measurements of SSNA (99) and MSNA (312) showed exaggerated responses to superficial skin cooling without cooling of the head in hypertensive subjects.

6.7 Strengths and limitations of the study

One strength of the present study is that we recruited the participants randomly from the general population, and therefore the results reflect typical cardiovascular responses among untreated middle-aged hypertensive men. Furthermore, people with untreated hypertension, or being unaware and untreated, form significant proportion, about half of the hypertensive population (366). In addition, we applied an exposure resembling habitual wintertime exposure to cold. Furthermore, we were able to produce a strictly controlled and equal thermal exposure for all subjects. Hence, we consider that our results have public health implications due to the population-based sample and the cold exposure used, which was similar to everyday winter circumstances in a cold climate.

Our study has a number of limitations. First, while minimizing the exclusion criteria, we allowed our study subjects to have some other chronic diseases in addition to hypertension. However, we conducted sensitivity analyses by excluding the subjects having additional chronic disease, such as diabetes, and did not detect any effects on the main findings. Second, performing a randomized trial, including control measurement visit without exposure to cold, would have reduced possible bias associating with the anticipation caused by the experiment. However, we familiarized all participants to the protocol and facilities beforehand to reduce the
stress caused by the measurements. Third, our study subjects were middle-aged Caucasian men with BP level between optimal and untreated moderate hypertension, and the results may well differ from other populations, such as women or elderly or people with other cardiovascular diseases.
7 Conclusions

The present study assessed how hypertension modifies cardiovascular responses to cold conditions by an experimental setup. We applied a population-based sample and identified hypertension by home BP measurements, representing a large population of middle-aged men with untreated hypertension. The chosen controlled exposure simulated habitual winter circumstances in subarctic areas, which people repeatedly confront during the cold season in their occupational and leisure time activities.

Exposure to moderate cold induced a substantial increase in brachial BP among men with and without untreated hypertension. The BP elevation occurred similarly at the level of the aorta, therefore posing strain to the central parts of the body. Among those with hypertension, the achieved BP level during exposure to cold was considerable, and reached in every fourth values of a hypertensive crisis in normal resting conditions. The considerably high BP level could act as a trigger for adverse cardio- or cerebrovascular events, especially in people with predisposing conditions, and may therefore contribute to the excess winter mortality and morbidity observed in epidemiological studies.

Our study also provided evidence that despite of a decline in HR, cardiac workload elevates during exposure to cold in middle-aged men, independent of hypertension. Cardiac repolarization changed towards an arrhythmogenic direction and frequency of ventricular ectopic beats slightly increased while exposed to cold. In addition, our results suggest preserved cardiac vagal activation (spontaneous BRS) but blunted sympathetic vascular activation (LF BP variability) in cold conditions among subjects with mild to moderate hypertension.

We further detected a direct association between home BP variability and BP responses to cold, independent of BP level. Therefore, the highest BP level in cold conditions was among those hypertensives with higher home BP variability. These results support the recent epidemiological findings on the level-independent significance of BP variability. Perhaps we should continue assessing the combined effects of BP level and variability, as they could provide a more meaningful risk indicator than either one alone.

Further research should be done involving those with severe hypertension, cardiac diseases, or co-morbidities, such as diabetes. Severe hypertension may amplify BP responses, or cardiac disease may exaggerate the observed changes in cardiac repolarization and arrhythmias, and diabetes, involving various neural complications, could further modify cardiovascular responses to cold exposure.
Detailing research is still needed to reveal cold-related cardiovascular pathophysiological mechanisms. Cardiovascular diseases may modify cold-related autonomic nervous control and end-organ responsiveness in different levels and e.g. central sympathetic activation, endothelial responses, or mechanical effects of stiffer arteries in cold conditions would be of interest to study. Research linking the epidemiological and experimental research is urgently needed to determine, amongst other things, whether and to what extent exaggerated or blunted responses to temperature exposure associate with cold-related morbidity and mortality. If such an association is found, it would be appealing to investigate the possibility of identifying those who are at risk from the clinically available BP variability indexes. Interesting would be also to study combined cardiovascular effects of physical activities and cold temperature, both known to independently increase cardiovascular load, by experiments in climatic chambers or by ambulatory measures during daily activities, and in different populations, such as cold workers, with or without chronic diseases. In addition, as medication reduces risk of temperature related sudden cardiac death, effects of those medications to acute cardiovascular responses in cardiac disease patients would be of interest.

Our results are important to hypertensive people and health care personnel treating them. Individuals can protect themselves by limiting exposure to cold by e.g. proper winter clothing that covers head and peripheries, and therefore reduce the effects of a cold environment. For health care personnel, our findings highlight the importance of year round BP control: the lower the BP is before entering outdoors, the lower it remains during occupational or leisure time activities in a cold environment. In addition, adjustments of antihypertensive medication taking account the season in order to avoid high BP in winter and overmedication in summer should be considered.

Globally, over a billion adults suffer from hypertension. High BP is the largest contributor to disability-adjusted life years, and cardiovascular diseases are the leading cause of death. Burden of hypertension and its comorbidities are projected to further increase due to population growth and aging. Global estimates suggest that nearly 7% of mortality is attributable to moderately cold temperature, mainly for cardiovascular and respiratory causes. In future, climate change is expected to cause larger variance in temperatures, with more common weather extremes, which makes it more difficult for individuals to protect themselves from cold environments. Understanding of cold-related cardiovascular mechanisms is needed as part of research aimed at reducing cold-related health burden.
List of references


320. Validated BP Monitors for Home Use [cited Mar 12, 2018].


### Table 12. Examples of studies assessing effects of cold temperature on blood pressure experimentally in humans.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cold exposure</th>
<th>Subjects, n</th>
<th>F/M</th>
<th>Age, years</th>
<th>BMI</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>HR, bmp</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole body cold air exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Arjamaa et al. 1999 (273)</td>
<td>-15°C, wind of 3.5m/s, 15min, three-layer winter clothing, vs. 18°C baseline.</td>
<td>12, exposed with and without sodium load</td>
<td>0/12</td>
<td>22-57</td>
<td>24</td>
<td>Δ ca. 25 (from 125),</td>
<td>Δ12±3, (from ca. 80)</td>
<td>na</td>
<td>Sodium load increased diastolic but not systolic BP responses.</td>
</tr>
<tr>
<td>Arjamaa et al. 2001 (339)</td>
<td>-15°C, wind of 3.5m/s, 15min, three-layer winter clothing, vs. 18°C baseline.</td>
<td>3/5</td>
<td>22-26</td>
<td>21</td>
<td>Δ ca. 20 (from ca. 125),</td>
<td>Δ18±4, (sodium loaded)</td>
<td>na</td>
<td>Sodium load did not alter BP responses.</td>
<td></td>
</tr>
<tr>
<td>Collins et al. 1985 (367)</td>
<td>6°C (A), 12°C (B) and 15°C (C) vs. 23°C, no wind, 2h, 1.5 clo, Later 6°C, 4h/day for 7-10 days.</td>
<td>4 younger, 5 older</td>
<td>18-24</td>
<td>63-70</td>
<td>1.25</td>
<td>Δ14±6, young (A)</td>
<td>Δ7±3, young (A)</td>
<td>Decresed Older had exaggerated but slower BP responses to cold.</td>
<td></td>
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<tr>
<td>Collins et al. 1995 (368)</td>
<td>6°C, 6h, 1.3 clo vs. baseline. Sedentary.</td>
<td>11 young, 11 older</td>
<td>0/11</td>
<td>20-31</td>
<td>61-71</td>
<td>Δ15±8&lt;</td>
<td>Δ31±15</td>
<td>na</td>
<td>Older had exaggerated BP responses.</td>
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133
<table>
<thead>
<tr>
<th>Author</th>
<th>Cold exposure</th>
<th>Subjects, n</th>
<th>F/M</th>
<th>Age, years</th>
<th>BMI</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>HR, bmp</th>
<th>Conclusions</th>
</tr>
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<tr>
<td>Gavhed et al. 2000</td>
<td>-10°C, wind of 0, 1, or 5m/s, 30min, cold protective clothing, standing. Pre-conditioning with 1h -5°C or 20°C, seated. Vs. baseline.</td>
<td>8</td>
<td>0/8</td>
<td>24±2</td>
<td>23±3</td>
<td>∆ 8±6 (prec., -5°C)</td>
<td>∆ 6±6 (prec., -5°C)</td>
<td></td>
<td>Decrease in the wind speed of 5m/s resulted in the larger SBP increase than no wind.</td>
</tr>
<tr>
<td>Inoue et al. 1992</td>
<td>17°C in summer (A) and winter (B) and 12°C in winter, wearing swimming trunks, 60 min. Seated. Vs. 28°C baseline.</td>
<td>9 young</td>
<td>0/9</td>
<td>20-25</td>
<td>22</td>
<td>∆ ca. 10 (from 120, A and C)</td>
<td>∆ ca. 10 (from 80, A and C)</td>
<td></td>
<td>Decrease BP increased more with 12°C than 17°C among older, but not young.</td>
</tr>
<tr>
<td>Keatinge et al. 1984</td>
<td>24°C with 10 m/s wind (cooling) vs. without wind, 6h, light clothing. Recumbent.</td>
<td>8</td>
<td>0/4</td>
<td>18-25</td>
<td>~22</td>
<td>∆12 (from ca. 125) with wind</td>
<td>∆18 (from ca. 70) with wind</td>
<td></td>
<td>Lower with wind. Wind increased BP and decreased HR compared to no wind.</td>
</tr>
<tr>
<td>Kingma et al. 2011</td>
<td>Baseline 30°C, 30min, vs. mild cold, 20°C, 1h, and recovery 34°C for 1h and 30°C 1h, underwear.</td>
<td>12 young</td>
<td>0/12</td>
<td>18-31</td>
<td>23±1</td>
<td>∆ ca. 5 (from ca. 120), young</td>
<td>na</td>
<td></td>
<td>∆3±1% Systolic BP increase was greater among elderly.</td>
</tr>
<tr>
<td></td>
<td>and recovery 34°C for 1h and 30°C 1h, elderly</td>
<td>12 elderly</td>
<td>0/12</td>
<td>66-78</td>
<td>26±1</td>
<td>∆ ca. 20 (from ca. 140), elderly</td>
<td>∆7±2% elderly</td>
<td></td>
<td>Elevation in SBP negatively related to cold-induced thermogenesis and in elderly to fat percentage.</td>
</tr>
<tr>
<td>Author</td>
<td>Cold exposure</td>
<td>Subjects, n</td>
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<tr>
<td>Kuo et al. 2014 (369)</td>
<td>16°C vs. 23°C, 55-60% RH, 24h, same clothes and blanket at night</td>
<td>12</td>
<td>0/12</td>
<td>24±1</td>
<td>22±1</td>
<td>Ns difference, 119±3 mmHg in 23°C and 123±2 mmHg in cold</td>
<td>Higher in cold (80±2 mmHg) than in 23°C (75±3 mmHg)</td>
<td>Ns difference,</td>
<td>Cold exposure elevated morning BP surge and caused late sleep stage sympathetic activation.</td>
</tr>
<tr>
<td>Li et al. 2009 (266)</td>
<td>-5°C, 15min, 4 exposures with different winter clothing ensembles</td>
<td>16 young</td>
<td>16/8</td>
<td>18-34</td>
<td>35-51</td>
<td>22±3 (all)</td>
<td>Δ ca. 10 (from ca. 114)</td>
<td>Returned to the baseline level in 25min post-exp.</td>
<td>Wearing a hat reduced BP responses to cold and promoted faster BP recovery.</td>
</tr>
<tr>
<td>Pettit et al. 1999 (370)</td>
<td>5°C, 43% RH, 2h, light clothing, mittens in cold, vs. 23°C baseline. Seated.</td>
<td>17, similar</td>
<td>9/8</td>
<td>24±3</td>
<td>26±3</td>
<td>∆ ca. 10 (from ca. 119)</td>
<td>∆ ca. 6 (from ca. 76)</td>
<td>Mean BP: Na change (Δ&lt;10)</td>
<td>CV responses to cold exposure did not differ between genders.</td>
</tr>
<tr>
<td>Raven et al. 1970 (293)</td>
<td>5°C, RH 70%, wearing shorts, wind &lt;4m/min, 1 or 2 exposures, vs. 28°C baseline with RH 45%. Recumbent.</td>
<td>11 men, unacclimatized</td>
<td>0/11</td>
<td>na</td>
<td>23±2</td>
<td>∆ ca. 22 (from 119±10)</td>
<td>∆ ca. 14 (from 76±10)</td>
<td>Ns</td>
<td>CV changes from baseline were largest at the end of the 2h exposure.</td>
</tr>
<tr>
<td>Reed 1991 et al. (371)</td>
<td>4°C, 30min, light clothing, vs. 25°C baseline and recovery</td>
<td>12, treated with placebo and propranolol</td>
<td>0/12</td>
<td>28±2</td>
<td>na</td>
<td>Mean BP: Δ13±3 (placebo) ∆18±2 (propranolol)</td>
<td>na</td>
<td>No change.</td>
<td>Propranolol failed to lower BP increase caused by cold exposure.</td>
</tr>
<tr>
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<tr>
<td>Saeki et al.</td>
<td>Weak room heating (A) (&lt;12°C, n=76), 11h, over night, vs. (randomized)</td>
<td>146/102</td>
<td>44/102</td>
<td>18-60</td>
<td></td>
<td>Morning: 121±15</td>
<td>Morning: 78±11</td>
<td>na</td>
<td>Intensive room heating decreased morning BP and the morning BP surge.</td>
</tr>
<tr>
<td></td>
<td>intensive room heating (B) (22°C, n=70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(A) &gt; 114±12 (B),</td>
<td>(A) &gt; 72±9 (B),</td>
<td></td>
<td>Evening BP was higher, but not after going to bed at night.</td>
</tr>
<tr>
<td>Wagner &amp;</td>
<td>Young vs. (randomized) 28°C, 2h</td>
<td>10/7</td>
<td>20-30</td>
<td>~22</td>
<td></td>
<td>∆ ns, young</td>
<td>∆ ca. max. 5, young</td>
<td>∆ ca. -5</td>
<td>Systolic BP increased in older but not younger subjects.</td>
</tr>
<tr>
<td>Hovarth 1985</td>
<td>RH 40, 2h, wearing swimsuits, Semi-reclining.</td>
<td>10/7</td>
<td>51-72</td>
<td>~25</td>
<td></td>
<td>∆ ca. max. 10,</td>
<td>∆ ca. max. 5, older</td>
<td></td>
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</tr>
<tr>
<td>Allen et al.</td>
<td>Forehead cooling (A), cooling of most of the face with ice bag (B), hand</td>
<td>18/18</td>
<td>18-22</td>
<td>~23</td>
<td></td>
<td>A and B, no effect</td>
<td>A and B, no effect</td>
<td></td>
<td>Hand CPT produces different BP and HR responses than cooling of face.</td>
</tr>
<tr>
<td></td>
<td>immersion (C), 90s each, paced breathing, seated.</td>
<td></td>
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<td></td>
<td>C ∆ ca. 15 (from</td>
<td>C ∆ ca. 14 (from</td>
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<td></td>
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<td></td>
<td></td>
<td>123±10)</td>
<td>67±10)</td>
<td></td>
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<tr>
<td>Hiramatsu et</td>
<td>4°C, 1h, winter (n=8) or summer (n=5)</td>
<td>19/34</td>
<td>young</td>
<td>na</td>
<td></td>
<td>∆ 31 (from 113±4),</td>
<td>A. Comparable</td>
<td></td>
<td>BP increased when wearing summer but not when wearing winter clothes. Hand CPT</td>
</tr>
<tr>
<td>al 1984</td>
<td>clothing (A) seated, and hand immersion (n=6), 0°C water, 10min, recumbent</td>
<td></td>
<td></td>
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<td></td>
<td>responses, B</td>
<td>responses, B</td>
<td></td>
<td>induced comparable BP increases.</td>
</tr>
<tr>
<td>(252)</td>
<td>(B) vs. 22°C baseline.</td>
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<tr>
<td>Kelsey et al. 2000</td>
<td>8-10°C, 10 min (A), and 3 min cold face test, 3-4°C (B), vs. 22°C baseline.</td>
<td>116,</td>
<td>65/1</td>
<td>15</td>
<td>21</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>CV responses to cold face test and whole-body cold air exposure correlated (r=0.15 for mean BP)</td>
</tr>
<tr>
<td>Korhonen 2006</td>
<td>10°C, 2h, wearing shorts, seated (A) and immersion of hands (B) and feet (C) to 2°C ice-water, 1min, recumbent, vs. 28°C baseline</td>
<td>20</td>
<td>0/20</td>
<td>25±3</td>
<td>~25</td>
<td>Δ 19 (from 126), A</td>
<td>Δ 17 (from 83), A</td>
<td>Δ -13, A</td>
<td>Rate of changes in BP during CPT and whole-body cold air exposure did not correlate. CPT but not cold air exposure caused pain sensation.</td>
</tr>
<tr>
<td>Tähtinen et al. 1999</td>
<td>5°C, 45 min (A), and hand immersion to 10°C water, 5min (B), vs. 28°C baseline.</td>
<td>14</td>
<td>0/14</td>
<td>23±3</td>
<td>23±2</td>
<td>Δ15 mean and Δ28 peak (from 120), A</td>
<td>Δ12 mean and Δ21 peak (from 76), A</td>
<td>Δ -6</td>
<td>Amlodipine decreased BP levels, but had no effect on the cold-induced rise of blood pressure.</td>
</tr>
<tr>
<td>Facial cooling</td>
<td>Cold (6-9°C) water bag applied on the forehead for 4 min, vs. baseline. Seated.</td>
<td>22/0</td>
<td>19</td>
<td>na</td>
<td>108±9</td>
<td>Δ ca. 6 (from 70±8)</td>
<td>Δ ca. 4 (from 70±8)</td>
<td>Δ ca. -3</td>
<td>Amlodipine decreased BP levels, but had no effect on the cold-induced rise of blood pressure.</td>
</tr>
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<tr>
<td>Muller et al.</td>
<td>1°C ice bag applied on forehead for 60s, vs. baseline. Recumbent.</td>
<td>17 young</td>
<td>8/9</td>
<td>na</td>
<td>13 older</td>
<td>66±2</td>
<td>Δ ca. 6 (from 60±1)</td>
<td>Δ ca. -3, in young and older</td>
<td>Systolic and diastolic BP responses did not significantly differ between young and older. Propranolol did not blunt BP response to cooling.</td>
</tr>
<tr>
<td>Pretorius et al.</td>
<td>Dorsal (A), facial (B), and whole-head (C) immersion in 17°C water, 60 min, vs. baseline. Supine and prone posture.</td>
<td>7</td>
<td>0/7</td>
<td>30±3</td>
<td>0/7</td>
<td>na</td>
<td>Δ ca. 4, (from 95), A</td>
<td>No change</td>
<td>Whole-head immersion elicited higher rate of vasoconstriction.</td>
</tr>
<tr>
<td>Reyners et al.</td>
<td>Ice-water filled bag with wet surface on face, individually varying durations (range 4-242s), vs. baseline. Recumbent.</td>
<td>6 to 11</td>
<td>6/8</td>
<td>21-45</td>
<td>24-45</td>
<td>na</td>
<td>Δ between 20 and 26 for different exposures</td>
<td>Δ between 1 to 18 for different exposures</td>
<td>Weaning goggles and varying bag masses did not alter the responses. Apnea tended to pronounced HR reduction, but neither this altered BP responses.</td>
</tr>
<tr>
<td>Schlader et al.</td>
<td>A bag of ice (n=10) and control water (n=10) (0 and 34°C) placed over cheeks, eyes, and forehead, 15min, vs. baseline. Recumbent.</td>
<td>10, cooling</td>
<td>3/7</td>
<td>22±2</td>
<td>10, control</td>
<td>6/4</td>
<td>26±4</td>
<td>Δ ca. 23 (from 116±11)</td>
<td>Δ ca. 15 (from 64±7)</td>
</tr>
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<td>Walsh et al. 1995 (379)</td>
<td>Cool (4°C) or control (22°C) stream of air at 5 m/s−1 on face, rest (and exercise), vs. baseline.</td>
<td>9</td>
<td>0/9</td>
<td>na</td>
<td>24-41</td>
<td>Ns change during cooling</td>
<td>Δ ca. 3 (from 86±3)</td>
<td>No change</td>
<td>Only rest values commented on here.</td>
</tr>
<tr>
<td>Gao et al. 2012 (36)</td>
<td>Water T 15-18°C, 20 min. Recumbent. Water T 15°C, 20 min vs. 35°C baseline, 6 min. Recumbent. Cooling to lower mean Tsk to 30.5°C, 30 min, rest (and handgrip), vs. baseline (Tsk 34°C)</td>
<td>10 young 12 older</td>
<td>2/8 5/7</td>
<td>18-35 23±1 60±2</td>
<td>22±1 20±1</td>
<td>Δ ca. 7 (from 115±2) &lt;Δ 14±2 (from 122±3)</td>
<td>Δ ca. 6 (from 65±1) 6± (from 76±2)</td>
<td>No No</td>
<td>Δ ca. 5 (from 73±3) Δ 7±1 (from 72±2) No 6± (from 76±2)</td>
</tr>
<tr>
<td>Greaney et al. 2014 (262)</td>
<td>11 young 12 older</td>
<td>2/8 5/7</td>
<td>18-35 23±1 60±2</td>
<td>22±1 20±1</td>
<td>Δ ca. 7 (from 115±2) &lt;Δ 14±2 (from 122±3)</td>
<td>Δ ca. 6 (from 65±1) 6± (from 76±2)</td>
<td>No No</td>
<td>Δ ca. 5 (from 73±3) Δ 7±1 (from 72±2) No 6± (from 76±2)</td>
<td>Systolic BP and sympathetic activity responses to cooling were higher in older. Only rest values commented here.</td>
</tr>
<tr>
<td>Hess et al. 2009 (261)</td>
<td>15-18°C water, 20min, vs. (randomized) 35°C water, 20min. Recumbent.</td>
<td>12 young 12 older</td>
<td>6/6 6/6</td>
<td>18-35 22±1 55-75 25±1</td>
<td>10 25, 105</td>
<td>Δ ca. 10 (from ca. 60)</td>
<td>Δ ca. 8, cold</td>
<td>No No</td>
<td>Δ ca. 8, cold</td>
</tr>
<tr>
<td>Wilson et al. 2007 (271)</td>
<td>Water T 15°C, 20 min vs. 35°C baseline.</td>
<td>14</td>
<td>8/6</td>
<td>22-35 ~22.5</td>
<td>Δ ca. 15 (from ca. 10)</td>
<td>Δ ca. 10 (from ca. 60)</td>
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<tr>
<td>Wilson et al. 2010 (275)</td>
<td>Water T 15°C, 20 min (n=22) vs. 35°C control trial (n=10), baseline 35°C. Recumbent.</td>
<td>11 young</td>
<td>3/8</td>
<td>20-34</td>
<td>23±1</td>
<td>∆ ca. 5 (from ca. 115)</td>
<td>∆ ca. 5</td>
<td>Na.</td>
<td>Increases in systolic BP were greater in older. Cooling increased rate-pressure product only in older.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 older</td>
<td>3/8</td>
<td>58-76</td>
<td>25±1</td>
<td>&lt; ∆ ca. 20 (from ca. 130)</td>
<td>∆ ca. 5</td>
<td>Decreased</td>
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Other types of cold exposure

<table>
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<tr>
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<th>Subjects, n</th>
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<tbody>
<tr>
<td>Frank et al. 2003 (380)</td>
<td>Intravenous cold (4°C) 11, with (A) saline (hypothermia) and without vs. warm (37°C) saline (control) propranolol</td>
<td>0/11</td>
<td>29±2</td>
<td>24</td>
<td>∆ ca. 25, B</td>
<td>na</td>
<td>∆ ca. 10, A</td>
<td>na</td>
<td>∆ ca. 20, B, no change, A Propranolol attenuated increase in systolic BP and prevented the increase in HR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>29±2</td>
<td>24</td>
<td>∆ ca. 10, A</td>
<td>(from baseline)</td>
<td>∆ cold &gt; ∆ control</td>
<td>A</td>
<td>Only rest values commented here.</td>
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<tr>
<td>Muller et al. 2011 (265)</td>
<td>Breathing cold (&lt;0°C) (A) or room T (B) air, 5 min, vs. baseline. Rest (and handgrip). Recumbent.</td>
<td>5/5</td>
<td>25±1</td>
<td>24</td>
<td>No change, A, B</td>
<td>No change, A, B</td>
<td>∆ &lt;5, A</td>
<td>No change, A, B Breathing cold air caused higher rate-pressure product.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>10</td>
<td>5/5</td>
<td>24</td>
<td>No change, A, B</td>
<td>No change, A, B</td>
<td>∆ &lt;5, A, B No change, A, B</td>
<td>Only rest values commented here.</td>
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<tr>
<td>Sramek et al. 2000 (263)</td>
<td>1h head-out immersions in 32°C (A), 20°C (B) and 14°C (C) water, swimming trunks, vs. baseline. Seated.</td>
<td>10</td>
<td>0/10</td>
<td>na</td>
<td>∆ -12, A</td>
<td>∆ -8, A</td>
<td>∆ -9, A</td>
<td>Thermoneutral water immersion reduced and cold water immersion increased BP and HR.</td>
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<tr>
<td></td>
<td></td>
<td>22±2</td>
<td>0/10</td>
<td>na</td>
<td>∆ -12, A</td>
<td>∆ -8, A</td>
<td>∆ -9, A</td>
<td>∆ -8, C</td>
<td>Thermoneutral water immersion reduced and cold water immersion increased BP and HR.</td>
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Systolic BP: ∆ ca. 5 (from ca. 115)  Diastolic BP: ∆ ca. 20 (from ca. 130)
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<th>F/M</th>
<th>Age, years</th>
<th>BMI</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>HR, bmp</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westerlund et al. 2004 (264)</td>
<td>Whole-body cryotherapy, A) -10°C, B) -60°C, and C) -110°C, 2min, wearing a bathing suit, surgical mask, cap, gloves, socks and shoes</td>
<td>22 (+cold swimming)</td>
<td>12/10</td>
<td>38±3</td>
<td>24±3</td>
<td>Δ14 (from 130±11), A</td>
<td>Δ3 (from 81±7), B</td>
<td>na</td>
<td>All exposures increased diastolic and systolic BP.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (cryotherapy only)</td>
<td>10/0</td>
<td>40±12</td>
<td>24±3</td>
<td>Δ15 (from 129±12), B</td>
<td>Δ5 (from 81±9), C</td>
<td></td>
<td>Systolic BP increased more with -110°C than with other exposures.</td>
</tr>
</tbody>
</table>

Blood pressure (BP) and heart rate (HR) responses to cold (Δ) or levels with different exposures (mean±standard deviation) presented. ~, BMI estimated approx. from reported weight and height. F, females; M, males, BMI, body mass index; RH, relative humidity; ns, non-significant; CV, cardiovascular; CPT, cold pressor test (immersion of hand or foot to ice water).
### Appendix 2

Table 13. Summary of regression analysis for variables explaining variation in rate-pressure product and systolic blood pressure changes while exposed to cold (IV).

<table>
<thead>
<tr>
<th>Variables</th>
<th>RPP, model 1 (n=74)</th>
<th>RPP, model 2 (n=74)</th>
<th>RPP, model 3 (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$</td>
<td>$SE$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>HBPV</td>
<td>170</td>
<td>60</td>
<td>0.33**</td>
</tr>
<tr>
<td>Fat %</td>
<td>40</td>
<td>20</td>
<td>0.18</td>
</tr>
<tr>
<td>HSBP</td>
<td>0</td>
<td>10</td>
<td>0.06</td>
</tr>
<tr>
<td>Age</td>
<td>-10</td>
<td>50</td>
<td>-0.01</td>
</tr>
<tr>
<td>AI</td>
<td>0</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>-160</td>
<td>300</td>
<td>-0.07</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.109</td>
<td></td>
<td>0.111</td>
</tr>
<tr>
<td>$F$</td>
<td>8.76**</td>
<td></td>
<td>4.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>SBP, model 1 (n=74)</th>
<th>SBP, model 2 (n=74)</th>
<th>SBP, model 3 (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$</td>
<td>$SE$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>HBPV</td>
<td>1.8</td>
<td>0.5</td>
<td>0.38**</td>
</tr>
<tr>
<td>Fat %</td>
<td>0.4</td>
<td>0.2</td>
<td>0.20*</td>
</tr>
<tr>
<td>HSBP</td>
<td>-0.1</td>
<td>0.1</td>
<td>-0.07</td>
</tr>
<tr>
<td>Age</td>
<td>-0.5</td>
<td>0.4</td>
<td>-0.13</td>
</tr>
<tr>
<td>AI</td>
<td>0.1</td>
<td>0.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking</td>
<td>-3.8</td>
<td>2.7</td>
<td>-0.17</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.143</td>
<td></td>
<td>0.148</td>
</tr>
<tr>
<td>$F$</td>
<td>11.97**</td>
<td></td>
<td>5.23**</td>
</tr>
</tbody>
</table>

Crude $R^2$ for one explanatory variable and adjusted $R^2$ for models including more explanatory variables. RPP, rate-pressure product; HBPV, daily systolic home blood pressure variability; HSBP, systolic blood pressure at home; AI, augmentation index; $F$, $F$ for change in $R^2$; SBP, systolic blood pressure. *$p<.05$, **$p<.01$ for contribution.
Original publications


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Original publications are not included in the electronic version of the dissertation.
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1459</td>
<td>Molecular and functional characterization of ABRAXAS and PALB2 genes in hereditary breast cancer predisposition</td>
<td>Bose, Muthiah (2018)</td>
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<tr>
<td>1461</td>
<td>Genetic susceptibility to childhood bronchiolitis</td>
<td>Pasanen, Anu (2018)</td>
</tr>
<tr>
<td>1462</td>
<td>Family history of mental disorders and long-term outcome in schizophrenia</td>
<td>Käkelä, Juha (2018)</td>
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<tr>
<td>1463</td>
<td>Role of Wnt1I in kidney ontogenesis and development of renal organoid based models to identify candidate oncogenes</td>
<td>Xu, Qi (2018)</td>
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<tr>
<td>1464</td>
<td>Making sense of hospital change project actuality</td>
<td>Lunkka, Nina (2018)</td>
</tr>
<tr>
<td>1465</td>
<td>Association of glucose metabolism, physical activity and fitness with peripheral nervous system function in overweight people</td>
<td>Isojärvi, Henri (2018)</td>
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<tr>
<td>1467</td>
<td>Preterm birth and parental and pregnancy related factors in association with physical activity and fitness in adolescence and young adulthood</td>
<td>Tikkanmäki, Marjaana (2018)</td>
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<td>1468</td>
<td>Work-related rehabilitation for strengthening working careers: a multiperspective and mixed methods study of its mechanisms</td>
<td>Juovinen-Posti, Pirjo (2018)</td>
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<tr>
<td>1469</td>
<td>Vitamin D status and its association with leukocyte telomere length, obesity and inflammation in young adults: a Northern Finland Birth Cohort 1966 study</td>
<td>Palaniswamy, Saranya (2018)</td>
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<td>1470</td>
<td>Biological prognostic and predictive markers in Hodgkin lymphoma</td>
<td>Bur, Hamid (2018)</td>
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<td>1471</td>
<td>Preconditioning against ischemic injury of the central nervous system in aortic surgery: an experimental study in a porcine model with remote ischemic preconditioning and diazoxide</td>
<td>Haapanen, Henri (2018)</td>
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<tr>
<td>1472</td>
<td>Genetic background and antenatal risk factors of bronchopulmonary dysplasia</td>
<td>Mahlman, Mari (2018)</td>
</tr>
<tr>
<td>1473</td>
<td>Etiology and outcome of PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome among patients operated with tonsillectomy in childhood</td>
<td>Lantto, Ulla (2018)</td>
</tr>
</tbody>
</table>

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CARDIOVASCULAR RESPONSES TO COLD EXPOSURE IN UNTREATED HYPERTENSION

Heidi Hintsala