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Silja Komulainen

EFFECT OF ANTIHYPERTENSIVE DRUGS ON BLOOD PRESSURE DURING EXPOSURE TO COLD

EXPERIMENTAL STUDY IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

FACULTY OF MEDICINE,
DEPARTMENT OF PUBLIC HEALTH SCIENCE AND GENERAL PRACTICE,
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EFFECT OF ANTIHYPERTENSIVE DRUGS ON BLOOD PRESSURE DURING EXPOSURE TO COLD

Experimental study in normotensive and hypertensive subjects

Academic dissertation to be presented, with the assent of the Faculty of Medicine of the University of Oulu, for public defence in the Auditorium of Kastelli Research Centre (Aapistie 1), on November 9th, 2007, at 12 noon

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Abstract

The aim of the present study was to describe the effects of different types of cold exposures on blood pressure (BP) and heart rate (HR) and to test how these cold-induced effects are modulated by antihypertensive drugs representing different kind of mechanisms of action. The tested drugs represented the following antihypertensive drug subgroups: metoprolol from beta-blocking agents, carvedilol from alfa- and beta-blocking agents, lisinopril from angiotensin converting enzyme inhibitors, eprosartan from angiotensin II antagonists, amlodipine from calcium channel blockers and hydrochlorothiazide from diuretics. The main outcome measures were the levels and changes in systolic (SBP) and diastolic blood pressure (DBP) and HR before, during and after cold exposure.

The normotensive and mildly hypertensive subjects were exposed either to –15°C for 15 minutes (with winter clothing), 5°C for 45 minutes (minimal clothing) or to a cold pressor test (CPT). Before measurements at –15°C, metoprolol, carvedilol, lisinopril, eprosartan, hydrochlorothiazide or placebo were given for a week in a double-blind and crossover manner. In one test procedure (5°C and CPT) the test subjects ingested amlodipine for three days or were without drug ingestion before the tests in a crossover manner.

Both SBP and DBP were markedly increased by all types of cold exposure. Cold-induced rises of SBP/DBP were higher during the exposure to 5°C and –15°C (19–35/20–24 mmHg) than during CPT (13/16 mmHg). Metoprolol, carvedilol, lisinopril, eprosartan and amlodipine decreased the level of BP during the exposure to 5°C and –15°C compared to placebo or no drug. The antihypertensive drugs, with dosages used in this study, did not affect the cold-induced rise of BP compared to no drug or placebo. HR increased during CPT, but decreased during exposure to 5°C and –15°C. Metoprolol and carvedilol decreased HR during exposure to –15°C compared to placebo.

The present study demonstrates for the first time the effects of antihypertensive drugs on BP in hypertensive subjects exposed to cold similar to normal outdoor exposure in winter. Although the magnitude of the cold-induced rise in BP was not affected by the drugs, the drug-induced decrease in the level of BP kept the peak values in the cold closer to the recommended threshold limit values.

Keywords: antihypertensive drugs, blood pressure, cold pressor test, heart rate, whole body cold exposure

Komulainen, Silja, Verenpainelääkkeiden vaikutus verenpaineeseen kylmässä. Kokeellinen tutkimus normo- ja hypertensiivisillä henkilöillä
Lääketieteellinen tiedekunta, Kansanterveystieteen ja yleislääketieteen laitos, Fysiologian laitos, Oulun yliopisto, PL 5000, 90014 Oulun yliopisto; Oulun aluetyöterveyslaitos, Aapistie 1, 90220 Oulu; Oulun Työterveys, PL 36, 90015 Oulun kaupunki; Yleislääketieteen yksikkö, Oulun yliopistollinen sairaala, PL 22, 90029 OYS
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Tiivistelmä

Tutkimuksen tarkoituksena oli selvittää eri mekanismeilla vaikuttavien verenpainelääkkeiden vaikutusta verenpainevasteisiin ja sydämen lyöntitiheyteen kylmässä sekä verrata erilaisten kylmäaltistusten vaikutusta verenpaineeseen ja sydämen lyöntitiheyteen. Tutkitut lääkkeet edustivat seuraavia verenpainelääkeryhmiä: metoprololi beetasalpaajia, karvediloli yhdistettyjä alfa- ja beetasalpaajia, lisinopriili ACE-estäjiä, eprosartaani angiotensiini II antagonisteja, amlodipiini kalsiumestäjiä ja hydroklooritiatsidi diureetteja. Tärkeimmät mitatut vasteet olivat systolisen ja diastolisen verenpaineen ja sydämen lyöntitiheyden tasot ja muutokset ennen kylmäaltistusta, kylmäaltistuksen aikana ja sen jälkeen. Lisäksi mitattiin lämpötilavasteita ja tuntemuksia.

Normo- ja hypertensiiviset koehenkilöt altistettiin joko –15°C:seen 15 minuutin ajaksi (talvivaatetuksessa), 5°C:seen 45 minuutin ajaksi (minimaalisella vaatetuksella) tai tehtiin ns. käden kylmävesitesti (CPT). Testisarjoissa (–15°C) metoprololi, karvediloli, lisinopriili, eprosartaani ja hydroklooritiatsidi tai plasebo annettiin viikon ajan kaksoissokko- ja vaihtovuoromenetelmällä. Yhdessä testisarjassa (5°C ja CPT) koehenkilöt ottivat amlodipiinia 3 päivän ajan tai olivat ilman lääkettä ennen testikertoja vaihtovuoroisessa järjestyksessä.

Kaikki kylmäaltistustyypit nostivat merkittävästi sekä systolista että diastolista verenpainetta. Systolisen ja diastolisen verenpaineen nousu oli korkeampi koko kehon kylmäaltistuksissa (5°C tai –15°C) (19–35/20–24 mmHg) kuin ns. kylmävesitestissä (13/16 mmHg). Metoprololi, karvediloli, lisinopriili, eprosartaani ja amlodipiini laskivat verenpaineen tasoja koko kehon kylmäaltistuksessa verrattuna plaseboon. Yksikään verenpainelääkkeistä ei vaikuttanut merkittävästi kylmän aiheuttamaan verenpaineen nousuun verrattuna tutkimuskertaan ilman lääkettä tai plaseboon. Sydämen lyöntitiheys nousi ns. kylmävesitestin aikana, mutta laski koko kehon kylmäaltistuksissa (5°C ja –15°C). Metoprololi ja karvediloli laskivat sydämen lyöntiheyttä kylmäaltistuksessa (–15°C) verrattuna plaseboon.

Tämä tutkimus kuvaa ensimmäistä kertaa, kuinka verenpainelääkkeet vaikuttavat verenpainetasoihin ja -vasteisiin kylmäaltistuksessa, joka simuloi tyypillisiä ulko-olosuhteita talvella. Vaikka lääkkeet eivät estäneet kylmän aiheuttamaa verenpaineen nousua, ne laskivat verenpaineen tasoa, jolloin verenpaine pysyi kylmässäkin lähempänä suositusrajoja.

Asiasanat: koko kehon kylmäaltistus, kylmävesitesti, sydämen lyöntitiheys, verenpaine, verenpainelääke

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Oulu, September 2007 Silja Komulainen

List of abbreviations and definitions

ABPM	ambulatory blood pressure monotoring
ACE	angiotensin converting enzyme
ANP	atrial natriuretic peptide
AT	angiotensin
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure (mmHg)
CI	cerebral infarction
CH	cerebral hemorrhage
Clo	clothing insulation value (clo)
CPT	cold pressor test
D	day
DBP	diastolic blood pressure (mmHg)
DM	diabetes mellitus
HCTZ	hydrochlorothiazide
HDL	high density cholesterol
HR	heart rate (beats/min)
HT	hypertensive
ICH	intracerebral hemorrhage
IHD	ischemic heart disease
MAP	mean arterial pressure (mmHg)
NO	nitric oxide
NT	normotensive
PP	pulse pressure (mmHg)
RAS	renin angiotensin system
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure (mmHg)
T3 & T4	Thyreoidea hormones 3 and 4
Wk	week

List of original papers

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

I Tähtinen T, Määttä S, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (1999) Effect of amlodipine on blood pressure responses in local and whole-body cooling in normotensive men. Arzneimittel-Forschung 49: 494–499.

II Komulainen S[1], Tähtinen T, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2000) Blood pressure responses to whole body cold exposure: effect of carvedilol. Eur J Clin Pharmacol 56: 637–642.

III Komulainen S[1], Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2004) Blood pressure responses to whole-body cold exposure: effect of metoprolol. J Hum Hypertens 18: 905–906.

IV Komulainen S[1], Oja T, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2004) Blood pressure and thermal responses to whole-body cold exposure in mildly hypertensive subjects. J Thermal Biol 29: 851–856.

V Komulainen S[1], Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2007) Blood pressure responses to whole-body cold exposure in mildly hypertensive subjects: effects of ACE-inhibitor and AT II receptor blocker agent. Manuscript.

[1]nee Määttä

Some unpublished result will also be presented in the thesis.

Contents

1 Introduction

Morbidity and mortality from cardiovascular diseases is high in Finland (Kastarinen *et al.* 1998, Antikainen *et al.* 2006) and in some European countries e.g. Sweden, Germany and Great Britain (Wolf-Maier *et al.* 2003, Antikainen *et al.* 2006). Elevated blood pressure is one of the risk factors for cardiovascular diseases. In Finland the prevalence of hypertension (in 1997) is 49% among those aged 25–64 years (Kastarinen *et al.* 1998, Wolf-Maier *et al.* 2003). In 1997, 25% of hypertensive persons took medication for hypertension (Kastarinen *et al.* 1998) and in 2006, 508,764 Finns received the special reimbursement for antihypertensive drugs from the Social Insurance Institution of Finland (Klaukka & Virta 2007). Moreover, only 26% of women and 22% of men treated at public health centres have reached the target of management (<140/85 mmHg) (Meriranta *et al.* 2004).

In the northern part of the world people are exposed to low outdoor temperatures for a considerable part of the year. In Finland, the daily mean temperature falls below 0°C on 90–220 days of the year. Approximately four million people live above the Arctic Circle (Bogoyavlenskiy & Siggner 2004), with more people living in sub-arctic regions. People are exposed to cold during work, commuting to and from work and during leisure time. In Finland the mean cold exposure time was 6 h/week during the winter months. (FINRISK 2002 cold sub-study, Raatikka *et al.* 2007.)

Cold environment is associated with increased cardiovascular morbidity and mortality. Mortality in Finland is lowest at 14°C (The Eurowinter group 1997, Näyhä 2005). Some 2,000–3,000 extra deaths occur during the winter, 33% of which are due to coronary heart disease and 20% to stroke (Näyhä 2005). Cold increases blood pressure (BP) during both acute and chronic exposure. Cold exposure causes vasoconstriction of peripheral vessels, restricting the flow of blood to inner organs. Cold-induced vasoconstriction does not happen in the head or neck. The cold-induced rise of BP depends on the intensity and duration of the cold exposure and on the part of body exposed to cold. (Raven *et al.* 1970.) BP is higher in winter than in summer (see Table 15).

There is a limited amount of data available concerning the question how antihypertensive drugs affect BP during cold exposure. Moreover, cold environment has not been taken into account in the management of hypertension in spite of the fact that hypertension is very common in the Finnish population and the evidence for cold related cardiovascular morbidity and mortality is strong.

In the present study the aim is to describe the effects of different types of cold exposures on BP and heart rate (HR) and to test how these cold exposure induced effects are modulated by antihypertensive drugs representing different kinds of mechanisms of action.

2 Literature review

2.1 Regulation of blood pressure and pathophysiology of hypertension

Blood pressure provides the driving force that moves blood through the vascular system. Regulation of BP is a complex physiological phenomenon, comprising e.g. the sympathetic nervous system, renin-angiontensin system (RAS), central nervous system, nitric oxide (NO) and endothelial function. The aim of this regulation is to confirm perfusion to critical organs (e.g. brain) and optimize perfusion of other organs and whole body functions. Moreover, BP regulation serves total-body homeostasis. (Delgado & Weder 2000.)

Mean arterial pressure (MAP) is the product of cardiac output and the systemic vascular resistance, which are modulated by numerous factors. According to the JNC 7 Report (Chobanian *et al*. 2003), normal BP is < 120/80 mmHg, pre-hypertension is 120–139/80–89 mmHg and hypertension is > 140/90 mmHg. Elevated BP can be essential or secondary hypertension. Essential hypertension is elevated BP with an unknown origin. Essential hypertension is accompanied by multiple underlying pathophysiological abnormalities. The increased preload and contractility of the heart increases cardiac output, which can elevate BP. (Delgado & Weder 2000.) A typical haemodynamic finding in chronic hypertension is an elevated peripheral resistance with normal cardiac output (Julius 1991). Functional and structural changes of the vessels are responsible for increased peripheral resistance. Vessel compliance (stiffness) is decreased in hypertension, the greatest loss of compliance occurring in the resistance vessels. Structural changes in small resistance arterioles are responsible for the loss of compliance and increased peripheral resistance. (Delgado & Weder 2000.)

The autonomic nervous system plays an important role in the development of hypertension. Sympathetic nervous system activity is increased, parasympathetic activity is decreased and baroreflex sensitivity reduced in hypertension. (Izzo 2000.) Increased sympathetic nervous system activity is an important part of the hypertension associated with obesity. Hyperinsulinemia and increased sympathetic nervous system activity have been proposed to be the pathophysiological links between obesity and hypertension (Hall 2003). Activation of the RAS results in the elevation of the BP through a number of

mechanisms. Besides its very potent direct vasoconstrictor action angiotensin II increases systemic vascular resistance through sympathetic nervous system stimulation. Angiotensin II increases extracellular blood volume through salt and water retention secondary to aldosterone production and antidiuretic hormone stimulation and through direct renal mechanisms. Both expansion of blood volume and increase in vascular resistance produce a rise in BP. (Fabiani *et al*. 2000.)

Moreover, abnormal renal excretory function is critical for the initiation, development and maintenance of primary hypertension. The increased sodium retention and plasma volume expansion leads to elevated BP and eventually to hypertension. An increase in arterial pressure (via increases in total peripheral resistance or cardiac output or both) leads to increased urinary sodium and water excretion via urinary natriuresis mechanism, with a consequent reduction in blood volume until arterial pressure is returned to normal. (Cowley 1992.) Increased renal sympathetic nerve activity is known to be a factor capable of decreasing renal excretory function (DiBona & Kopp 1997).

Endothelins are powerful vasocontrictor peptides. Endothelin-1 is the most important of these peptides in blood vessels. Endothelin-1 has direct vascular effects, influences homeostasis of salt and water, alters central and peripheral sympathetic activity and stimulates the renin-angiotensin-aldosterone system. (e.g. Haynes & Webb 1998.) Vascular expression of endothelin-1 is enhanced in hypertension (e.g. Schiffin 2005).

Moreover, e.g. the central nervous system (Smith *et al.* 2002) and genetic factors (Timberlake *et al.* 2001) take part in development of hypertension. In conclusion, the development of hypertension is a complex cascade in which many different regulation mechanisms have a role, interacting with each other in a complex manner. These interactions can be modulated by environmental factors such as a cold environment.

2.2 Mechanisms of actions of antihypertensive drugs

There is a numerous amount of drugs on the market that can be used to lower the BP. They differ from each other in many respects, and the mechanisms of action by which they lower BP differ from each other as well. Antihypertensive drugs can be classified on the basis of the antihypertensive action in lowering the BP. The main classes of antihypertensive drugs are beta-receptor blocking agents, alfa receptor blocking agents, calcium channel blockers, angiotensin converting

enzyme inhibitors (ACE inhibitor), angiotensin II receptor antagonists and diuretics. There are antihypertensive drugs that have properties from different classes (e.g. combined alfa- and beta-receptor blockers). The drugs in these different classes lower BP by different mechanisms, and there are also some pharmacological differences in the mechanisms of action within the classes.

Beta-blocking agents inhibit β-adrenoceptors, but the differences between different β-adrenoceptor blocking agents are in cardioselectivity (the extent to which they block β_1- and β_2-receptors) and intrinsic sympathomimetic activity (e.g. Frishman & Jorde 2000). For example metoprolol blocks myocardial β_1-adrenoceptors selectively without any intrinsic sympathomimetic activity and with weak membrane stabilizing activity (Benfield *et al.* 1986).

Alfa-blocking agents affect BP by blocking α-adrenoceptors and can be classified into two types, α_1-and α_2-adrenoreceptors. α-adrenoceptors are present in the brain, kidney, heart and vasculature. Most alfa-blocking agents affect via α_1-adrenoreceptors. These lower BP through the reduction of vascular resistance without significant effects on heart rate, cardiac output or central haemodynamics. Some drugs such as carvedilol have combined alfa- and beta-blocking properties in blocking both β- and α_1-adrenoceptors to some extent. Carvedilol is a non-selective beta-blocking agent with additional alfa-blocking properties. This leads to a reduction in peripheral vascular resistance that may maintain cardiac output. (e.g. Pool 2000.)

Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor antagonists affect the renin-angiotensin-aldosterone system at a different site. ACE inhibitors inhibit the activity of angiotensin converting enzyme (ACE) and reduce the levels of angiotensin II. ACE catalyses the conversion of angiotensin I into angiotensin II and also affects the degradation of bradykinin. In long-term treatment the effects of ACE inhibitors on lowering BP are due to reduced levels of angiotensin II and partly to reduced activity of the sympathetic nervous system, elevated bradykinin levels (NO production increase and release of prostacyclin is induced) ACE inhibitors are a structurally heterogeneous group in how they bind to and diminish the activity of ACE, and they also contain different side groups capable of binding to ACE. Lisinopril is a long-acting compound in the group of ACE inhibitors. (e.g. Sica & Gehr 2000.)

Angiotensin II receptor antagonists affect the renin-angiotensin-aldosterone system at a different site by inhibiting the effects of angiotensin II by blocking type I angiotensin receptor. Angiotensin II receptor antagonists differ from one another by their bioavailability, rate of absorption, tissue distribution, metabolism

and rate of elimination. For example Eprosartan is a nonphenyl, nontetrazole angiotensin II receptor antagonist with a high affinity to angiotensin$_1$ receptor sites. (e.g. Ruddy & Kostis 2000.)

Most calcium channel blockers act by blocking the L-type calcium channel in vascular smooth muscle cell membranes. Calcium channel blockers are divided into three major classes: phenylalkylamines, benzothiazepines and dihydropyridines. Vasodilation occurs predominantly at the level of the resistance vessels, causing a reduction in elevated peripheral resistance in hypertensive subjects. Dihydropyridines such as amlodipine are vascular-selective: the effects on the vascular system are stronger than on the heart. (e.g. Zwieten 2000.)

All diuretics have natriuretic action, which leads to a decrease in total body sodium. Diuretics can be classified into thiazides (such as hydrochlorothiazide, HCTZ), its related sulphonamide compounds, loop diuretics and potassium sparing agents. For example HCTZ acts via natriuresis and is one of the most commonly used diuretic agents in the treatment of hypertension. The response rate to thiazide monotherapy in hypertension is variable; that is why thiazide diuretics are much more effective in combination. (Shah *et al.* 2004.)

2.3 Human exposure to cold in normal living and working environment

Human thermal environment and the effects of the environment on humans can be classified in several ways. In meteorological autumn and spring the temperature is 0–10°C, and in the winter it is below 0°C. In Finland the length of meteorological winter is 90–220 days per year. In occupational classification, cold hazards (discomfort, decreased performance) are usually regarded as starting at 10–15°C. The limit of cold work is defined to be 10–12°C (BS7915 1998, ISO CD15743 2002). Thermal responses are usually first seen as a cooling of hands and feet. Cold can also be defined by health outcomes (mortality and morbidity). In southern Finland the lowest temperature related mortality has been showed to be at 14°C. The corresponding temperature in southern Europe is 22–25°C. (The Eurowinter Group 1997, Keatinge *et al.* 2000, Näyhä 2005.)

In the northern part of the world people are exposed to low outdoor temperatures for a considerable part of the year. Approximately four million people live above the Arctic Circle (Bogoyavlenskiy & Siggner 2004), with an additional number of people living in subarctic regions. In Finland the self-reported median total cold exposure time was 7 h/week at work and 4h/week at

leisure-time in winter months. In occupations involving cold exposure, 23% of men and 27% of women are exposed to cold 1-10h/week. (Mäkinen *et al.* 2006.) Moreover, cold store workers are exposed to low air temperatures, commonly −25°C, all year round. People are also exposed to cold while commuting to and from work. Both occupational and leisure time cold exposure is greater among men than women. (Mäkinen *et al.* 2006.) Thermal sensations of cold at 5°C to −5°C were reported by 35% of men and 46% of women. According to the same study, episodic peripheral circulation symptoms were reported by 12% and 15%, respiratory symptoms by 25% and 29%, white fingers by 12% and 12% and cardiovascular symptoms by 4% and 4% of men and women, respectively. (Raatikka *et al.* 2007.)

In Finland people protect themselves against low outdoor temperatures in the winter better than in central and southern Europe. People (over 50 years old) wear more hats, gloves and anoraks in Finland. At 7°C 13% of the inhabitants in Athens wore hats, while the corresponding number in southern Finland was 72%. Moreover, in warmer countries, for example in the southern part of Europe, the heating systems in homes are often not efficient enough for the few colder months. At an outdoor temperature of 7°C, the mean living-room temperature was 19.2°C in Athens and 21.7°C in southern Finland. (The Eurowinter group 1997.)

2.4 Physiological responses to cold

2.4.1 The thermoregulatory system

The body (core) temperature is regulated within a narrow range around 37°C in order to maintain optimal physiological function. The thermoregulatory system has been divided into temperature sensors in the skin and inner organs, afferent neural pathways, the hypothalamic thermoregulatory centre (integration of thermal inputs) and effector pathways for autonomic and behavioural regulation. In cold the human body decreases heat loss via vasoconstriction of arteries and arterioles in the skin and peripheral parts of the body, e.g. hands and feet. Vasoconstriction of arteries in the skin and peripheral parts can elevate the BP by 20–40 mmHg. The heat produced by basal metabolism comes to ca 58 W/m^2. Additional heat is produced by muscle work and shivering. Heat is also produced by brown adipose tissue of infants less than two months old.

2.4.2 Neural control of temperature regulation

Cold and warm thermoreceptors located in the skin and in deeper tissues sense and provide the thermoregulatory centre with peripheral information. These receptors are free nerve endings. The thermoreceptors can be divided to quick and slow adapting receptors. (Hensel 1981.) The receptors responsible for thermal sensation have been in the focus of recent study: thermal sensitivity is based on the function of ion channels by cold and menthol sensitive receptors. Cooling opens these channels by allowing potassium and calcium ions to flood into the nerve cell. (McKemy *et al.* 2002.) Afferent signals from peripheral and central thermoreceptors are transferred by Aδ myelinated fibres, which collect in the anterior hypothalamus and in the reticular formation. The thermoregulatory control centre is located in the preoptic area of the anterior hypothalamus. (Mehler *et al.* 1960, Grashaw *et al.* 1990.)

The link between sensory input and effector output is complex and there are many models by which the mechanisms have been explained. The experimental results support the notion that the thermal signals are integrated at different levels in the spinal cord and brain (Zeisberger 1998). The sympathetic effects are mediated via α_1- and α_2-adrenoceptors in the walls of blood vessels and via β_1 and α_1 in the heart (Zelis 1983). Cold-induced vasoconstriction has been shown to be mediated mainly via α_2-adrenoceptors (Zelis 1983, Flavahan *et al.* 1985, Ekenvall *et al.* 1988), but also via α_1-adrenoceptors (Harada *et al.* 1996, Klemsdahl *et al.* 1996). Subtype α_{2C}-adrenoceptors may play a selective role in thermoregulation (Savino & Varela 1999, Jeyaraj *et al.* 2001, Chotani *et al.* 2005). Kanagy (2005) has recently published a review about how α-adrenergic receptor signalling are divided in hypertension. β-adrenoceptors have been shown to have a minor role in cold-induced vasoconstriction (Reed *et al.* 1991).

2.4.3 Hormonal responses to cold

Cold exposure affects the circulating levels of many hormones. Some of these hormones and vasoactive peptides take part in BP regulation. In brief, norepinephrine has been shown to be increased by different cold exposure temperatures and times (O'Malley *et al.* 1984, Thomas *et al.* 1990, Leppäluoto *et al.* 1998, Marino *et al.* 1998) and in lower temperatures during prolonged Antartic exposure (Budd & Warhaft 1970). Plasma angiotensin II levels did not change during whole body cold exposure or cold pressor test (CPT) of hands (Hiramitsu

et al 1984). Plasma endothelin-1 levels increased during CPT of hands (Fyhrqvist *et al.* 1990), while they were not affected during whole body cold exposure (Hassi *et al.* 1991). NO did not change during a short cold exposure, but higher levels could been seen in winter compared to summer (Ringqvist *et al.* 1997). Table 1 shows how cold exposure or cold season affects the levels of some hormones and vasoactive peptides.

Table 1. Some vasoactive peptides and hormones responses to cold (modified from Pääkkönen & Leppäluoto 2002, original references are in the text)

Hormone	Short cold exposure	Cold Season
Thyroid gland		
T4	No	No
Free T4	No	Decreases
T3	No	Decreases
Free T3		Decreases
Adrenal Cortex		
Cortisol	Increases	Increases
Aldosterone	Increases	Increases
Adrenal medulla and nerve endings		
Epinephrine	No	No
Norepinephrine	Increases	Increases in hypertensive patients
Pancreas		
Insulin	No	Increases
Glucagon	Increases	
Others		
Atrial natriuretic peptides (ANP, BNP)	Increases or decreases	
Endothelin-I	No or increases	
Nitric oxide (NO)	No or increases	Increases
Angiotensin II	No	

2.4.4 Cardiovascular responses to cold

Cold exposure causes vasoconstriction in the skin and extremities, which directs blood flow to the inner organs. Vasoconstriction takes place in the skin, hands and feet but not in the head and neck. Cold-induced vasoconstriction is mainly mediated via α_2-adrenoceptors (Zelis 1983, Flavahan *et al.* 1985, Ekenvall *et al.* 1988).

Arteriovenous anastomoses, specialized shunt vessels, permit blood to be shunted directly from the arterial side to the venous vascular bed. Arteriovenous

anastomoses are located in the skin of the fingertips, nail beds, feet, lips, elbow, nose and cheek. The muscle wall of arteriovenous anastomoses is predominantly equipped with α-adrenoceptors and richly innervated by sympathetic nerves. Activation of the sympathetic nervous system leads to active vasoconstriction, while a decrease of sympathetic nervous system activity leads to passive vasodilatation. The arteriovenous anastomoses are almost closed in a mildly cold environment. The arteriovenous anastomoses thus play an important role in thermoregulation: they open and close according to peripheral temperature changes. (Daanen 1997.)

Skin vasoconstriction causes increased total peripheral resistance. End-diastolic volume and cardiac output are also increased by cold exposure (Rowell 1986). Strong vasoconstriction of vessels increases BP (Raven *et al*. 1970).

HR can be unchanged, increased or decreased depending on the rate and time of body cooling (Granberg 1991). Cold exposure of the face causes increased BP (e.g. Mannino & Washburn 1987, McLean *et al.* 1992, Kilgour & Calvalho 1994, Collins *et al.* 1996) while the HR was decreased (Mannino & Washburn 1987, Heath & Downey 1990, Allen *et al*. 1992, Collins *et al.* 1996), increased (McLean *et al.* 1992) or without change (Kilgour & Calvalho 1994).

Haemoconcentration has also been observed. Significant seasonal effects were found for increased fibrinogen and plasma viscosity. (Stout & Crawford 1991.)

2.4.5 Respiratory responses in the cold

Cold air blown on face skin or other cold stimulation of the face elicits reflex bronchoconstriction in both patients with respiratory diseases and non-asthmatic subjects (Koskela & Tukiainen 1995, Koskela *et al.* 1996, McDonald 1997). These reflexes may be mediated by sensory receptors in the nasal cavity, pharynx, larynx, face and trunk (Giesbrecht 1995). The ventilation rate is decreased by cold (McFadden 1983). An increase of evaporative heat loss from the airways to the environment may contribute to the symptoms observed in asthmatics after breathing cold air. Inhalation of cold dry air would be a problem especially at higher ventilation rates in normal subjects and patients with respiratory diseases. (Jaeger *et al*. 1980.*)* Respiratory infections increase during cold seasons, and mortality due to respiratory infection rises markedly. The reasons for this phenomenon are unclear. (Donaldson & Keatinge 1997.)

2.4.6 Heat production and energy expenditure

Cold environment increases energy consumption due to heat production stimulated by body cooling and/or heavier clothing. A decrease of environmental temperature causes great differences in individual response to cold: some humans increase their metabolism to protect them against the cold, while others decrease heat loss via cooling of peripheral parts of the body. (e.g. Westerterp-Plantega *et al.* 2002.)

2.4.7 Adaptation to cold

Cold acclimatization may be developed in two different ways: via blunted or enhanced responses to cold. The type of cold acclimatization is affected by the properties of the cold exposure: duration, severity, the distribution of tissue cooling in the body, the number of cold exposures and individual factors such as diet, physical fitness and anthropometry. (Young 1996.) Blunted responses to cold are been divided into decreased BP (LeBlanc *et al*. 1975) and metabolic rate (Radomski & Boutelier 1982, Castellani *et al.* 1998, Hesslink *et al.* 1992), delayed onset of shivering (Budd *et al.* 1993), diminished superficial and peripheral vasoconstriction (Brown & Page 1952), less intense sensations of cold (Leppäluoto *et al.* 2001), decreased stress as judged by circulating catecholamine and cortisol levels (Radomski & Boutelier 1982, Hesslink *et al.* 1992) and possibly decreased core temperature (Castellani *et al.* 1998). Enhanced responses to cold are divided into increased metabolic rate and shivering (Scholander 1958), enhanced skin and peripheral vasoconstriction (Young 1996), improved muscle circulation, and possibly improved insulation due to a thicker subcutaneous adipose tissue layer. If only the skin and peripheral parts of the body are cooled and cold thermal sensations are experienced, blunted thermoregulatory responses are developed. Habituation of this kind is the most common adaptive response to cold. (Young 1996.)

2.4.8 Thermal strain criteria

Table 2 shows the approximate thermal state criteria for comfort, performance decrement, tolerance and tissue damage.

Table 2. Approximate thermal strain criteria for some physiological parameters (Lotens 1988)

Variable	Comfort	Discomfort	Performance degradation	Tolerance	Damage
Mean skin temperature (°C)	33	< 31	30	25	< 15
Finger skin temperature (°C)	27–34	< 20	< 15	5	−2 << 15
Toe skin temperature (°C)	27–34	< 17	< 15	5	−2 << 15
Core temperature (°C)	37	−	< 36	< 35	28
Body heat loss (J/g)	0	4	6	12	20

2.5 Blood pressure in cold

2.5.1 Cold provocation methods to increasing blood pressure

Experimental exposure to cold can be achieved by exposing the whole body or part of the body to cold or by intravenous infusion of cold fluids. The body parts exposed to cold are usually the face, hand or foot. In the standard procedure, cold pressor test (CPT), one hand is immersed up to the wrist in ice water (0–4°C) for 1–2 minutes. CPT has been described as early as in 1932 by Hines & Brown. The test has many modifications, e.g. immersed foot/feet, both hands or variable water temperatures (see Tables 3–6) from 0°C to 5°C, or variations in the duration of immersions from 30 seconds to 5 minutes. CPT of hand or foot is widely used to test cardiovascular reactions and pain (e.g. Chang *et al.* 2002, al'Absi & Petersen 2003, Hentschel & Bijleveld 2004). Also endothelin is released in CPT (Fyhrqvist *et al.* 1990), while none is released in whole body cold exposure (Hassi *et al.* 1991). CPT is a test for measuring the activation of the sympathetic nervous response and does not simulate normal outdoor cold exposure. The face can also be exposed to cold, e.g. air and wind, or cold baths may be used.

Whole body human cold exposure can be used with clothed or naked subjects. With clothing normal outdoor exposure to cold in the wintertime can be simulated. Because of the microclimate under the clothing only a minor part of the body, usually the face, is exposed directly to cold, while other parts of the body, with different amounts of clothing, are exposed to cold slowly, depending on the insulation of the clothing and the degree of the cold exposure. Whole body cold exposure can be performed in a climate chamber where standardized conditions of air temperature, air velocity and humidity can be adjusted.

Moreover, deeper body parts can be cooled by intravenous infusion of cold infusion fluids (e.g. Frank *et al.* 1996). These kinds of methods have implications for anaesthesiology and surgery.

2.5.2 Blood pressure during cold pressor test and whole body cold exposure

CPT is a strong stimulus for the sympathetic nervous system. The results collected in tables 3–6 show, for example, that CPT cold-induced rises of BP were 7–26/5–24 mmHg in normotensive subjects (NT) and 26–31/15–24 mmHg in hypertensive subjects (HT) in these studies, reporting their results as exact values of BP responses (see Tables 3–6). Only few studies have reported the exact amount of cold-induced rise of BP, and the cold-induced rise of BP varies strongly in these studies. Most of the highest BP responses (> 20 mmHg) have been measured in older age groups (> 45 years old). BP responses to CPT exceeding 20 mmHg have been measured in normotensive and hypertensive subjects, patients with diabetes mellitus (DM) and ischemic heart disease (IHD). The studies collected (Tables 3–6) have mostly been conducted by CPT of the hand, with only one study on the foot (de Mey *et al*. 1989). Normotensive and hypertensive subjects have similarities in BP reaction during CPT in earlier studies (e.g. Benetos & Safar 1991). Older studies have a more pronounced systolic blood pressure (SBP) reaction than diastolic blood pressure (DBP) reaction during CPT compared to more recent ones (Huisman *et al.* 2002). However, CPT is a test for cardiovascular reactivity; it is not applicable as a predictor for future hypertension (Benetos & Safar 1991).

During whole body cold exposure BP increases markedly in normotensive, healthy persons (Leon *et al.* 1970, Riggs *et al.* 1983, Wagner & Horvath 1985, Mitchell *et al.* 1990, Reed *et al.* 1991, Emmett 1995, Headley *et al.* 1996, Gavhed *et al.* 2000, Arjamaa *et al.* 2001, Korhonen 2006). Emmett (1995) has published a review about the effect of cold exposure on BP and HR in healthy subjects and coronary heart disease patients. At 4–5°C BP increased 12–16/5–10 mmHg in healthy subjects with minimal clothing (Riggs *et al.* 1983, Reed *et al.* 1991, Headley *et al.* 1996). Correspondingly, at 10°C BP increased 16/16 mmHg (Korhonen 2006). Moreover, MAP increased 4–5 mmHg at 5°C (Mitchell *et al.* 1990). In colder test conditions (−15°C and wind 3.5 m/s) BP increased ad 15/13 mmHg in healthy test subjects wearing adequate winter clothing with 2 clo thermal insulation (Arjamaa *et al.* 2001). Moreover, SBP increased about 20

mmHg during exposure to −16°C (Leon *et al.* 1970). At −10°C the mean increase of BP was 15/13 mmHg. The highest increase of BP was 51/45 mmHg in one test subject. Wind (5 m/s) increased BP more than cold exposure without wind (at −10°C). (Gavhed *et al.* 2000.) In older subjects (51- to 72-year-old) SBP increased more than in younger ones (20- to 30-year-old), but there was no difference between the cold-induced rise of DBP during exposure to 15°C and 10°C (Wagner & Horvath 1985).

Whole body cold exposure also increases BP in patients with IHD (Epstein *et al.* 1969, Lassvik & Areskog 1979, Brown & Oldridge 1985, Juneau *et al.* 1989). SBP increased 14–22 mmHg (10°C…−10°C) (Lassvik & Areskog 1979). In another study SBP/DBP changed 10/0 mmHg at rest during exposure to −8°C in patients with angina pectoris (Juneau *et al.* 1989). During a milder cold exposure (15°C) MAP increased 13 mmHg at rest (Epstein *et al.* 1969). There are no whole-body human cold exposure studies available with hypertensive subjects.

2.6 Cold-related morbidity and mortality from cardiovascular diseases

In Europe, the prevalence of hypertension is high (WHO 2002, Wolf-Maier *et al.* 2003, Antikainen *et al.* 2006). In Finland in 1997 the prevalence of hypertension based on epidemiological studies (one repeated measurement) was 56% in men and 42% in women aged 25–64 years (Kastarinen *et al.* 1998, Wolf-Maier *et al.* 2003). Long-term exposure to cold in poorly heated and/or insulated homes in relatively cold areas in Great Britain has been shown to increase the risk for diastolic hypertension significantly (Mitchell *et al.* 2002). Moreover, occurrence of unrecognized hypertension is higher in winter than in summer (Narang & Wasir 1996, Corsonello *et al.* 2003). Cold exposure may be a risk factor for hypertension. Men who work about third of their working time (total work time eight hours) in cold departments of factories have significantly more frequently unrecognized hypertension and significantly higher blood pressure levels compared to men working in warm areas. (Kim *et al.* 2003.)

Elevated BP is one of the most important risk factors for serious cardiovascular events. Increased morbidity and mortality due to cardiovascular diseases in the cold season is well documented (see Tables 12–15). Increased morbidity and mortality from cardiovascular diseases is also seen in colder and warmer areas around the world. However, there are a few studies in which the results are contradictory or where seasonal variation is lacking (Donaldson *et al.*

1998a, Field & Hill 2002, Yamasaki *et al.* 2002, Hakan *et al.* 2003, Inagawa *et al.* 2003). Short-term falls in temperature increase BP and cause haemoconcentration, which can explain why deaths from arterial diseases are more prevalent in the wintertime (Donaldson & Keatinge 1997). In Finland mortality is lowest at 14°C (The Eurowinter group 1997, Näyhä 2005). Daily rates of coronary events correlate with the average temperature over the current and previous three days (Barnett *et al.* 2005). During cold periods, coronary event rates increase more in populations living in warm climates than in populations living in cold climates. In Finland, about 2,000–3,000 extra deaths occur in the winter, most of them in people over 65 years, but approximately 20% in working age population. The excess winter mortality is due to coronary heart disease (33%), cerebrovascular strokes (20%) and respiratory causes (20%). (Näyhä 2005.) Moreover, mortality related to air pollution can be partly caused by cold weather (Keatinge & Donaldson 2001).

2.7 Effect of antihypertensive drugs on blood pressure during cold

2.7.1 During cold pressor test

Tables 3–6 show how BP is affected by antihypertensive drugs in CPT. Double-blind, placebo-controlled and randomized trials have been included in the tables (25 studies). The number of the test subjects varies from 6 to 36. Duration of the antihypertensive drug treatment varies from one initial dosage to 6 weeks' treatment. The results are reported as levels of BP during CPT, as cold-induced rise of BP, or both. The groups of antihypertensive drugs used in these studies are beta-blocking agents, combined alfa- and beta-blocking agents, alfa-blocking agents, angiotensin converting enzyme inhibitors and calcium channel blockers. There are no studies with diuretics or angiotensin II receptor antagonists.

Eleven of the 25 studies were made in normotensive and healthy subjects (see Tables 3–6). Most of the antihypertensive drugs do not affect the rise of BP during CPT compared to placebo in normotensive subjects (see Tables 3–6). Only atenolol (Pandhi & Sharma 1987) and labetalol (Pandhi & Sharma 1987) decrease the BP response during CPT statistically significantly compared to placebo in normotensive subjects.

Fourteen of the 23 studies were made in hypertensive subjects (Tables 3–6). Most antihypertensive agents do not affect the cold-induce rise of BP (see Tables

3–6). Only verapamil (McInnes *et al.*1986), clonidine (Puybasset *et al*. 1993) and prazosin (Pandhi & Sharma 1987) decreased the cold-induced rise of BP. In one study clonidine decreased the response of MAP, but not statistically significantly (Cohen *et al*. 1981). On the contrary, Weder *et al.* (1989) have reported that clonidine did not affect the rise of BP during CPT. In the most recent study, cold-induced rise of BP in CPT was blunted by eprosartan and losartan (Israel *et al.* 2006).

Table 3. Effects of beta-blocking and combined alfa and beta-blocking agents on blood pressure during CPT. Data have been collected from double-blind, randomised and placebo-controlled studies.

Author	Drug	Dosage	Duration	CPT	Subjects	N	F/M	Age	Results Level SBP/DBP	Cold-induced rise in SBP/DBP	Comments
Andren & Hansson	propranolol	0.1 mg	iv. x 1	ice water	HT	13		48			Drugs did not affect cold
1981	metoprolol	0.2 mg		0°C 5 min							induced rise in BP
											compared to placebo
Dikshit & Patrick	propranolol	120 mg	X 1	ice water	NT	7	3/4		112/90	16/16	Levels of BP
1986	placebo			5°C 2 min					120.5/85	10/11	significantly lower
O'Connor &	propranolol	80–320 mg	4–6 wk	ice water	HT	12	0/12	51	109	24	MAP
Preston 1982	placebo			1 min					126	27	
Harris *et al.*	propranolol	240	2 wk	ice water	IHD	18	3/15	58	160/99	32/19	Levels of BP
1982[1)]	nifedipine	to 480 mg		2 min					139/93	23/17	significantly lower
	+propranolol										compared to placebo
	placebo								169/110	30/25	
Klemsdal *et al.*	carvedilol	25 mg	X 1	ice water	NT	18	0/18	33	126/87	18/13	
1996	atenolol	50mg		0°C 1 min					122/86	14/13	
McInnes *et al.*	propranolol	240 mg	4 wk	ice water	HT	13	8/5		No affect	No effect	
1986 [2)]	propranolol+			2 min					Significantly lower		
	verapamil										
Pandhi *et al.*	propranolol	40 mg po	X 1	ice water	NT	14	0/14	26–34	138/95		
1986	labetalol	100 mg po		0°C					141/84		
	placebo								145/93		
	propranolol	40 mg po			HT	7	0/7	30–48	174/109		
	labetalol	100 mg po							164/104		
	placebo								197/116		
Pandhi & Sharma	propranolol	80 mg	13 days	ice water	NT	7	0/7	22–28		18/22	
1987 [3)]	atenolol labetalol	200 mg		0°C 40 sec						13/10	
	placebo	200 mg								10/14	
										26/24	
Weder *et al.*	atenolol	50 mg	3 wk	ice water	HT	12	0/12	36			No effect on cold
1989 [4)]											induced rise in BP
Pörsti *et al.*	atenolol	100 mg	× 1	ice water	NT	8		19–23			SBP levels significantly
1990 [5)]											lower
Fasano *et al.*	tertalol	5 mg	4 wk	ice water	HT	20	8/12	39	163/92	12/7%	
1991	placebo			4–5°C						6/3%	

Table 4. Effects of alfa-blocking agents on blood pressure during CPT. Data have been collected from double-blind, randomised and placebo-controlled studies.

Author	Drug	Dosage	Duration	CPT	Subjects	N	F/M	Age	Results Level SBP/DBP	Cold-induced rise in SBP/DBP	Comments
Cohen *et al*. 1981	clonidine placebo	0.2–0.6 mg	1 month	Ice water 1 min	HT	13	0/13	54		MAP 25 MAP 32	No effect on cold induced rise in MAP compared to placebo
Puybasset *et al*. 1993	clonidine placebo	150 ug	× 1	ice water 4°C 90 sec	HT	18	7/11	45		18/5 31/15	Cold-induced rise in DBP was significantly lower compared to placebo
Pandhi & Sharma 1987[3)]	prazosin placebo	2.5 mg	13 d	ice water 0°C 40 sec	HT	7	0/7	22–28		12/10 26/24	Circa Prazosin decreased significantly compared to placebo
Weder *et al*. 1989[4)]	clonidine	0.2 mg x2	3 wk		HT	12	0/12	36			No effect on cold induced rise in compared to placebo
de Mey *et al*. 1989	SK&F 86466 α_2 blocking drug placebo	10 mg 25 mg 50 mg placebo	× 1	ice water 3 min foot	NT	8	0/8	27		9/5 8/8 7/7 7/5	No effect on cold induced rise in BP compared to placebo

Table 5. Effects of angiotensin converting enzyme inhibitors on blood pressure during CPT. Data have been collected from double-blind, randomised and placebo-controlled studies.

Author	Drug	Dosage	Duration	CPT	Subjects	N	F/M	Age	Results Level SBP/DBP	Cold-induced rise in SBP/DBP	Comments
Ajayi *et al.* 1986	perindopril	8 mg	× 1	ice water 2 min	NT	10	0/10	18–28		20/16	
	placebo									21 /19	
Moore *et al. 1987*	captopril	25 mg	× 1	ice water 2 min	DM	8	6/2	54		7/9	No effect on cold induced rise in BP compared to placebo
	placebo									22/10	
Beaulieu *et al.* 1994	fosinopril	20 mg	× 1 4 wk	ice water 1 min	HT	10		43			No effect on cold induced rise in BP compared to placebo
Campbell *et al.* 1985	captopril	50 mg	1	ice water 2 min	NT	6	0/6	22–39		9/18	No effect on cold induced rise in BP compared to placebo
	placebo									9/18	
De Cesaris *et al.* 1993	nicardipin	80 mg	4 wk	ice water 30 sec	HT	36	19/17	56		20%/18%	No effect on cold induced rise in BP compared to placebo
	placebo									18%/16%	
Duprez *et al.* 1991	isradipine	10 mg	6 wk	ice water 4°C	HT	9	5/4	48	147/92		Level of BP was significantly lower
	placebo								161/102		
Kahan & Eliasson 1999	ramipril	5 mg	6 wk	ice water 3 min	HT	28	10/18	49		28%/29%	Level of BP was significantly lower, but no effect on cold induced rise in BP compared to placebo
	placebo									29%/30%	
Pörsti *et al.* 1990 [5)]	quinapril	40 mg	× 1	ice water 2 min	NT	8		19–23			No effect on cold induced rise in BP compared to placebo
Sugimoto *et al.* 1989	ramipril	5 mg	× 1	ice water 1 min	NT	8	0/8	22–26		MAP 12	No effect on cold induced rise in BP compared to placebo
	placebo									MAP 17	
Wu *et al.* 1994	ramipril	10 mg	10 d	ice water 0°C 1 min	HT	13	5/8	58.6		27/18	No effect on cold induced rise in BP compared to placebo
	enalapril	10 mg	10 d							27/20	
	placebo									27/19	

Table 6. Effects of calcium channel blockers on blood pressure during CPT. Data have been collected from double-blind, randomised and placebo-controlled studies.

Author	Drug	Dosage	Duration	CPT	Subjects	N	F/M	Age	Results Level SBP/DBP	Cold-induced rise in SBP/DBP	Comments
Harris *et al.* 1982 [1]	nifedipine	30mg to 60 mg	2 wk	ice water	IHD	18	3/15	58	152/95	28/16	Levels of BP and cold-induced rise in DBP were significantly lower compared to placebo
	placebo		2 wk	2 min					169/110	30/25	
Hanko & Rostrup 1996	felodopine er	5 mg	2 pv	ice water	NT	16	1/15	37	135/98		
	placebo			0°C 1 min					134/96		
Malhotra *et al.* 2001	amlodipine	5 mg	NT 2 d	ice water	NT	6		53		32/17	No effect on level or cold-induced rise in BP compared to placebo
	lacipine	4 mg	HT 7 d	0°C 40 sec	HT	28	12/16			31/17	
	placebo									28/15	
McInnes *et al.* 1986 [2]	verapamil	360 mg	4 wk	ice water	HT	13	8/5				Level of BP and cold-induced rise in DBP were lower significantly compared to placebo
				2 min							

2.7.2 During whole body cold exposure

There are only a few studies available about the effect of antihypertensive agents on BP during whole body cold exposure. Studies by beta-blocking agents (atenolol and propranolol) have been made in healthy normotensive subjects (Headley *et al.* 1996, Reed *et al.* 1991). Two studies have been made in patients with congestive heart failure (Juneau *et al.* 2002, Blanchet *et al.* 2003) and one study in patients with IHD (Juneau *et al.* 1989). In these studies, beta-blocking agents were used: propranolol, metoprolol and carvedilol (Juneau *et al.* 1989, Blanchet *et al.* 2003), lisinopril (Juneau *et al.* 2002) and diltiazem (Juneau *et al.* 1989). There are no published data on studies made with hypertensive subjects.

In normotensive, healthy men, SBP increased from 103 mmHg (at 25°C) to 124 mmHg (at 5°C) during atenolol treatment. SBP was lower with atenolol compared to placebo. DBP increased to a higher level with atenolol than with placebo during cold. DBP increased from 60 mmHg (at 25°C) to 77 mmHg (at 5°C), while during placebo treatment DBP increased from 69 mmHg (at 25°C) to 74 mmHg (at 5°C). The cold-induced rise of DBP was also higher with atenolol than with placebo. In the same study DBP acted similarly to propranolol: DBP increased from 66 mmHg (at 25°C) to 79 mmHg (at 5°C). (Headley *et al.* 1996.) In another study (Reed *et al.* 1991), SBP was lower with propranolol (124 mmHg) than with placebo (128 mmHg) during cold exposure (at 4°C), but DBP increased to the same level with propranolol as it did with placebo (83 mmHg). Therefore, the cold-induced rise of SBP/ DBP was higher with propranolol (20/15 mmHg) than with placebo (12/10 mmHg). (Reed *et al.* 1991.)

Two studies were conducted in patients with heart failure (Juneau *et al.* 2002, Blanchet *et al.* 2003) and one in patients with IHD (Juneau *et al.* 1989), and beta-blocking agents, ACE inhibitors and calcium channel blockers were used during cold exposure (Juneau *et al.* 1989, Juneau *et al.* 2002, Blanchet *et al.* 2003). SBPs of patients with heart failure increased only 8–10 mmHg by the cold (Juneau *et al.* 2002, Blanchet *et al.* 2003). There was no difference in SBP between drug and placebo during cold exposure. In cold (−8°C), SBP was lower with propranolol than with placebo and diltiazem in patients with IHD (Juneau *et al.* 1989).

2.8 Seasonal variation in blood pressure

Rosenthal (2004) has recently published a review about seasonal variation of BP. Table 15 shows how BP varies seasonally in healthy, normotensive and hyper-

tensive subjects. There is strong evidence that BP is higher in the cold season compared to the warm season (see Table 15). However, there are some studies that do not show differences in BP between the seasons. Seasonal variation in BP is also described in children (Prineas *et al.* 1980, de Swiet *et al.* 1984, Polat *et al.* 2006) and patients with renal failure (e.g. De Castro *et al.* 1998, Tozawa *et al.* 1999, Sposito *et al.* 2000, Argani & Javanshir 2004, Argiles *et al.*2004). Seasonal variation in BP is described in both the northern and the southern parts of the world. Moreover, during periods of cold weather, an increase in BP variability may complicate the diagnosis and management of hypertension and contribute to the higher cardiovascular mortality observed in the winter (Jehn *et al.* 2002).

2.8.1 Effects of antihypertensive drugs on seasonal variation in blood pressure

The use of antihypertensive drugs and their dosages has been shown to increase in winter and decrease in summer in 18% of hypertensive patients in an Italian study (Seguro *et al.* 1992). Moreover, similar seasonal variation in BP was seen in patients using one, two or more antihypertensive drugs or no drug in a Japanese study (Minami *et al.* 1998). Table 16 shows that antihypertensive drugs do not prevent seasonal variation in BP (see Table 16). In hypertensive patients treated with diuretics, BPs were the same in winter and in summer: 143/94 mmHg (Seguro *et al.* 1992). In a Japanese study the frequency of patients with adequately controlled BP (< 140/90 mmHg) was lower in winter (36%) than in summer (44%). Moreover, in hypertensive patients younger than 69 years, the prevalence of adequately controlled BP (< 130/85 mmHg) was 15.5% in winter and 18.6% in summer. (Mori *et al.* 2006.)

3 Aims of the study

The purpose of the study was to evaluate and compare the effects of antihypertensive drugs on blood pressure responses in normotensive and mildly hypertensive subjects during cold exposure tests, especially during whole body cold exposure test. The test simulates outdoor cold exposure in winter.

Specific aims were:

1. To describe the effects of the cold exposure tests on blood pressure and heart rate.
2. To evaluate the effects of main classes of antihypertensive drugs on blood pressure and heart rate during cold exposure tests. The classes of drugs studied comprise a beta-blocking agent, an angiotensin converting enzyme inhibitor, a combined alfa- and beta-blocking agent, an angiotensin II antagonist, a calcium channel blocker and a diuretic.
3. To compare the effects of these drugs on blood pressure and heart rate during cold exposure and rewarming.

4 Subjects and methods

4.1 Test subjects

In the trial of the exposure to 5°C and CPT (Paper I) fourteen healthy normotensive male medical students served as voluntary test subjects. The test subjects were as aged 23 years (SD 3 years). Their body mass index (BMI) was 23 (SD 2) and fat percentage 14 (SD 3).

In the exposure to −15°C (Papers II–V), healthy persons, not older than 45 years with DBP between 90–105 mmHg and/or SBP higher than 140 mmHg as measured several times during the past year, were invited to participate in the study by announcement. Moreover, for one study (Paper II) healthy normotensive persons, not older than 45 years, were invited to participate in the study. Voluntary subjects, mainly university students and personnel, responded to the written announcement to participate in the study (Table 7). All subjects went on 24-h ambulatory blood pressure monitoring (ABPM) before the cold exposure. In hypertensive groups (Papers II–V) according to 24-h ABPM the subjects fulfilled the criteria of hypertension (DBP load >30%, which means that 30% of the measurements exceeded 85 mmHg in ABPM during daytime (at 7–23)). In the normotensive group (Paper II) according to 24-h ABPM the subjects fulfilled the criteria of normotension (DBP load <30%, which means that <30% of the measurements lowered 85 mmHg in ABPM during daytime (at 7–23)).

Table 7. Formation and characteristics of the normotensive (NT) and hypertensive (HT) test subjects in the exposure to −15°C. (Papers II–V)

Variable	Carvedilol		Eprosartan	HCTZ	Lisinopril	Metoprolol
	NT (II)	HT (II)	HT (V)	HT (IV)	HT (V)	HT (III)
Formation of the study groups						
ABPM studies (N)	14	14	10	8	13	12
Excluded subjects (N)	2	4	1	2	6	5
Test subjects (N)	12	10	9	6	7	7
Characteristics of the test subjects as means (SD)						
Female/male (N)	5/7	2/8	4/5	4/2	5/2	4/3
Age (year)	24 (3)	27 (8)	28 (5)	28	32 (8)	30 (9)
Height (cm)	176 (7)	179 (11)	175 (8)	169 (12)	170 (8)	171 (8)
Weight (kg)	71 (11)	76 (21)	80 (11)	71 (11)	77 (17)	71 (15)
BMI	23 (3)	24 (5)	26 (4)	25 (3)	28 (6)	24 (5)
ABPM: Daytime (7–23)						
SBP (mmHg)	118 (4)	131 (8)	127 (5)	128 (9)	127 (85)	130 (3)
DBP (mmHg)	71 (5)	85 (8)	85 (5)	85 (7)	84 (4)	85 (5)
SBP; Time index > 135 mmHg (%)	14 (6)	43 (24)	24 (14)	29 (24)	26 (16)	34 (8)
DBP; Time index > 85 mmHg (%)	13 (8)	52 (16)	43 (16)	51 (27)	39 (14)	58 (13)

4.2 Thermal exposures

Three types of cold exposures were used in this study:

1. CPT (Paper I), where the test subject immersed his right hand up to the wrist into stirred cold water (10.0 ± 0.5°C) for 5 minutes. The test was performed at room temperature.
2. Whole body cold exposure to 5°C (Paper I) with minimal clothing (shorts and jogging shoes). Air velocity was <0.2 m/s and relative humidity 50%. The cold exposure lasted for 45 minutes, as did the preceding stabilization at 27°C (air velocity < 0.2 m/s, relative humidity 30%).
3. Whole body cold exposure to −15°C (Papers II–V) with adequate winter clothing (thermal insulation ca. 2.0 clo). Air velocity was 3.5 m/s and relative humidity 50%. The cold exposure lasted for 15 minutes. The 15 minutes stabilization before the cold exposure took place at 18°C (air velocity < 0.2

m/s, relative air humidity 50%), as did the 15 minutes rewarming after the cold exposure.

In most studies, whole body cold exposure to −15°C (exposure type 3, Papers II–V)) was used. The purpose of this test was to simulate natural cold exposure in winter instead of using test protocols (exposure types 1 and 2, Paper I), which occur very rarely in everyday life, although they have been widely used in earlier studies. A standardized protocol was developed for the cold exposure test to −15°C, as described later in 4.3.2.

4.3 Measurement protocol

4.3.1 CPT and whole body exposure to 5°C (paper I)

Every subject (see section: test subjects) participated in the same crossover test procedure twice, with a one-week interval between the tests during winter from January to March 1995.

Seven randomly selected participants ingested 5 mg of amlodipine (Norvasc®) at 8 a.m. 49 and 25 hours before the test and on the morning of the testing day. One week later the test was repeated without prior ingestion of amlodipine. Seven participants did not take amlodipine before the first test, but ingested 5 mg amlodipine 49, 25 and 1 hour before their second test one week later. Two or three participants at a time attended the test at 8 a.m. after a normal breakfast. No smoking or coffee was allowed in the morning before the test. The subjects had had no infections during the 2 weeks before the experiments. The previous evening and night had been normal.

At the beginning of the test, the subjects, wearing their normal indoor clothes, sat on a chair with minimal movement and talk for 30 minutes at a room temperature of 21°C. After this adaptation time, each participant immersed his right hand up to the wrist into stirred cold water (10.0 ± 0.5°C) and held the hand in the water for 5 minutes without any movement or talk.

After the CPT, the subjects undressed to shorts, and their height, weight and skin fold thickness were measured. Thereafter, the subjects walked calmly into a warm climatic chamber (27°C, air velocity < 0.2 m/s and relative humidity 30%) nearby and sat there on a chair without any movement or talk, listening to neutral music from earphones for 45 minutes. After this stabilizing period, the test subjects walked slowly into the cold climatic chamber in the next room (5°C, air

velocity <0.2 m/s, relative humidity 50%) and sat there for 45 minutes in the same way as in the first chamber.

4.3.2 Whole body exposure to −15°C (Papers II–V)

Every subject participated three times in the same test procedure, with a one-week interval between the tests during winter from January to March, in 1997–2001. In the first test the subjects were familiarized with the test protocol in order to minimize stress during later measurements. The second and third tests were arranged in a random, double-blind and crossover fashion. The participants ingested antihypertensive drug or placebo once a day for one week in random order before the second and the third tests.

Test procedure has been described in Figure 1. A cuff of the ABPM was put around the right upper arm. SBP, DBP and HR were measured oscillometrically from the right upper arm using an indirect ambulatory blood pressure monitor device (Meditech ABPM-02, Meditech Co, Hungary). SBP, DBP and HR were recorded every three minutes before, during and after the cold exposure. In the hydrochlorothiazide trial (Paper IV) thermistors (YSI-400 series, Yellow Springs, USA) were attached by adhesive tape on the skin of forehead, chest, shoulder, back of hand, anterior femur and calf, dorsal back and foot. A rectal temperature probe (at 10 cm depth) was attached. Skin and rectal temperature was measured continuously and stored at 1 min intervals by Squirrel 1200 -Datalogger (Grant, UK). After fixing the instruments, the subjects wore winter clothing with the thermal insulation of ca. 2.0 clo units, which represents adequate winter clothing. For stabilization, the test subjects sat for 15 minutes on a chair in a climatic chamber (18°C, air velocity < 0.2 m/s and relative air humidity 50%). Thereafter the subjects walked slowly 5 m to the wind tunnel. Subjects sat in the wind tunnel (−15°C, air velocity 3.5 m/s and relative air humidity 50%) on a chair for 15 minutes. After the cold exposure the subjects walked slowly back to the climatic chamber and sat there for 15 minutes. Subjective ratings of the thermal sensation (ISO/DP 10551) and cold pain (5-point scale) were asked just before the cold exposure and 3, 9 and 15 minutes after the start of the cold exposure.

4.4 Outcome measures

During exposure to 5°C, the SBP and DBP and HR were measured oscillometrically every five minutes from the left upper arm using an indirect

ambulatory blood pressure monitor (Meditech ABPM-02, Meditech Co, Hungary). Correspondingly, during exposure to −15°C, SBP, DBP and HR were measured every three minutes. In the hydrochlorothiazide trial (Paper IV) skin and rectal temperatures were measured. Thermistors (YSI-409b series, Yellow Springs, USA) were used to measure skin temperatures from eight skin areas (forehead, chest, shoulder, back of hand, dorsal back, foot, anterior femur and calf). Rectal temperature was measured by YSI 401 thermistors, Yellow Springs, USA. The temperatures were measured continuously and stored at 1 min intervals by a Squirrel 1200 Datalogger (Grant, UK).

Subjective ratings of the thermal sensations (ISO/DP 10551) and cold pain (5-point scale) were asked just before the cold exposure and 3, 9 and 15 minutes after the start of the exposure to −15°C. Thermal sensations and cold pain were not enquired during the exposure to 5°C.

		Climate chamber (before cold exposure)		Wind tunnel (cold exposure)		Climate chamber (after cold exposure)
	1.	2.	3.	4.	5.	6.
Environmental conditions:						
Temperature		18°C		-15°C		18°C
Velocity of air		<0.2 m/s		3.5 m/s		<0.2 m/s
Relative humidity of air		50%		50%		50%
Activity and clothing of the subjects	Wearing winter clothes	Sitting without movement or talking	Wearing outer garment and walking slowly to wind tunnel; distance 5 m	Sitting without movement or talking	Walking slowly to wind tunnel; distance 5 m and taking off the outer garment	Sitting without movement or talking
Measurement of blood pressure and heart rate		x x x x x x		x x x x x x		x x x x x x
Recording thermal sensations		x		x x x		
Time (min)		0 3 6 9 12 15	ca. 5	0 3 6 9 12 15	ca. 3	0 3 6 9 12 15

Fig. 1. Measurement protocol in exposure to −15°C and 3.5 m/s (Papers II–V)

4.5 Formation of the variables

CPT (Paper I)

1. Initial SBP, DBP and HR before immersion were calculated from five values measured before the test. The lowest and highest values were excluded, and the mean of the remaining three measurements was used as the initial value.
2. The peak values and the rise of SBP, DBP and HR during the immersion were recorded as the effects of the CPT.

Whole body cold exposure to 5 ℃ (Paper I)

The following levels of BP and HR variables were calculated or estimated:

Before cold exposure:

1. Means of the last nine measurements values

During cold exposure

1. Means of the last nine measurements values
2. Peak values

The following cold-induced changes in blood pressure and heart rate variables were calculated:

1. Mean cold-induced change: Mean values during the cold exposure – mean values before the cold exposure.
2. Peak cold-induced change: Peak value during the cold exposure – mean value before the cold exposure.

Whole body cold exposure to −15 ℃ (Studies II–V):

The following levels of BP, HR, skin and rectal temperature variables were calculated or estimated:

1. Mean arterial blood pressure (MAP) was calculated as follows: MAP = DBP + (SBP-DBP)/3.
2. Pulse pressure (PP) was calculated as follows: PP = SBP − DBP.

3. Mean skin temperature was calculated as an area-weighed average (Hardy & DuBois 1938).

Before cold exposure:

1. Mean of 9, 12, 15 minutes values before the cold exposure

During cold exposure:

1. Mean values during the cold exposure excluding the highest and lowest values
2. Peak values
3. Values measured three minutes after the start of the cold exposure

After cold exposure:

1. Mean of 9, 12, 15 min, the last three values after the cold exposure

The following cold-induced changes in blood pressure, heart rate, skin and rectal temperature variables were calculated:

1. Rapid cold-induced change: values of three minutes after the start of the cold exposure – mean values before the cold exposure
2. Mean cold-induced change: Mean values during the cold exposure – mean values before the cold exposure.
3. Peak cold-induced change: Peak value during the cold exposure – mean value before the cold exposure.
4. Restoration after the cold exposure: Mean values after the cold exposure – mean values the before the cold exposure.

4.6 Antihypertensive drugs

From every main class of antihypertensive drugs one generic representative has been selected for the study (beta-blocking agent, angiotensin converting enzyme inhibitor, combined alfa- and beta- blocking agent, angiotensin II antagonist, calcium channel blocker and diuretic). All antihypertensive drugs were ones that are widely used for the management of hypertension. The dosages were a typical dosage for starting drug treatment for hypertension. The details of the antihypertensive drugs are described in Table 8.

Table 8. Antihypertensive drugs used the studies (Names, classes, dosages, durations and exposures)

Drug name	Class of antihypertensive drug	Dosage per day	Duration	Exposure
amlodipine (Norvasc ®)	calcium channel blocker	5 mg × 1	3 days	5°C and CPT
eprosartan (Teveten®)	AT II receptor antagonist	600 mg × 1	1 week	−15°C
hydrochlorothiazide, HCTZ (Hydrex®)	diuretic	25 mg × 1	1 week	−15°C
carvedilol (Cardiol®)	combined alfa- and beta-blocking agent	12.5 mg × 1 2 days, 25 mg × 1 5 days	1 week	−15°C
lisinopril (Lisipril®)	ACE-inhibitor	10 mg × 1	1 week	−15°C
metoprolol (Selopral®)	beta-blocking agent	100 mg × 1	1 week	−15°C

4.7 Statistical analysis

The data from exposure to 5°C and CPT were analyzed by SPSS for Windows 5.0 software for statistical analysis. The data from exposures to −15°C were analyzed by SPSS for Windows version 7.5. Data from the exposure to 5°C, −15°C and CPT are given as means + standard deviation (SD). After controlling for normality of distributions of variables, Student's two-tailed paired t-test was used to compare the values of the same subjects with or without drug or placebo. Repeated measured ANOVA was used to compare blood pressures, heart rate, skin and rectal temperature between drugs during −15 °C. Thermal sensations and cold pain are given as median and analyzed by Mann-Whitney Test. P-value <0.05 was regarded as statistically significant.

4.8 Ethical aspects

The study was approved by the Ethics Committee of the Medical Faculty at the University of Oulu. The participants were informed about the test and asked to give written consent. The test subjects were voluntary, and they were able to withdraw from the study at any time without giving an explanation. The test subjects were healthy, part of them having mildly elevated BP. Although the cold exposures caused slight discomfort, they were regarded as tolerable. The cold exposures were of the kind that people could be exposed to outdoors in the wintertime. Moreover, the test subjects had adequate winter clothing during the exposure to −15°C and minimum clothing during exposure to 5°C. The

antihypertensive drugs were ones that are widely used for the management of hypertension. The dosages used were the same as used conventionally to start drug treatment for hypertension.

5 Results

5.1 Thermal responses

During the whole body cold exposure test the mean skin temperature (T_{sk}) decreased significantly from 32.0°C (pre-exposure) to 27.1°C (minimum) during the cold exposure with placebo (Paper IV). Skin temperatures of different body areas decreased significantly during cold exposure. The lowest skin temperature was measured on the cheek (12.9°C), where the temperature decreased rapidly. Skin temperature of the back of the hand decreased from 31.8°C to 29.0°C, of the foot from 30.6°C to 24.7°C, and that of the chest decreased from 34.5°C to 32.5°C during the cold exposure. Rectal temperature was not affected by the cold exposure. During the subsequent rewarming at 18°C, skin temperatures increased slowly but did not reach pre-exposure level in 15 minutes: T_{sk} reached 28.2°C and skin temperatures of the cheek, back of the hand, thigh and foot reached 22.9, 30.7, 27.0 and 25.5°C, respectively.

Thermal sensations ranged from “cold” to “extremely cold” and cold pains from “no pain” to “slight pain” (Table 9).

Table 9. Median of thermal sensations (ISO 10551) and cold pain during active drug and placebo at the end of the cold exposure to −15°C.

Drug	Test subjects	Thermal sensations		Cold pain	
		Active drug	Placebo	Active drug	Placebo
Metoprolol	Hypertensive	Cold	Cold	No pain	No pain
Carvedilol	Normotensive	Cold	Cold	No pain	Slight pain
Carvedilol	Hypertensive	Cold	Cold	No pain	Slight pain
Lisinopril	Hypertensive	Extremely cold	Extremely cold	No pain	No pain
Eprosartan	Hypertensive	Cold	Cold	No pain	No pain
HCTZ	Hypertensive	Cold	Cold	No pain	No pain

5.2 Blood pressure and heart rate responses to the cold exposures without drug

Cold pressor test (Paper I)

CPT increased SDP/DBP from 131/80 mmHg to 144/96 mmHg in CPT. In CPT the peak rise of SBP/DBP was 13/16 mmHg in normotensive subjects (Fig 4). HR increased from 76 beats/min to 83 beats/min in CPT.

Whole body cold exposure to 5℃ (Paper I) and −15℃ (Papers II–V)

In normotensive subjects SBP/DBP increased from same the level (120/76 mmHg and 121/75 mmHg) (before the cold exposures) to 148–147/97–98 mmHg during exposure to 5°C and −15°C (Table 10). SBP/DBP were higher in hypertensive than in normotensive subjects before cold exposure to −15°C. BDP/DBP increased from 125–133/84–91 mmHg maximally to 145–164/105–111 mmHg in hypertensive subjects (Fig 4).

SBP/DBP increased rapidly by exposure to cold (Fig 2). Peak cold-induced rises in normotensive subjects were equal during both cold exposures: SBP/DBP increased 28/21 mmHg during exposure to 5°C and 26/23 mmHg during exposure to −15°C with placebo (Fig 4). The mean rises of SBP/DBP were 15/12 mmHg during exposure to 5°C without drug and 18/16 mmHg during exposure to −15°C with placebo in normotensive subjects (Fig 3). Moreover, in hypertensive subjects peak rises of SBP/DBP were 19–35/20–24 mmHg (exposure to −15°C) (Fig 4), while mean rises of SBP/DBP were 16–23/13–19 mmHg during exposure to −15°C with placebo (Fig 3).

Table 10. SBP, DBP and HR values before, during and after the cold exposure with placebo or without drug in normotensive and mildly hypertensive subjects during whole body cold exposure to 5°C and −15°C. The results are given as means.

Variable	Normotensives		Hypertensives
	Exposure 5°C	Exposure −15°C	Exposure −15°C
SBP			
Before the cold exposure	120	121	125–133
3 min after starting the cold	Not measured	136	140–152
Mean in cold	135	139	141–152
Peak in cold	148	147	145–164
After the cold exposure	Not measured	126	128–134
DBP			
Before the cold exposure	76	75	84–91
3 min after starting the cold	Not measured	89	99–104
Mean in cold	88	91	101–104
Peak in cold	97	98	105–111
After the cold exposure	Not measured	82	89–93
HR			
Before the cold exposure	71	71	71–75
3 min after starting the cold	Not measured	72	63–71
Mean in cold	65	71	65–72
After the cold exposure	Not measured	66	63–66

After the exposure to −15°C SBP/DBP stayed on a higher level (NS) than values before the cold exposure in normo- and hypertensive subjects. (Table 10, Fig 5).

In normotensive subjects, HR decreased during exposure to 5°C and stayed at the same level during exposure to −15°C (Table 9). In hypertensive subjects, HR decreased during exposure to −15°C from values prior to the cold exposure. After the cold exposure to −15°C HR decreased in both normo- and hypertensive subjects.

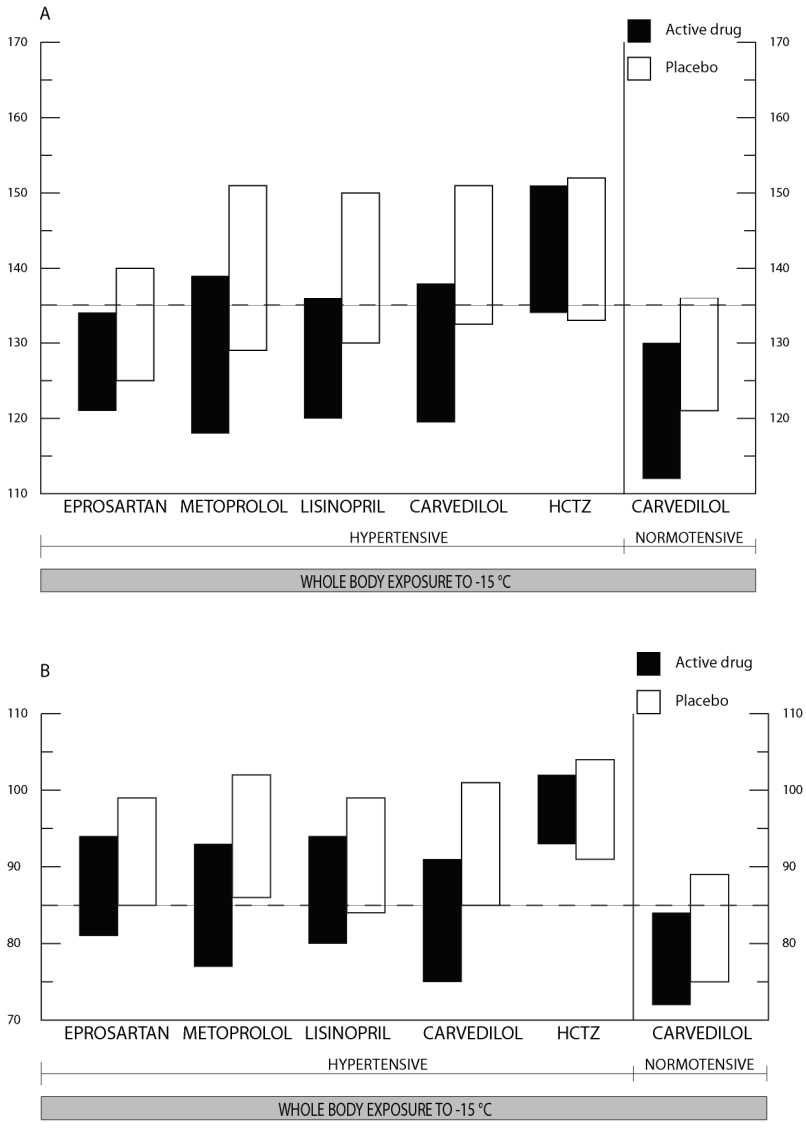

Fig. 2. Rise of systolic blood pressure, SBP (A) and diastolic blood pressure, DBP (B) with drug (eprosartan, metoprolol, lisinopril, carvedilol and HCTZ) and placebo in normotensive and mildly hypertensive subjects. Bottom lines of the columns describe mean BP levels before the cold exposure. Top lines of columns describe mean BP levels three minutes after starting the whole body cold exposure to −15°C.

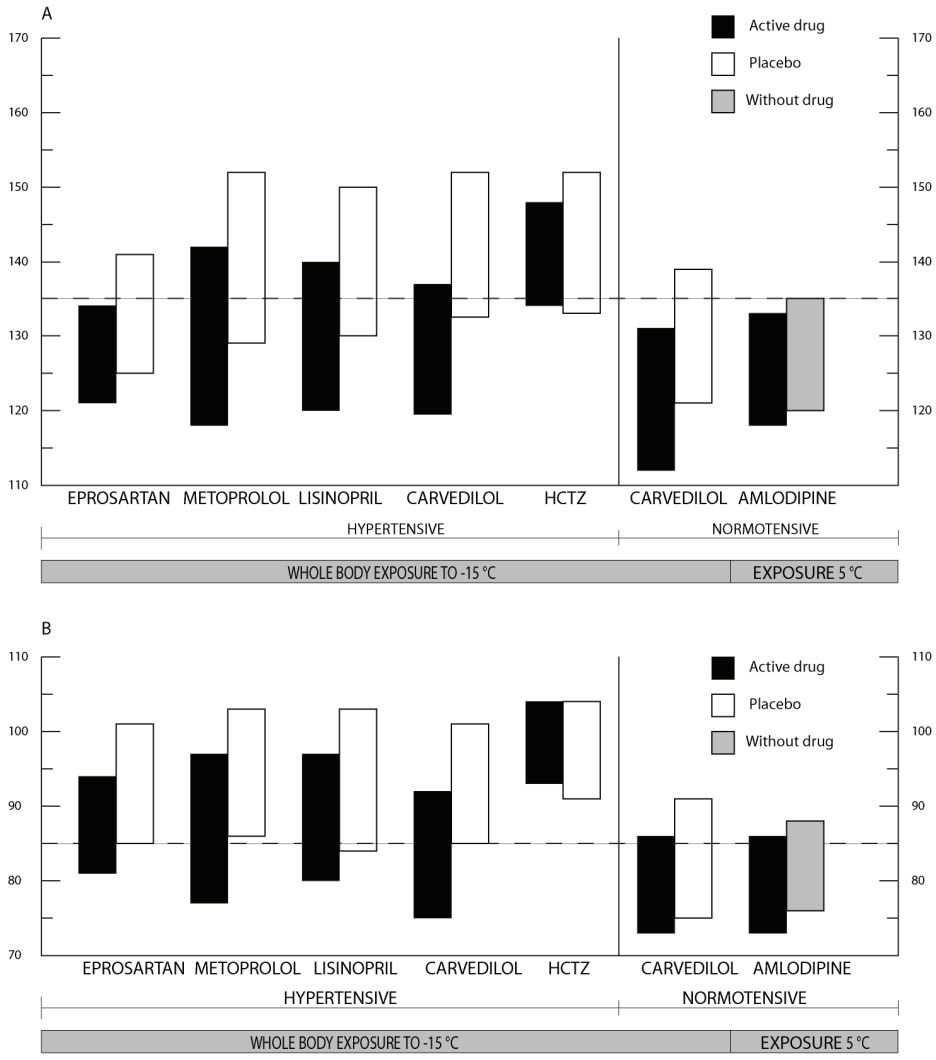

Fig. 3. Mean rise of systolic blood pressure, SBP (A) and diastolic blood pressure, DBP (B) with drug (eprosartan, metoprolol, lisinopril, carvedilol, HCTZ and amlodipine) and placebo or no drug in normotensive and mildly hypertensive subjects. Bottom lines of the columns describe mean BP levels before the cold exposure. Top lines of columns describe mean BP levels during the whole body cold exposure to −15°C and 5°C.

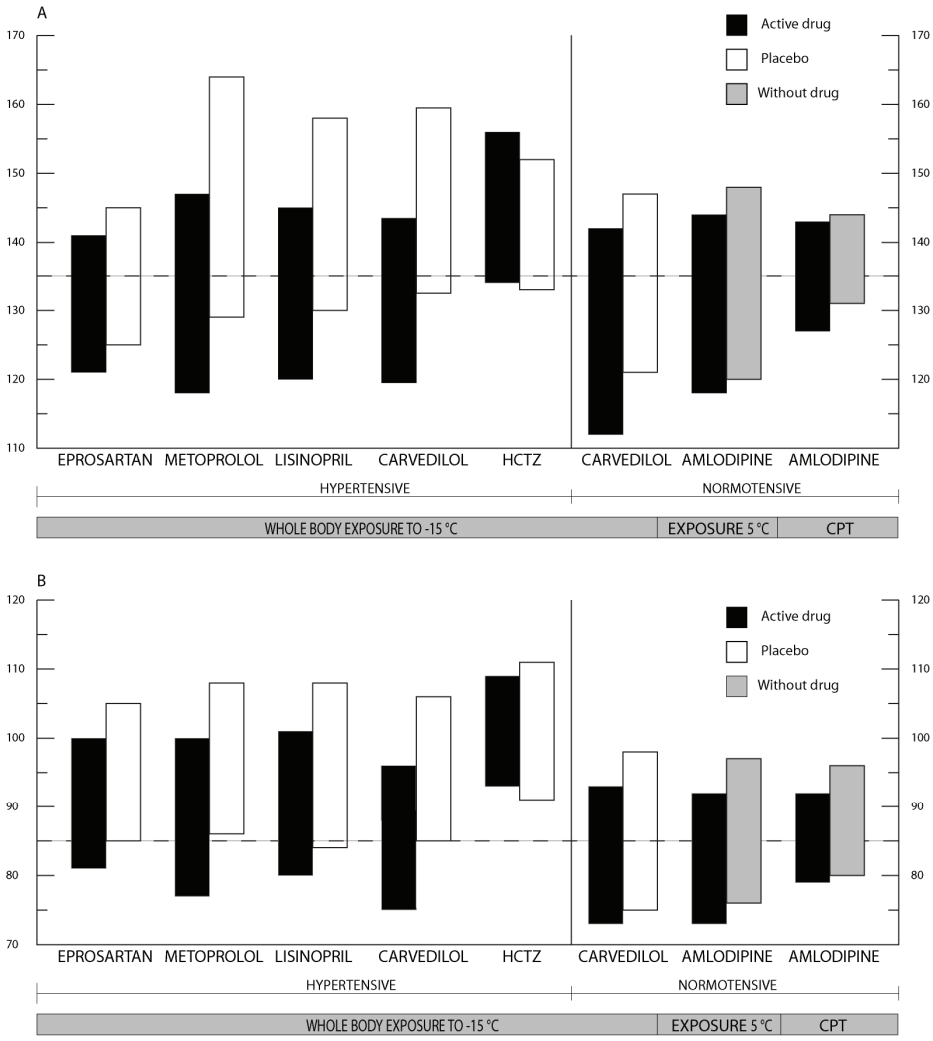

Fig. 4. Peak rise of systolic blood pressure, SBP (A) and diastolic blood pressure, DBP (B) with drug (eprosartan, metoprolol, lisinopril, carvedilol, HCTZ and amlodipine) and placebo or no drug in normotensive and mildly hypertensive subjects. Bottom lines of the columns describe mean BP levels before the cold exposure. Top lines of columns describe peak BP levels during the whole body cold exposure to −15°C and 5°C and CPT (cold pressor test).

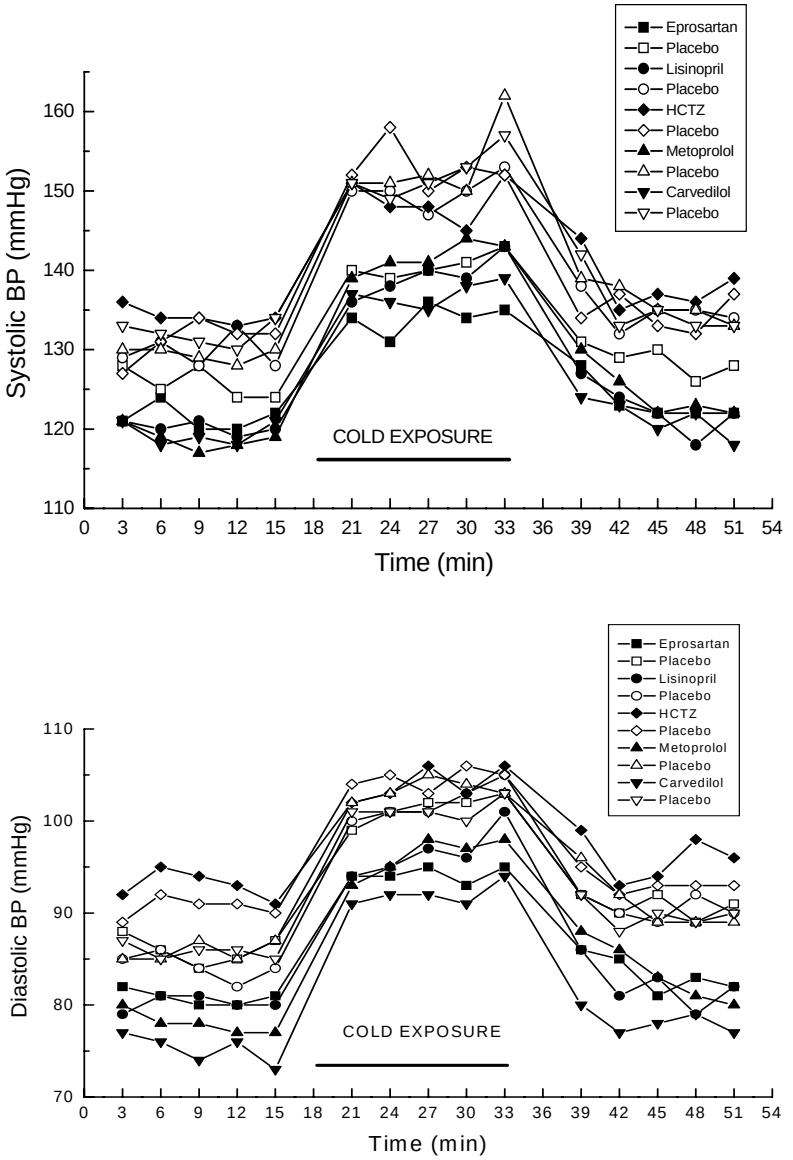

Fig. 5. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) before, during and after the cold exposure to −15ºC with metoprolol, carvedilol, lisinopril, eprosartan and HCTZ and their placebo in mildly hypertensive subjects.

5.3 Effect of antihypertensive drugs on blood pressure and heart rate during cold exposure tests

5.3.1 Blood pressure before the cold exposure

Before the exposure to 5°C SBP/DBP measured 118/73 mmHg with amlodipine and 120/76 mmHg without drug in normotensive subjects (Paper I). The difference was not statistically significant. SDB/DBP prior to exposure to −15°C and 3.5 m/s was 112/72 mmHg with carvedilol and 121/75 mmHg with placebo in normotensive subjects (Paper II). The difference in SBP between carvedilol and placebo was statistically significant (P =0.012). Before the CPT SDP/DBP measured from 127/79 mmHg with amlodipine and 131/80 mmHg without drug in normotensive subjects (Paper I).

Metoprolol, carvedilol, lisinopril and eprosartan decreased SBP, DBP and MAP compared to placebo before exposure to −15°C in hypertensive subjects (Papers II–V, Table 11, Fig 5). The differences compared to placebo were statistically significant in the case of metoprolol, carvedilol and eprosartan, but not lisinopril. HCTZ did not decrease SBP, DBP and MAP compared to placebo in hypertensive subjects before exposure to −15°C. PP varied from 39 mmHg (lisinopril) to 45 mmHg (carvedilol) before the exposure to −15°C during the active antihypertensive drug. PP with lisinopril was statistically significantly lower than with placebo before exposure to −15°C in hypertensive subjects. With other antihypertensive agents PP did not differ statistically significantly from placebo.

5.3.2 Blood pressure during the cold exposure

During the exposure to 5°C SBP/DBP increased maximally to 144/92 mmHg with amlodipine and to 148/97 mmHg without drug in normotensive subjects (Paper I). Difference between amlodipine and without drug was statistically significant. Peak SBP/DBP during the exposure to −15°C was 142/93 mmHg with carvedilol and 147/98 mmHg with placebo in normotensive subjects (Paper II). There was statistically significant difference in DBP between drug and no drug or placebo. Mean SBP/DBP in exposure in exposure to 5°C was 133/86 mmHg with amlodipine and 135/88 mmHg without drug in normotensive subjects (Paper I). There was no statistical difference between amlodipine and no drug. Mean SBP/DBP during exposure to −15°C was 131/86 mmHg with carvedilol and

139/91 mmHg with placebo in normotensive subjects (Paper II). The difference between carvedilol and placebo was statistical significant. In CPT SDP/DBP increased from 127/79 mmHg to 143/92 mmHg with amlodipine in normotensive subjects (Paper I). With no drug SBP/DBP increased from 131/80 mmHg to 144/96 mmHg.

Metoprolol, carvedilol, lisinopril and eprosartan tended to decrease SBP, DBP and MAP compared to placebo during cold exposure to −15°C in hypertensive subjects (Papers II–III & V, Table 11, Fig. 5). HCTZ did not affect SBP, DBP and MAP during cold exposure to −15°C (Paper IV). PPs were statistically significantly lower with carvedilol and lisinopril compared to placebo during the exposure to −15°C in hypertensive subjects, and other drugs (metoprolol, eprosartan and HCTZ) did not affect PP compared to placebo (Papers II–V, Table 11).

There were no statistically significant differences in peak, mean and rapid rises of SBP/DBP between active antihypertensive drugs and placebo or no drug either normo- or hypertensive subjects in whole body cold exposure (Fig 2–4).

5.3.3 Blood pressure after the cold exposure

After the exposure to −15°C SBP/DBP was statistically significantly lower with carvedilol (116/74 mmHg) than with placebo (126/82 mmHg) in normotensive subjects (Paper II, Table 11). Metoprolol, carvedilol, eprosartan and lisinopril, but not HCTZ, decreased the level of SBP, DBP and MAP statistically significantly compared to placebo after the exposure to −15°C in hypertensive subjects (Papers II–V, Table 11, Fig. 5). Mean SBP, DBP and MAP remained at a slightly higher level after the exposure to −15°C in hypertensive subjects compared to the mean values prior to exposure during the active antihypertensive trials, but they were lower than during placebo trials.

5.3.4 Heart rate responses

Metoprolol and carvedilol lowered the HR during the cold exposure to −15°C (Papers II–III, Table 11). Other antihypertensive drugs (eprosartan, lisinopril, amlodipine and HCTZ) did not affect the HR during the cold exposures (Papers I, IV–V).

5.4 Mutual comparison of antihypertensive drugs

Amlodipine (Paper I) and carvedilol (Paper II) were tested in normotensive subjects, but in different exposures: amlodipine at exposure to 5°C and carvedilol at exposure to −15°C. In different cold exposures peak and mean values of SBP/DBP increased an same manner with placebo (carvedilol) and no drug (amlodipine) (Fig. 3–4). Moreover, amlodipine and carvedilol decreased peak and mean DBP in an equal manner (Fig. 3–4), but in prior to exposure carvedilol decreased SBP more than amlodipine (Fig. 4). The peak and mean cold-induced rise of SBP was slightly lower with amlodipine (26/15 mmHg) than carvedilol (30/19 mmHg), while peak and mean increases in DBP were equal (19/13 mmHg with amlodipine and 20/13 mmHg with carvedilol) (Fig. 3–4).

The level of SBP, DBP and MAP was highest with HCTZ before, during and after the exposure to −15°C in hypertensive subjects (Table 11). SBP was lowest with eprosartan (Fig. 5a) and DBP with carvedilol (Fig. 5b). There were no statistical differences in the level of SBP, DBP and MAP between metoprolol, carvedilol, lisinopril and eprosartan during exposure to −15°C in hypertensive subjects. PP varied from 40 mmHg (eprosartan) to 49 mmHg (HCTZ) at the first measurements three minutes after the starting of the cold exposure. Peak PP values varied from 41 mmHg (eprosartan) to 53 mmHg (HCTZ) during the exposure to −15°C in hypertensive subjects. Moreover, mean PP values varied from 40 mmHg (eprosartan) to 45 mmHg (metoprolol, carvedilol and HCTZ).

In hypertensive subjects, there were differences between the drugs in the cold-induced rise of BP. In rapid responses (3-minute value) SBP/DBP varied from 13/13 mmHg (eprosartan) to 21/19 mmHg (metoprolol) (Fig. 2). However, the differences between the drugs were not statistically significant. Peak responses in SBP varied from 20 mmHg (eprosartan) to 29 mmHg (metoprolol) and those of DBP varied from 16 mmHg (HCTZ) to 23 mmHg (metoprolol) (Fig. 4). The differences in the mean rises of SBP/DBP were statistically significant between metoprolol (24/19 mmHg) and eprosartan (13/13 mmHg) and in the mean rise of SBP between eprosartan (13 mmHg) and lisinopril (20 mmHg) (Fig. 3).

SBP/DBP stayed slightly higher after the exposure to −15°C than before the cold exposure (1–4 mmHg) (Table 11). There were no differences between antihypertensive drugs or between antihypertensive drug and placebo after the exposure to −15°C in normo- and hypertensive subjects.

Metoprolol and carvedilol lowered HR, but other antihypertensive drugs did not affect HR (Table 11).

Table 11. SBP, DBP, MAP, PP and HR values before, during and after the cold exposure to −15°C with active drug (metoprolol, carvedilol, lisinopril, eprosartan and HCTZ) and placebo trials in mildly hypertensive subjects. The results are given as means with standard deviations.

Variable	Metoprolol trial		Carvedilol trial		Lisinopril trial		Eprosartan trial		HCTZ trial	
	Metoprolol	Placebo	Carvedilol	Placebo	Lisinopril	Placebo	Eprosartan	Placebo	HCTZ	Placebo
SBP										
Before cold exposure	118 (10)**	129 (9)	119 (11)*	132 (4)	120 (8)	130(13)	121 (8)*	125 (7)	134 (4)	133 (3)
After 3 min cold	139 (10)*	151 (7)	138 (10)	151(6)	136 (11)*	150 (13)	134 (13)	140 (11)	151 (14)	152 (16)
Peak in cold	147 (8)*	164 (14)	143 (9)**	159 (8)	145 (11)*	158 (17)	141 (11)*	145 (9)	156 (5)	152 (6)
Mean in cold	142 (7)*	152 (6)	137 (9)**	152 (7)	140 (9)*	150 (16)	134 (11)*	141 (7)	148 (4)	152 (4)
After cold exposure	122 (8)*	134 (6)	120 (6)**	134 (5)	121 (10)*	132 (10)	122 (8)*	128 (8)	134 (3)	134 (6)
DBP										
Before cold exposure	77 (7)**	86 (7)	75 (7)*	85 (5)	80 (11)	84 (10)	81 (9)*	85 (9)	93 (3)	91 (3)
After 3 min cold	93 (4)*	102 (4)	91 (7)	101 (8)	94 (9)	100 (11)	94 (11)	99 (10)	102 (6)	104 (10)
Peak in cold	100 (3)*	108(5)	96 (6)*	106 (7)	101 (10)	108 (10)	100 (8)	105(8)	109 (2)	111(3)
Mean in cold	97 (3)*	103 (4)	92 (5)*	101 (7)	97 (8)	103 (10)	94 (9)*	101 (8)	104 (2)	104 (2)
After cold exposure	81 (8)*	89 (5)	78 (8)**	89 (7)	82 (9)*	91 (7)	82 (10)*	90 (7)	96 (3)	93 (4)
MAP										
Before cold exposure	91 (7)**	101 (7)	89 (7)	101 (4)	94 (10)	99 (11)	94 (9)**	99 (8)	106 (3)	105 (3)
After 3 min cold	102 (4)*	108 (5)	107 (7)	118 (6)	108 (9)	117 (11)	108 (11)	113 (9)	118 (8)	120 (10)
Peak in cold	115 (4)*	124 (5)	110 (6)	122 (5)	115 (10)	124 (12)	113 (9)*	118 (7)	122 (2)	126 (3)
Mean in cold	112 (4)*	120 (4)	107 (6)	118 (6)	111 (8)	121 (16)	108 (9)**	114 (8)	119 (3)	120 (2)
After cold exposure	95 (7)*	104 (5)	92 (6)	104 (6)	95 (9)*	105 (8)	96 (9)*	103 (7)	110 (3)	107 (4)
PP										
Before cold exposure	41 (8)	43 (5)	45 (9)	46 (7)	39 (4)*	45 (8)	40 (7)	40 (4)	41 (6)	42 (4)
After 3 min cold	45 (9)	49 (5)	46 (9)*	50 (8)	42 (6)**	50 (11)	40 (6)	41 (8)	49 (11)	48 (12)
Peak in cold	47 (6)	56 (11)	48 (7)*	54 (8)	44 (6)**	51 (9)	41 (7)	40 (8)	53 (10)	58 (8)
Mean in cold	45 (5)	49 (7)	45 (8)*	51 (6)	43 (4*)	47 (8)	40 (6)	40 (5)	45 (8)	47 (7)
After cold exposure	41 (5)*	45 (5)	42 (7)	44 (5)	39 (4)	42 (8)	40 (5)	37 (5)	42 (6)	41 (5)
HR										
Before cold exposure	55 (7)*	74 (9)	66 (8)*	75 (11)	70 (9)	73 (12)	70 (16)	71 (10)	77 (5)	72 (5)
After 3 min cold	53 (8)*	71 (12)	60 (11)*	71 (11)	64 (13)	67 (16)	68 (13)	67 (12)	74 (10)	63 (8)
Mean in cold	53 (7)*	72 (12)	61 (11)	68 (8)	66 (10)	71 (11)	68 (13)	68 (9)	72 (3)	65 (3)
After cold exposure	51 (6)*	65 (7)	60 (9)	66 (10)	65 (8)	64 (8)	66 (11)	65 (9)	70 (4)	63 (4)

*= $p<0.05$ drug compared to placebo ** $p\leq 0.001$ drug compared to placebo

6 Discussion

6.1 Rationale for the study

In Europe, the prevalence of hypertension is high and elevated BP is one of the most important risk factors for serious cardiovascular diseases (WHO 2002). Increased morbidity and mortality due to cardio- and cerebrovascular diseases has also been associated with cooler temperatures (e.g. Lejeune *et al.* 1994, Lanska & Hoffmann 1999, Näyhä 2000, Feigin *et al*. 2001, Braga *et al.* 2002, Näyhä 2005) as well as winter or colder months (e.g. Capon *et al.* 1992, Jakovljevic *et al.* 1996, Gyllerup 2000, Passero *et al.* 2000, Nyquist *et al*. 2001, van Rossum *et al.* 2001, Näyhä 2005). Heavy physical exercise in the cold is also a clinically important risk factor for cardiovascular hazards. Heavy snow shovelling in the cold increases the occurrence of cardiac attacks, e.g. myocardial infarction. (Franklin *et al.* 2001, Sipilä *et al*. 2005.)

More than four million people live north of the Arctic Circle (Bogoyavlenskiy & Siggner 2004), with an additional number living in subarctic regions. The daily exposure to cold may vary considerably. For example in Finland, mean daily temperatures are below 0°C 120–200 days per year. The self-reported median total cold exposure time in winter months was 7 h/week at work and 4h/week at leisure-time in Finland according to the National FINRISK 2002 sub-study (Mäkinen *et al.* 2006). People are also exposed to cold while commuting to work.

The present study provides for the first time information about the effects of antihypertensive drugs on BP responses in hypertensive subjects exposed to cold in a similar way as during normal outdoor exposure in winter.

6.2 Cold exposure tests and thermal responses to cold

Human beings may be exposed to cold in different ways. The present study has made use of widely used cold exposure tests such as CPT and whole body cold exposure test. The whole body cold exposure test with adequate winter clothing simulated real outdoor cold exposure in the winter, including rapid face cooling and slower and milder whole body cooling.

CPT (immersion in cold water) of the hand or foot is a widely used cold exposure test and has been seen as “golden standard” because it is easy to carry

out in any laboratory. CPT of the hand or foot causes rapid and strong local cooling with pain sensations (Chang *et al.* 2002*)*. CPT causes a rapid increase in BP. CPT produces a maximal sympathetic response and does not simulate normal outdoor cold exposure, except in fishermen, who immerse their hands repeatedly into cold water (e.g. Krog *et al.* 1960, LeBlanc *et al.* 1960). CPT was used in Paper I where the aim was to investigate how a vasodilating antihypertensive drug (amlodipine) affects BP responses in normotensive test subjects. As CPT-like cold exposure is very rare in normal life, these tests were not continued in further test series.

Whole body cold exposure to 5°C with minimum clothing corresponds to the Mediterranean climate in the wintertime when people wear light clothing (The Eurowinter group 1997). Whole body cold exposure to 5°C was used in Paper I, but as a more natural simulation of cold exposure during the winter in Nordic countries was desired, it was not used in further test series.

Whole body cold exposures to −15°C with adequate winter clothing were used in most of the test series in the present study. This kind of exposure simulates the cold exposure in outdoor conditions during winter in northern Finland. The selected conditions were sufficient to cause a marked rise in BP, but thermal sensations were still tolerable for the test subjects. During the exposure, thermal sensations were described as “cold” – “extremely cold” in different groups, and cold pain was described as “no pain” – “slight pain”. Antihypertensive drugs did not affect thermal sensations or cold pain compared to placebo.

Whole body exposure to −15°C decreased skin temperatures significantly (Paper III). The peripheral parts of the body, e.g. cheek, foot and hand, were markedly cooled, while cooling in the middle parts of body was less marked. The cheek skin temperature decreased to 12.9°C, which was the lowest value measured. In the first six minutes of the cold exposure cheek skin temperature decreased by 5°C. This means that face cooling happened very fast. However, even in the chest, which was well clothed, skin temperature decreased ca. 2°C during the whole 15-minute cold exposure to −15°C. Correspondingly, in peripheral parts of the body skin temperature on the back of the hand decreased ca. 3°C and in the foot ca. 6°C during the whole 15-minute cold exposure to −15°C. These results mean that the first effects of cold exposure resulted from face cooling and later also from whole body cooling. Cooling was therefore not restricted to uncovered and peripheral parts of the body. However, cooling was always superficial, as rectal temperature was not affected by the cold exposure.

This highly standardized test procedure was used in the remaining tests series (Papers II–V). The test subjects were familiarized with the test conditions to minimize the effect of stress before the drug and placebo trials. Moreover, the test subjects prepared themselves for the tests in the same way before all test procedures. During the test the subjects were sitting and did not speak. Moreover, the test subjects were transported to the tests by car to minimize the differences in outdoor cold exposure and physical activity before the test procedures.

All tests series were carried out during wintertime between January and March. The test subjects had consequently recent experiences about exposure to natural cold. Responses to the same cold exposures could have been stronger if the measurements had been carried out in a warm or temperate season. (Mäkinen *et al*. 2004.)

6.3 Test subjects

Both healthy normotensive (Papers I–II) and mildly hypertensive (Papers III–V) subjects were used. Normotension and mild hypertension were confirmed by 24-h ABPM in all series except for amlodipine measurements. In the amlodipine series the 24-h ABPM was not performed, as the test subjects were supposed to be healthy and normotensive. According to 24-h ABPM, BP was lower in normotensive than in hypertensive subjects. DBPs were almost at the same level in all hypertensive groups (84–85 mmHg). SBP varied slightly (127–131 mmHg). According to 24-h ABPM, hypertensive subjects could be classified as “mildly hypertensive”. Persons with so-called “white coat hypertension” were excluded from the study by 24-h ABPM.

Normotensive test subjects (Papers I–II) were 23–24 (mean) years old. They were healthy and without medication. The hypertensive subjects were slightly older (mean 27–32 years) (Papers II–V). BMI was lower in the normotensive (23) than in the hypertensive subjects (24–28). The youngest subjects (mean 27 years) were in the carvedilol group and the oldest (mean 32 years) in the lisinopril group. Moreover, BMI was the lowest in the carvedilol and metoprolol (mean 24) groups and the highest in the lisinopril group (mean BMI 28).

6.4 Measurement protocol

A lot of effort was used to make the measurements as repeatable as possible and to avoid the influence of any other factors (such as physical activity and talking)

besides cold. During the tests the subjects sat quietly during the measurements. After a stabilization period, the test subjects walked slowly a few meters to a wind tunnel, where the cold exposure took place. Physical activity was minimized during the whole test procedure. BP and HR were measured by an ambulatory blood pressure monitoring device. BP was measured semiautomatically and the BP measurements were started manually at 3–5 min intervals. During the cold exposures the researcher was present in the climate chamber and wind tunnel. BP values were downloaded from the BP monitor and recorded on paper. In the HCTZ series (Paper IV) also skin and rectal temperatures were measured.

6.5 Blood pressure and heart rate responses during cold exposure and rewarming

BP was markedly increased by cold exposure from the resting values in all types of cold exposures. The cold-induced rise of BP was higher during whole body cold exposure than during CPT. The magnitude on the cold-induced rise of BP was the same in hypertensive and normotensive subjects. BP seems to be at a slightly higher level after whole body cold exposure than before it.

In the present study BP was markedly increased by all types of cold exposures. This could be seen in both normo- and hypertensive subjects. A widely used cold provocation test, CPT, caused a 13/16 mmHg maximal rise of SBP/DBP in healthy subjects. In earlier studies CPT has induced rises of BP to the level of 9–26/16–24 mmHg in normotensive subjects (see references from Tables 3–6). The response of BP to CPT in the present study was within the range of BP measured in earlier studies (see Tables 3–6).

Compared to CPT, whole body exposure to 5°C with minimal clothing caused a stronger response: 28/21 mmHg vs. 13/16 mmHg (CPT). In other earlier studies (exposure to ca. 4–5°C), BP of normotensive subjects increased 16/5 mmHg (Headley *et al.* 1996) and 12/10 mmHg (Reed *et al.* 1991). These increases in BP were smaller than in the present study. During exposure to −15°C the peak rise (maximal response) of BP was 26/23 mmHg in the normotensive subjects. Both whole body cold exposures to 5°C and −15°C thus caused a rise in BP of a similar magnitude, although different duration of exposure and different clothing of test subjects was used in these cold exposures. Moreover, the present results are supported by Leon *et al.* (1970), who showed an about 20 mmHg maximal increase in SBP at −16°C.

In the present study the mean cold-induced rise of BP was 15/12 during exposure to 5°C and 18/16 mmHg during exposure −15°C and 3.5 m/s wind in normotensive subjects. The present results from normotensive subjects are almost similar to those of Arjamaa *et al*. (2001) who also used whole body cold exposure to −15°C and 3.5 m/s with adequate winter clothing: the increase in BP was ad 17/12 mmHg in healthy subjects. Gavhed *et al*. (2000) have reported the mean increase of SBP/DBP to be 15/13 mmHg during exposure to −10°C and 5 m/s wind. These results are in line with the responses in the present study.

In hypertensive subjects the cold-induced rise of SBP/DBP was 19–35/20–24 mmHg during exposure to −15°C. In the present study the cold-induced rise of BP was similar in hypertensive and normotensive subjects during exposure to −15°C. Moreover, BP was statistically significant higher in hypertensive than normotensive subjects during cold. To our knowledge, there are no earlier published results from hypertensive subjects during whole body cold exposure. During CPT the cold-induced rise of BP was ca. 27–28/15–19 mmHg in hypertensive subjects (see references from Tables 3–6). In earlier studies (Juneau *et al.* 1989, Juneau *et al.* 2002, Blanchet *et al.* 2003) in patients with angina pectoris and heart failure, cold-induced rises of BP were lower than in hypertensive subjects in the present study.

After the cold exposure SBP/DBP seem to be slightly higher in both normo- and hypertensive subjects compared to the pre-exposure levels. During the 15 minutes, the initial BP did not reach the level measured prior to exposure.

In earlier cold exposure studies, HR has been unchanged (Kilgour & Calvalho 1994), increased (McLean *et al.* 1992) or decreased (e.g. Allen *et al.* 1992, Collins *et al*. 1996) depending on the cooling rate and time (Granberg 1991). In this study HR decreased during both whole body cold exposures (5°C and −15°C). On the contrary, HR increased during CPT, as also shown by Victor *et al*. (1987) and Fagius *et al.* (1989). After the whole cold exposure, the decrease in heart rate continued. The reason for this could be psychological: end of the cold stress or an associated decrease in HR caused by warmth.

6.6 The effect of antihypertensive drugs on blood pressure and heart rate responses in cold and rewarming

Antihypertensive drugs (metoprolol, carvedilol, lisinopril, eprosartan and amlodipine) decreased the level of BP, but did not affect markedly the size of the cold-induced rise of BP in mildly hypertensive subjects. There were some slight

differences between antihypertensive drugs: the mean cold-induced rise of SBP/DBP was lower with eprosartan compared to metoprolol. HCTZ did not affect the level of BP during the cold exposure in mildly hypertensive subjects. The short treatment time (one week) may partly explain why HCTZ did not affect BP. Moreover, the dosage of HCTZ was low, but that is a typical dosage (12.5–25 mg) in combination antihypertensive drug therapy.

In the present study, BP levels were decreased by metoprolol, carvedilol, lisinopril, eprosartan and amlodipine, but not HCTZ. However, the drugs did not markedly affect the cold-induced rise in BP in either normo- or hypertensive subjects. In normotensive subjects (amlodipine and carvedilol) the effect of the drug on BP levels was smaller than in hypertensive subjects (carvedilol, eprosartan, lisinopril and metoprolol) during cold. In hypertensive subjects, carvedilol, eprosartan, lisinopril and metoprolol decreased BP nearly to the levels of normotensive subjects during cold. This is well known in warm conditions, and the present study shows that the drugs work in the cold. The mean rise of SBP/DBP in the eprosartan group was lower than the mean rise of SBP/DBP in the metoprolol group, but the difference between eprosartan and its placebo was not statistically significant. In other groups the cold-induced rises of BP did not differ significantly from each other. In earlier studies, atenolol (Headley *et al.* 1996) and propranolol (Reed *et al.* 1991, Headley *et al.* 1996) decreased SBP, but not DBP during exposure to 4–5^{o}C in healthy normotensive subjects. The cold-induced rise of SBP/DBP was also higher with atenolol (Headley *et al.* 1996) and propranolol (Reed *et al.* 1991, Headley *et al.* 1996) than with placebo. These results differ from the results of the present study. To our knowledge, there are no studies with whole body cold exposure in hypertensive subjects.

The dosages were typical starting dosages for the management of elevated BP. Because of this, the dosages could not be quite equivalent to each other. The antihypertensive drugs were not studied in the same study with regard to their dosage and lowered BP. The dosages of metoprolol and carvedilol could also be considered to be equivalent: carvedilol 25 mg to 50 mg and metoprolol 100 mg to 200 mg daily have an equivalent efficacy in mild to moderate essential hypertension (Weber *et al.* 1996). Lisinopril 10–20 mg and metoprolol 100–200 mg were equivalent (Fimodt-Moeller *et al.* 1991). Double doses of lisinopril (20 mg) and metoprolol (200 mg) are almost equivalent (de Cesaris *et al.* 1993). Moreover, the treatment was of short duration, i.e. one week, meaning that no steady state was reached.

The effects of cold exposure are mainly mediated via α_2-adrenoceptors (Zelis 1983, Flavahan *et al*. 1985, Ekenvall *et al.* 1988), but also via α_1-adrenoceptors (Harada *et al*. 1996, Klemsdahl *et al.* 1996). There is evidence that subtype α_{2C}-adrenoceptors may play a selective role in thermoregulation (Savino & Varela 1999, Jeyaraj *et al.* 2001, Chotani *et al.* 2005). β-Adrenoceptors have been shown to play a minor role in cold-induced vasoconstriction (Reed *et al.* 1991). The main mechanisms of effects are well known in the case of the antihypertensive drugs studied. However, the drugs could also have other unknown mechanisms of effect. None of the tested antihypertensive drugs affected α_2-adrenoceptors directly. Carvedilol, a combined alfa- and beta-blocking agent, blocks α_1- and β-adrenoceptors. Metoprolol, a selective beta-blocking agent, blocks β_1-adrenoceptors. No significant differences could be seen in the effect on BP during cold between the antihypertensive drugs studied (metoprolol, carvedilol, lisinopril and eprosartan).

In addition to vasomotor mechanisms, cold-induced rise of BP could have, at least partially, another cause: increase in muscular tonus. For example, 20% of maximal voluntary contractions in handgrip exercise increased BP by the same amount (Lind *et al.* 1964) as the cold-induced rise in the present study. Knee extension (15% of MCV) and CPT also caused the same rise in BP as cold-induced rise of BP. Together these provocations caused a greater effect on BP than each test separately. (Peikert & Smolander 1991.) The present data offer no parameters to analyze the possible effect of muscle tonus. If that phenomenon is true, cold-induced rise of BP might be lowered by drugs of a different kind from antihypertensive drugs.

The duration of treatment by drugs was relatively short and steady state could not be reached. In the amlodipine trials the treatment time was three days and in most of trials one week. Moreover, the halftime of amlodipine is 36 hours and steady state was not reached after three days of treatment. In spite of that, amlodipine decreased BP slightly during cold. For example HCTZ could cause vasoconstriction at the beginning of the treatment and vasodilatation later on. It is difficult to arrange treatments of sufficiently long duration as confounding factors become stronger; for example, test subjects do not take drugs, thermal adaptation may change (outdoor temperature may increase and response to cold may become stronger) and test subjects might get an infection with fever, which is a contraindication for participation in the study. Moreover, there are ethical aspects associated with how long treatment can be give to subjects who do not normally need drug treatment.

During the use of antihypertensive drugs SBP/DBP decreased better after cold exposure than during placebo treatment. There were no significant differences between the drugs, but SBP/DBP tended to decrease faster to rest level with carvedilol than other antihypertensive drugs. That may be due to the alfa-blocking effect of carvedilol. Going back to warm temperature caused vasodilation and a decrease in BP. The vasodilation effect of alfa-blocking may have caused stronger and faster vasodilation.

Metoprolol and carvedilol decreased HR significantly compared to placebo during whole body cold exposure. Lisinopril, eprosartan and HCTZ did not affect HR during whole body cold exposure. These results were in line with what could be hypothesized. Metoprolol and carvedilol decreased HR via their beta-blocking effect. Metoprolol had a slightly greater effect than carvedilol; this is known from earlier studies in treatment trials.

In the present study the test subjects sat during the exposures without moving or speaking. Exercise may modulate the cold-induced rise of BP. It has been shown that light exercise (walking ca. 2.8 km/h) markedly inhibits the cold-induced rise of BP (Gavhed 2003), while heavy dynamic exercise and light isometric exercise increase BP more than does exposure to cold (Lind *et al.* 1964, Peikert & Smolander 1991).

6.7 Strengths and limitations of the study

The test conditions in exposure to −15°C were highly standardized and simulated normal outdoor cold exposure in winter, which makes the results applicable to everyday life. These tests conditions have been developed based on the exposure to 5°C. Cold exposure to −15°C corresponds to outdoor cold exposure in northern Scandinavia. The clothing with 2 clo insulation corresponds to normal good winter clothing. The cold exposure to −15°C caused a strong and repeatable rise in blood pressure. All the test series in cold exposure to −15°C were arranged in the same way, but during the HCTZ trial thermal measurements were made (skin and rectal temperatures). During the test the test subjects sat without movement or talking. The test subjects were familiarized with the test procedure to minimize the effect of stress on BP responses. Moreover, the test subjects were transported to the tests by car to minimize cold exposure and physical activity before the tests. Antihypertensive drugs and placebos were given in a double blind manner and random order. In cold exposures to −15°C the test subjects were mildly

hypertensive subjects, which was carefully verified by ambulatory measurements before the tests.

The number of subjects in the study groups was quite low, varying from six to fourteen. This can be regarded as one of the limitations of the study. However, the number of test subjects was similar as or higher than in other published studies with this type of experimental protocol, and in this study the test circumstances were highly standardized. If small study groups fail to show statistically significant differences, that does not exclude the possibility that there were real differences (beta error). None of the antihypertensive drugs in the present study prevented cold-induced rise of BP, but the drugs did decrease BP levels, except in the HCTZ trials. The antihypertensive treatment was short, three days in the case of amlodipine and one week with the last ones. The short treatment might explain why HCTZ did not decrease BP and why steady state was not reached. In addition, the subjects were only mildly hypertensive, so the results are not applicable to severely hypertensive population. Furthermore, the test subjects were young adults, so the results cannot be directly applied to older patients. The doses of antihypertensive drugs used were typical starting dosages and there might be some differences in equivalence between the doses of different drugs. The amlodipine study (Paper I) had no placebo and familiarization to test procedure; these could affect the BP responses. In addition, the effects of exercise were excluded, which affects responses in both positive and negative ways: there was an abnormal situation compared to normal life when the subjects stayed in the cold without movement – the only exception being waiting for the bus.

6.8 Clinical implications

Antihypertensive drugs (metoprolol, carvedilol, lisinopril and eprosartan) decreased significantly BP levels during cold exposure in mildly hypertensive subjects. Antihypertensive drugs did not affect the size of the rise of BP compared to placebos. It is important that the BP level decreased, because if a person has elevated BP and that is decreased by antihypertensive drugs, we could suppose that BP decreases in lower environment temperatures as well. Based on this, we could suppose that the occurrence of complications related to cold exposure, e.g. cardiovascular morbidity and mortality, could also be lowered.

In the present studies DBP was markedly increased by cold in spite of the fact that the test subjects sat during the test without any physical activity. In the present study maximal levels of DBP were 105–111 mmHg in placebo trials and

96–109 mmHg in active antihypertensive drug trials. That phenomenon may have clinical importance, because DBP was measured at rest as reference BP values according to management guidelines (Guidelines Committee 2003, Mancia *et al.* 2007). It has also been shown that DBP is a stronger predictor than SBP in young hypertensive subjects (Greenberg 2006). Each 20 mmHg increment in SBP or 10 mmHg in DBP doubles the risk of cardiovascular disease across the entire BP range from 115/75 to 185/115 mmHg in individuals aged 40 to 70 years (Lewington *et al.* 2002). Stroke mortality rate was about eight-fold when DBP was about 100 mmHg compared to 75 mmHg in DBP (Lewington *et al.* 2002).

After the cold exposure BP decreased slowly and remained slightly higher in normo- and hypertensive subjects compared to BP prior to exposure with placebo. This phenomenon may have clinical significance, because on some occasions the measurement of BP is done after a very short time period after coming into room temperature, even though hypertension management guidelines recommend a longer waiting time before the measurements (Guidelines committee 2003). These are sources of error for measurements of BP and may indicate higher BP values than at rest. Secondly, that phenomenon is important in persons who work repeatedly both indoors and outdoors, possibly with frequent changes between a warm and a cold work environment.

Should the present findings be taken into account in the treatment of hypertensive patients exposed to a cold environment? According to the newest guidelines (Mancia *et al.* 2007) the first-line antihypertensive drugs for monotherapy and in combination are diuretics, betablocker (including combined alpha and betablocker), ACE inhibitor, angiotensin II antagonist or calcium channel blocker. The use of betablockers should be preferred in patients with ischaemic heart disease or heart failure. Betablockers should not be used in patients with a metabolic disease and at high risk for incident diabetes. Vasodilator betablockers (e.g. Carvedilol) are better in these situations compared to older betablockers. Diuretics also impair lipid metabolism. The present results suggest that the hypertensive subjects exposed to cold, either during work or leisure, can be treated according to the newest guidelines. However, it is possible that cold-exposed subjects need higher dosages and more frequently combination therapy because of higher BP in cold. Moreover, cold-exposed subjects must have a more careful follow-up.

7 Conclusions

In the present study, resting BP was markedly increased by all types of cold exposure. Whole body cold exposures (5°C and −15°C) increased both SBP and DBP more than CPT. Cold exposure to −15°C with adequate winter clothing and to 5°C with minimal clothing caused a similar increase in BP. There were no differenced in the cold-induced rise in BP between normotensive and mildly hypertensive subjects. The whole body cold exposures (5°C and −15°C) decreased HR, whereas CPT increased it.

Antihypertensive drugs (metoprolol, carvedilol, lisinopril, eprosartan, amlodipine and HCTZ) did not markedly affect the size of the cold-induced rise of BP compared to placebo or no drug in normo- and hypertensive subjects. Metoprolol, carvedilol, lisinopril and eprosartan, but not HCTZ, decreased the level of BP during the cold exposure compared to placebo in mildly hypertensive subjects, due to the drug-induced decrease in the initial level of BP before exposure to cold. Antihypertensive drugs (metoprolol, carvedilol, lisinopril, eprosartan), but not HCTZ, affected BP generally in a similar way during exposure to −15°C. However, there were small differences in BP between the antihypertensive drugs during exposure to −15°C and after the exposure: carvedilol tended to decrease BP faster during rewarming, while HCTZ did not affect the level of BP during the cold exposure in mildly hypertensive subjects. Although the magnitude of the cold-induced rise in BP was not affected by the drugs, the drug-induced decrease in the level of BP kept the peak values in the cold closer to the recommended threshold limit values.

The present study provides for the first time information about the effects of antihypertensive drugs on BP responses in hypertensive subjects exposed to cold in a similar manner as during normal outdoor exposure in winter. Future studies on the effects of antihypertensive drugs on BP in cold conditions should focus especially on the effects of natural cold exposure in everyday life, both at work and in leisure time conditions.

References

Ajayi AA, Lees KR & Reid JL (1986) Effects of angiotensin converting enzyme inhibitor, perindopril, on autonomic reflexes. Eur J Clin Pharmacol 30: 177–182.

Andren L & Hansson L (1981) Circulatory effects of stress in essential hypertension. Acta Med Scand 646 (Suppl): 69–72.

Anderson T & Le Riche W (1970) Cold weather and myocardial infarction. Lancet 1: 291–296.

Anderson TW & Rochard C (1979) Cold snaps, snowfall and sudden death from ischemic heart disease. Can Med Assoc J 121: 1580–1583.

Al'Absi M & Petersen K (2003) Blood pressure but not cortisol mediates stress effect on subsequent pain perception in healthy men and women. Pain 106: 285–295.

Allen MT, Shelley KS & Boquet AJ Jr (1992) A comparison of cardiovascular and autonomic adjustments to three types of cold stimulation tasks. Int J Psychophysiol 13: 59–69.

Antikainen RL, Moltchanov VA, Chukwuma C Sr, Kuulasmaa KA, Marques-Vidal PM, Sans S, Wilhelmsen L, Tuomilehto JO & for the WHO MONICA Project (2006) Trends in the prevalence, awareness, treatment and control of hypertension: the WHO MONICA Project. Eur J Cardiovasc Prev Rehabil 13: 13–29.

Argani H & Javanshir MR (2004) Seasonal variations of blood pressure in hemodialysis and renal transplant recipients. Transplant Proc 36(1): 148–149.

Argiles A, Lorho R, Servel MF, Chong G, Kerr PG & Mourad G (2004) Seasonal modifications in blood pressure are mainly related to interdialytic body weight gain in dialysis patients. Kidney Int 65(5): 1795–1801.

Arjamaa O, Mäkinen T, Turunen L, Huttunen P, Leppäluoto J, Vuolteenaho O & Rintamäki H (2001) Are the blood pressure and endocrine responses of healthy subjects exposed to cold stress altered by an acutely increased sodium intake? Eur J Appl Physiol 84: 48–53.

Aronow W & Ahn C (2004) Elderly nursing home patients with congestive heart failure after myocardial infarction living in New York City have a higher prevalence of mortality in cold and warm weather months. J Gerontol A Biol Sci Med Sci 59(2): 146–147.

Azegami M, Hongo M, Yazaki Y, Yanagisava S, Yamazaki A & Imamura H (2005) Seasonal difference in onset of coronary heart disease in young Japanese patients: comparison with older patients. Circ J 69: 1176–1179.

Aylin P, Morris S, Wakefield J, Grossinho A, Jarup L & Elliot P (2001) Temperature, housing, deprivation and their relationship to excess winter mortality in Great Britain, 1986–1996. Int J Epidemiol 30: 1100–1108.

Baker-Blocker A (1982) Winter weather and cardiovascular mortality in Minneapolis-St. Paul. Am J Public Health 72(3): 261–265.

Barnett AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S & WHO MONICA Project (2005) Cold periods and coronary events: an analysis of populations worldwide. J Epidemiol Community Health 59(7): 551–557.

Bean WB & Mills CA (1938) Coronary occlusion, heart failure, and environmental temperatures. Am Heart J 16: 701–713.

Beaulieu M, Lacourciere Y & Cleroux J (1994) Unchanged neurogenic vasoconstrictor response after exercise during angiotensin converting enzyme inhibition with fosinopril. Am J Hypertens 7: 763–766.

Benetos A & Safar ME (1991) Response to the cold pressor test in normotensive and hypertensive patients. Am J Hypertens 4 (7 Pt 1): 627–629.

Benfield P, Clissold SP & Brogden RN (1986) Metoprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. Drugs 31: 376–429.

Blanchet M, Ducharme A, Racine N, Rouleau JL, Tardif JC, Juneau M, Marquis J, Larivee L, Nigam A, Fortier A & White M (2003) Effects of cold exposure on submaximal exercise performance and adrenergic activation in patients with congestive heart failure and the effects of beta-adrenergic blockade (carvedilol or metoprolol). Am J Cardiol 92(5): 548–553.

Bogoyavlenskiy D & Siggner A (2004) Arctic Demography. In: AHDR (Arctic Human Development Report). Akureyri: Stefansson Arctic Institute, 27–41.

Boulay F, Berthier F, Sisteron O, Gendreike Y & Gibelin P (1999) Seasonal variation in chronic heart failure hospitalizations and mortality in France. Circulation 100: 280–286.

Braga A, Zanobetti A & Schwartz J (2002) The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. Environ Health Perspect 110(9): 859–863.

Brennan PJ, Greenberg G, Miall WE & Thompson SG (1982) Seasonal variation in arterial blood pressure. Br Med J 285: 919–923.

Brown CF & Oldridge NB (1985) Exercise-induced angina in the cold. Med Sci Sports Exerc 17(4): 607–612.

Brown GM & Page J (1952) The effect of chronic exposure to cold on temperature and blood flow of the hand. J Appl Physiol 5: 221–227.

Brueren MM, Schouten BJ, Schouten HJ, van Weel C, de Leeuw PW & van Ree JW (1998) No relevant seasonal influences on office and ambulatory blood pressure: data from a study in borderline hypertensive primary care patients. Am J Hypertens 11: 602–605.

BS7915 (1998) Ergonomics of thermal environment. Guide to design and evolution of working practices for cold indoor environments. British Standards Institution.

Budd GM, Brotherhood JR, Beasley FA, Hendrie AL, Jeffery SE, Lincoln GJ & Solaga AT (1993) Effects of acclimatization to cold baths on men's responses to whole-body cooling air. Eur J Appl Physiol Occup Physiol 67: 438–449.

Budd GM & Warhaft N (1970) Urinary excretion of adrenal steroids, catecholamines and electrolytes in man, before and after acclimatization to cold in Antarctica. J Physiol 210(4): 799–806.

Bull GM (1973) Meteorological correlates with myocardial and cerebral infarction and respiratory disease. Br J Prev Soc Med 27(2): 108–113.

Campbell BC, Sturani A & Reid JL (1985) Evidence of parasympathetic activity of the angiotensin converting enzyme inhibitor, captopril, in normotensive man. Clin Sci 68: 49–56.

Capon A, Demeurisse G & Zheng L (1992) Seasonal variation of cerebral hemorrhage in 236 consecutive cases in Brussels. Stroke 23: 24–27.

Carson C, Hajat S, Armstrong B & Wilkinson P (2006) Declining vulnerability to temperature-related mortality in London over the 20th century. Am J Epidemiol 164(1): 77–84.

Castellani JW, Young AJ, Sawka MN & Pandolf KB (1998) Human thermoregulatory responses during serial cold-water immersions. J Appl Physiol 85(1): 204–209.

Chang PF, Arendt-Nielsen L & Chen AC (2002) Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. Brain Res Bull 57(5): 667–675.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ & The National High Blood Pressure Education Program Coordinating Committee (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 report. JAMA 289: 2560–2572.

Chotani MA, Mitra S, Eid AH, Han SA & Flavahan NA (2005) Distinct cAMP signaling pathways differentially regulate α_{2C}-adrenoceptor expression: role in serum induction in human arteriolar smooth muscle cells. Am J Physiol Heart Circ Physiol 288: H69–H76.

Cohen IM, O'Connor DT, Preston RA & Stone RA (1981) Long-term clonidine effects on autonomic function in essential hypertensive man. Eur J Clin Pharmacol 19: 25–32.

Collins KJ, Abdel-Rahman TA, Easton JC, Sacco P, Ison J & Dore CJ (1996) Effects of facial cooling on elderly and young subjects: interactions with breath-holding and lower body negative pressure. Clin Sci 90(6): 485–492.

Cordioli E, Pizzi C & Martinelli M (2000) Winter mortality in Emilia-Romagna, Italy. Int J Circumpolar Health 59: 164–169.

Corsonello A, Incalzi RA, Pedone C, Corica F, Mazzei B, Carosella L, Perticone F, Carbonin P & GIFA Investigators (2003) Seasonal hypertension: a clue to explain the high prevalence of unrecognized hypertension in the elderly? Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA). Aging Clin Exp Res 15(4): 296–300.

Cowley AW (1992) Long-term control of arterial blood pressure. Physiol Rev 72: 231–300.

Crawford V, McCann M & Stout R (2003) Changes in seasonal deaths from myocardial infarction. QJM 96: 45–52.

Daanen H (1997) Central and peripheral control of finger blood flow in the cold. Dissertation, Vrije Universitet.

Danet S, Richard F, Montaye M, Beuchant S, Lemaire B, Graux C, Cottel D, Marecaux N & Amouyel P (1999) Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths. A 10-year survey: The Lille-World Health Organization MONICA project (Monitoring trends and determinants in cardiovascular disease). Circulation 100(1): E1–E7.

de Castro MC, Mion Junior D, Marcondes M & Sabbaga E (1998) Seasonal variation of blood pressure in maintenance hemodialysis. Sao Paulo Med J 116(4): 1774-1777.

De Cesaris R, Ranieri G, Andriani A, Filitti V, Bonfantino MV, Lamontanara & Ferrieri A. (1993) [Antihypertensive action of nicardipine retard in 24 hours and its effect on stress]. (in Italian). Minerva Med 84: 533–539.

de Mey C, Enterling D, Hansen-Schmidt S & Meineke I (1989) SK&F 86466, a novel alpha-adrenolytic drug: effects on heart rate, blood pressure, and neuroendocrine function in supine resting position and in response to postural and cold stimulation in normal humans. J Cardiovasc Pharmacol 13(1): 25–31.

de Swiet M, Fayers PM & Shinebourne EA (1984) Blood pressure in four and five-year-old children: the effects of environment and other factors in it's measurement--the Brompton study. J Hypertens 2(5): 501–505.

Delgado C & Weder AB (2000) Pathophysiology of hypertension. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London: 595–599.

DiBona GF & Kopp UC (1997) Neural control of renal function. Physiol Rev 77: 75–197.

Dikshit MB & Patrick JM (1986) Beta-adrenoceptor blockade and cardiovascular response to the cold pressor test. Indian J Physiol Pharmacol 30: 1–10.

Donaldson GC, Ermakov SP, Komarov YM, McDonald CP & Keatinge WR (1998a) Cold related mortalities and protection cold in Yakutsk, eastern Siberia: observation and interview study. BMJ 317: 978–982.

Donaldson GC, Tchernjavskii VE, Ermakov SP, Bucher K & Keatinge WR (1998b) Winter mortality and cold stress in Yakaterinburg, Russia: interview survey. BMJ 316: 514–518.

Donaldson GC & Keatinge WR (1997) Mortality related to cold weather in elderly people in southeast England 1979–1994. BMJ 315: 1055–1056.

Duprez D, De Backer T, De Pue N, Hermans L, De Buyzere M & Clement DL (1991) Effects of isradipine on peripheral hemodynamic reflex responses in mild-to-moderate essential hypertension. Am J Hypertens 4: 194S–196S.

Ekenvall L, Lindblad LE, Norbeck O & Etzell BM (1988) α-Adrenoceptors and cold-induced vasoconstriction in human finger skin. Am J Physiol 255: H1000–H1003.

Emmett JD (1995) A review of heart rate and blood pressure responses in the cold in healthy subjects and coronary artery disease patients. J Cardiopulm Rehabil 15: 19–24.

Eng H & Mercer JB (1998) Seasonal variations in mortality caused by cardiovascular diseases in Norway and Ireland. J Cardiovasc Risk 5(2): 89–95.

Epstein SE, Stamber M, Beiser GD, Goldstein RE & Braunwald E (1969) effects of a reduction in environmental temperature on the circulatory response to exercise in mam. Implications conserning angina pectoris. N Engl J Med 280: 7–11.

Fabiani ME, Dinh D, Nassis L & Johnston CI (2000) Angiotensin-converting enzyme: Basic properties, distribution, and functional role. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 595–599.

Fagius J, Karhuvaara S & Sundlof G (1989) The cold pressor test: effects on sympathetic nerve activity in human muscle and skin nerve fascicles. Acta Physiol Scand 137: 325–334

Fasano ML, Gaeta I, De Simone G, Iannuzzi R & Ferrara LA (1991) Cardiovascular response to adrenergic stimulation during treatment with tertatolol. A new non-cardioselective beta-blocking agent in primary hypertensive patients. Jpn Heart J 32: 435–444.

Feigin V, Anderson C, Anderson N, Broad J, Pledger M, Bonita R & for the Australasian Co-operative Research Group on Subarachnoid Haemorrhage Study (ACROSS) and Aucland Stroke Studies (2001) Is there a temporal pattern in the occurrence of subarachnoid hemorrhage in southern hemisphere? Pooled data from 3 large, population-based incidence studies in Australasia, 1981 to 1997. Stroke 32: 613–619.

Field TS & Hill MD (2002) Weather, Chinook, and stroke occurrence. Stroke 33: 1751–1758.

Flavahan NA, Lindblad LE, Verbeuren TJ, Shepherd JT & Vanhoutte PM (1985) Cooling and α_1- and α_2 -adrenergic responses in cutaneous veins: role of receptor reserve. Am J Physiol 249: H950–H955.

Frank SM, el-Gamal N, Raja SN & Wu PK (1996) Alpha-adrenoceptor mechanisms of thermoregulation during cold challenge in humans. Clin Sci 91(5): 627–631.

Franklin BA, George P, Henry R, Gordon S, Timmis GC & O'Neill WW (2001) Acute myocardial infarction after manual or automated snow removal. Am J Cardiol 87(11): 1282–1283.

Frimodt-Moeller J, Poulsen D, Kornerup HJ & Bech P (1991) Quality of life, side effects and efficacy of lisinopril compared with metoprolol in patients with mild to moderate essential hypertension. J Hum Hypertens 5: 215–221.

Frishman WH & Jorde U (2000) β-adrenergic blockers. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 590–594.

Frost DB, Auliciems A & de Freitas C (1992) Myocardial infarct death and temperature in Auckland, New Zealand. Int J Biometeorol 36(1): 14–17.

Fujiwara T, Kawamura M, Nakajima J, Adachi T & Hiramori K (1995) Seasonal differences in diurnal blood pressure of hypertensive patients living in a stable environmental temperature. J Hypertens 13: 1747–1752.

Fyhrqvist F, Saijonmaa O, Metsärinne K, Tikkanen I, Rosenlof K & Tikkanen T (1990) Raised plasma endothelin-1 concentration following cold pressor test. Biochem Biophys Res Commun 169(1): 217–221.

Gavhed D (2003) Human responses to cold and wind. Dissertation. Karolinska Institutet, Stockholm, Sweden.

Gavhed D, Mäkinen T, Holmer I & Rintamäki H (2000) Face temperature and cardiorespiratory responses to wind in thermoneutral and cool subjects exposed to −10°C. Eur J Appl Physiol 83: 449–456.

Giaconi S, Ghione S, Palombo C, Genovesi-Ebert A, Marabotti C, Fommei E & Donato L (1989) Seasonal influences on blood pressure in high normal to mild hypertensive range. Hypertension 14(1): 22–27.

Giaconi S, Palombo C, Genovesi-Ebert A, Marabotti C, Volterrani D & Ghione S (1988) Long-term reproducibility and evaluation of seasonal influences on blood pressure monitoring. J Hypertens Suppl 6(4): S64–S66.

Giesbrecht GG (1995) The respiratory system in a cold environment. Aviat Space Environ Med 66: 890–902.

Goodwin J, Pearce VR, Taylor RS, Read KL & Powers SJ (2001) Seasonal cold and circadian changes in blood pressure and physical activity in young and elderly people. Age Ageing 30(4): 311–317.

Granberg P (1991) Human physiology under cold exposure. Arctic Med Res 50 (Suppl 6): 23–27.

Grawshaw L, Wollmuth L, O'Connor C, Rausch R & Simpson L (1990) Body temperature regulation in vertebrates: comparative aspects and neuronal elements. In: Schönbaum E and Lomax P (eds) Thermoregulation: physiology and biochemistry. New York. Pergamon press, 209–220.

Grech V, Aquilina O & Pace J (2001) Gender differences in seasonality of acute myocardial infarction admissions and mortality in a population-based study. J Epidemiol Community Health 55: 147–148.

Greenberg J (2006) Are blood pressure predictors of cardiovascular disease mortality different for prehypertensives than for hypertensives? Am J Hypertens 19: 454–461.

Guidelines Committee (2003) 2003 European Society of Hypertension - European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 21: 1011–1053.

Gyllerup S (2000) Cold climate and coronary mortality in Sweden. Int J Circumpolar Health 59: 160–163.

Hakan T, Kizilkilic O, Adaletli I, Karabagli H, Kocer N & Islak C (2003) Is there any seasonal influence in spontaneous bleeding of intracranial aneurysms and/or AVM in Istanbul? Swiss Med Wkly 133: 267–272.

Hall JE (2003) The kidney, hypertension, and obesity. Hypertension 41: 625–633.

Hanko E & Rostrup M (1996) Calcium antagonist treatment and cardiovascular responses to a cold pressor test at high altitude. Eur J Clin Pharmacol 51: 265–267.

Harada K, Ohashi K, Fujimura A, Kumagai Y & Ebihara A (1996) Effect of α_1-adrenoceptor antagonists, prazosin and urapidil, on a finger skin vasocontrictor response to cold stimulation. Eur J Clin Pharmacol 49: 371–375.

Hardy JD & DuBois EF (1938) The technic of measuring radiation and convection. J Nutr 15: 461–475.

Harris L, Dargie HJ, Lynch PG, Bulpitt CJ & Krikler DM (1982) Blood pressure and heart rate in patients with ischaemic heart disease receiving nifedipine and propranolol. Br Med J 284: 1148–1151.

Hassi J, Rintamäki H, Ruskoaho H, Leppäluoto J & Vuolteenaho O (1991). Plasma levels of endothelin-1 and atrial natriuretic peptide in men during a 2-hour stay in a cold room. Acta Physiol Scand 142(4): 481–485.

Hata T, Ogihara T, Maruyama A, Mikami H, Nakamaru M, Naka T, Kumahara Y & Nugent CA (1982) The seasonal variation of blood pressure in patients with essential hypertension. Clin Exp Hypertens A 4: 341–354.

Haynes WG & Webb DJ (1998) Endothelin as a regulator of cardiovascular function in health and disease. J Hypertens 16(8): 1081–1098.

Headley SA, Moser CD, Golan R, Kendrick ZV, Finck A & Paolone AM (1996) Cardiovascular responses to β-blockade and 5 ºC cold air stress. Can J Physiol Pharmacol 74: 112–115.

Heath ME & Downey JA (1990) Cold face test (diving reflex) in clinical autonomic assessment: methodological considerations and repeatability of responses. Clin Sci 78: 139–147.

Heller RF, Rose G, Pedoe HD & Christie DG (1978) Blood pressure measurement in the United Kingdom Heart Disease Prevention Project. J Epidemiol Community Health 32(4): 235–238.

Hensel H (1981) Thermoreception and temperature regulation. Monographs of the physiological society No 38. Academic Press, London.

Hentschel U & Bijleveld C (2004) After images and pain tolerance: A descriptive study on their interrelationship. Scand J Psychol 45: 191–196.

Hermida RC, Calvo C, Ayala DE, Lopez JE, Fernandez JR, Mojon A, Dominguez MJ & Covelo M (2003) Seasonal variation of fibrinogen in dipper and nondipper hypertensive patients. Circulation 108(9): 1101–1106.

Hesslink RL Jr, D'Alesandro MM, Armstrong DW 3rd & Reed HL (1992). Human cold air habituation is independent of thyroxine and thyrotropin. J Appl Physiol 72(6): 2134–2139.

Hines EA & Brown GE (1932) A standard stimulus for measuring vasomotor reactions: Its application in the study of hypertension. Mayo Clin Proc 7: 332–335.

Hiramatsu K, Yamada T & Katakura M (1984) Acute effects of cold on blood pressure, renin-angiotensin-aldosterone system, catecholamines and adrenal steroids in man. Clin Exp Pharmacol Physiol 11(2): 171–179.

Hoxie HJ (1940) Seasonal incidence of coronary occlusion in a mild climate. A study based upon autopsy material. Am Heart J 19:475–477.

Huisman HW, Van Rooyen JM, Malan NT, Eloff FC, Laubscher PJ, Steyn HS & Pretorius PJ (2002) Cardiovascular reactivity pattern elicited by the cold pressor test as a function of aging. Aging Clin Exp Res 14: 202–207.

Imai Y, Munakata M, Tsuji I, Ohkubo T, Satoh H, Yoshino H, Watanabe N, Nishiyama A, Onodera N, Kato J, Sekino M, Aihara A, Kasai Y & Abe K (1996) Seasonal variation in blood pressure in normotensive women studied by home measurements. Clin Sci 90(1): 55–60.

Inagawa T, Ohbayashi N, Takechi A, Shibukawa M & Yahara K (2003) Primary intracerebral hemorrhage in Izumo City, Japan: incidence rates and outcome in relation to the site of hemorrhage. Neurosurgery 53(6): 1283–1297.

ISO/DP 10551 (1995) Ergonomics of the thermal environment - Assessment of the influence of the thermal environment using subjective judgement scales. International Standards Organization, Geneva.

ISO CD15743 (2002) Ergonomics of the thermal environment –Working practices in cold: strategy for risk assessment and management. International Standards Organization, Geneva

Israel A, Zavala L, Cierco M, Gutierrez A & del Rosario Garrido M (2006) Effect of eprosartan on the sympathetic response to cold pressor test in healthy volunteers. Auton Neurosci 126–127: 179–184.

Izzo JL Jr (2000) Sympathetic nervous system in acute and chronic blood pressure elevation. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 42–58.

Izzo JL Jr, Larrabee PS, Sander E & Lillis LM (1990) Hemodynamics of seasonal adaptation. Am J Hypertens 3: 405–407.

Jaeger JJ, Deal EC Jr, Roberts DE, Ingram RH Jr & McFadden ER Jr (1980) Cold air inhalation and esophageal temperature in exercising humans. Med Sci Sports Exerc 12(5): 365–369.

Jakovljevic D, Salomaa V, Sivenius J, Tamminen M, Sarti C, Salmi K, Kaarsalo E, Narva V, Immonen-Raiha P, Torppa J & Tuomilehto J (1996) Seasonal Variation in the occurrence of Stroke in a Finnish Adult Population. The FINMONICA Stroke Register. Finnish Monitoring Trends and Determinants in Cardiovascular Disease. Stroke 27: 1774–1779.

James GD, Yee LS & Pickering TG (1990). Winter-summer differences in the effects of emotion, posture and place of measurement on blood pressure. Soc Sci Med 31(11): 1213–1217.

Jehn M, Appel LJ, Sacks FM, Miller ER 3rd & DASH Collaborative Research Group (2002) The effect of ambient temperature and barometric pressure on ambulatory blood pressure variability. Am J Hypertens 15: 941–945.

Jeyaraj SC, Chotani MA, Mitra S, Gregg HE, Flavahan NA & Morrison KJ (2001) Cooling evokes redistribution of α_{2C}-adrenoceptors from Golgi to plasma membrane in transfected human embryonic kidney 293 cells. Mol Pharmacol 60: 1195–1200.

Julius S (1991) Clinical implications of pathophysiologic changes in the midlife hypertensive patient. Am Heart J 122: 886–891.

Juneau M, Larivee L & White M (2002) Cold temperature impairs maximal exercise performance in patients with heart failure: attenuation by acute ACE inhibitor therapy. Can J Cardiol 18(9): 981–986.

Juneau M, Johnstone M, Dempsey E & Waters DD (1989) Exercise-induced myocardial ischemia in a cold environment. Effect of antianginal medications. Circulation 79: 1015–1020.

Kahan T & Eliasson K (1999) The influence of long-term ACE inhibitor treatment on circulatory responses to stress in human hypertension. Am J Hypertens 12: 1188–1194.

Kanagy NL (2005) Alpha(2)-adrenergic receptor signalling in hypertension. Clin Sci 109(5): 431–437.

Kastarinen MJ, Salomaa VV, Vartiainen EA, Jousilahti PJ, Tuomilehto JO, Puska PM & Nissinen AM (1998) Trends in blood pressure levels and control of hypertension in Finland from 1982 to 1997. J Hypertens 16: 1379–1387.

Keatinge WR & Donaldson GC (2001) Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. Environ Res 86(3): 209–216.

Keatinge WR, Donaldson GC, Bucher K, Jendritzky G, Cordioli E, Martinelli M, Katsouyanni K, Kunst AE, McDonald C, Näyha S, Vuori I & Eurowinter Group (2000) Winter mortality in relation to climate. Int J Circumpolar Health 59(3–4): 154–159.

Kilgour RD & Carvalho J (1994) Gender differences in cardiovascular responses to the cold hand pressor test and facial cooling. Can J Physiol Pharmacol 72: 1193–1199.

Kim JY, Jung KY, Hong YS, Kim JI, Jang TW & Kim JM (2003) The relationship between cold exposure and hypertension. J Occup Health 45(5): 300–306.

Klaukka T & Virta L (2007) Lääkkeiden erityiskorvausoikeus lähes joka neljännellä. (in Finnish) SLL 14–15: 1514–1516.

Klemsdahl TO, Mundal HH & Gjesdal K (1996) Effects of carvedilol and atenolol on arterial curves (plethysmography) and finger temperature after hand cooling. Eur J Clin Pharmacol 50: 483–489.

Kochar MS, Ristow S & Kalbfleisch JH (1985) Effect of seasonal temperature change on blood pressure in a treated hypertensive population. J Clin Hypertens 1(1): 49–52.

Korhonen I (2006) Blood pressure and heart rate responses in men exposed to arm and leg cold pressor tests and whole-body cold exposure. Int J Circumpolar Health 65(2): 178–184.

Koskela H, Koskela AK & Tukiainen HO (1996) Bronchoconstriction due to cold weather in COPD. The roles of direct airway effects and cutaneous reflex mechanisms. Chest 110: 632–636.

Koskela H & Tukiainen H (1995) Facial cooling, but not nasal breathing of cold air, induces bronchoconstriction: a study in asthmatic and healthy subjects. Eur Respir J 8: 2088–2093.

Kristal-Boneh E, Harari G & Green MS (1997) Seasonal change in 24-hour blood pressure and heart rate is greater among smokers than nonsmokers. Hypertension 30: 436–441.

Kristal-Boneh E, Harari G, Green MS & Ribak J (1996) Body mass index is associated with differential seasonal change in ambulatory blood pressure levels. Am J Hypertens 9: 1179–1185.

Kristal-Boneh E, Harari G, Green MS & Ribak J (1995) Seasonal changes in ambulatory blood pressure in employees under different indoor temperatures. Occup Environ Med 52(11): 715–721.

Krog H, Folkow B, Fox RH & Andersen KL (1960) Hand circulation in the cold of Lapps and North Norwegian fishermen. J Appl Physiol 15(4): 654–658.

Kunes J, Tremblay J, Bellavance F & Hamet P (1991) Influence of environmental temperature on the blood pressure of hypertensive patients in Montreal. Am J Hypertens 4: 422–426.

Lanska DJ & Hoffmann RG (1999) Seasonal variation in stroke mortality rates. Neurology 52(5): 984–990.

Lassvik C & Areskog NH (1979) Effects of various environmental temperatures on effort angina. Ups J Med Sci 84: 173–180.

LeBlanc J, Dulac S, Cote J & Girard B (1975) Autonomic nervous system and adaptation to cold in man. J Appl Physiol 39(2): 181–186.

LeBlanc J, Hildes JA & Heroux O (1960) Tolerance of Gaspe fischermen to cold water. J Appl Physiol 15: 1031– 1034.

Lejeune JP, Vinchon M, Amouyel P, Escartin T, Escartin D & Christiaens JL (1994) Association of occurrence of aneurysmal bleeding with meteorologic variations in the north of France. Stroke 25(2): 338–341.

Leon DF, Amidi M & Leonard JJ (1970) Left heart work and temperature responses to cold exposure in man. Am J Cardiol 26: 38–45.

Leppäluoto J, Korhonen I & Hassi J (2001) Habituation of thermal sensations, skin temperatures, and norepinephrine in men exposed to cold air. J Appl Physiol 90(4): 1211–1218.

Leppäluoto J, Sikkilä K & Hassi J (1998) Seasonal variation of serum TSH and thyroid hormones in males living in subarctic environmental conditions. Int J Circump Health 57: 383–385.

Lewington S, Clarke R, Qizilbash N, Peto R & Collins R (2002) Age-spesific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360: 1903–1913.

Lind AR, Taylor SH, Humphreys PW, Kennelly BM & Donald KW (1964) The circulatory effects of sustained voluntary muscle contraction. Clin Sci 27: 229–244.

Lotens WA (1988) Comparison of thermal predictive models for clothed humans. ASHRAE Trans 94: 1321–1340.

Madsen C & Nafstad P (2006) Associations between environmental exposure and blood pressure among participants in the Oslo Health Study (HUBRO). Eur J Epidemiol 21(7): 485–491.

Mäkinen TM, Raatikka VP, Rytkönen M, Jokelainen J, Rintamäki H, Ruuhela R, Näyhä S & Hassi J (2006) Factors affecting outdoor exposure in winter: population-based study. Int J Biometeorol 51(1): 27–36.

Mäkinen TM, Pääkkönen T, Palinkas LA, Rintamäki H, Leppäluoto J & Hassi J (2004) Seasonal changes in thermal responses of urban residents to cold exposure. Comp Biochem Physiol A Mol Integr Physiol 139: 229–238.

Malhotra S, Kumari S & Pandhi P (2001) Effect of calcium antagonists on stress-induced rise in blood pressure and heart rate: a double-blind, placebo-controlled study. Int J Clin Pharmacol Ther 39: 19–24.

Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL (2007) 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28(12): 1462–1536.

Manfredini R, Boari B, Smolensky MH, Salmi R, Gallerani M, Guerzoni F, Guerra V, Maria Malagoni A & Manfredini F (2005) Seasonal variation in onset of myocardial infarction- a 7-year single-center study in Italy. Chronobiol Int 22: 1121–1135.

Mannino JA & Washburn RA (1987) Cardiovascular responses to moderate facial cooling in men and women. Aviat Space Environ Med 58(1): 29–33.Marchant B, Ranjadayalan K, Stevenson R, Wilkinson P & Timmis AD (1993) Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmental temperature. Br Heart J 69: 385–387.

Marino F, Sockler JM & Fry JM (1998) Thermoregulatory, metabolic and sympathoadrenal responses to repeated brief exposure to cold. Scand J Clin Lab Invest 58(7): 537–545.

McDonald JS, Nelson J, Lenner KA, McLane ML & McFadden ER (1997) Effects of the combination of skin cooling and hyperpnea of frigid air in asthmatic and normal subjects. J Appl Physiol 82: 453–459.

McFadden ER Jr (1983) Respiratory heat and water exchange: physiological and clinical implications. J Appl Physiol; 54: 331–336.

McInnes GT, Findlay IN, Murray GD & Dargie HJ (1987) Effects of calcium antagonism and beta-blockade on haemodynamic responses to stress. Nephron 47(suppl 1): 128–131.

McKemy DD, Neuhausser WM & Julius D (2002) Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 416: 52–58.McLean J, Sathasivam P, MacNaughton K & Graham T (1992) Cardiovascular and norepinephire responses of men and women to two cold pressor tests. Can J Physiol Pharmacol 70: 36–42.

Mehler WH, Peferman ME & Nauta WHJ (1960) Ascending axon degeneration following anterolateral cordotomy. An Experimental study in the monkey. Brain 83: 718–750.

Meriranta P, Tikkanen I, Kumpusalo E & workgroup (2004) Verenpainepotilas terveyskeskuksessa: hoitotulokset paranemassa. (in Finnish) SLL 59: 3253–3258.

Messner T & Lundberg V (2003) Trends in sudden cardiac deaths in northern Sweden MONICA area 1985–1999. J Int Med 253: 320–328.

Minami J, Ishimitsu T, Kawano Y & Matsuoka H (1998) Seasonal variations in office and home blood pressure in hypertensive patients treated with antihypertensive drugs. Blood Press Monit 3(2): 101–106.

Miquel A, Martinez MA, Vendrell JJ, Hidalgo Y, Nevado A, Puig JG & Grupo de Trabajo MAPA-Madrid (2001) (Seasonal blood pressure changes in mild hypertension.) (in Spanish) Med Clin 117(10): 372–374.

Mitchell JB, Flynn MG, Goldfarb AH, Ben-Ezra V & Copmann TL (1990) The effect of training on the norepinephrine at rest and during exercise in 5°C than in 20°C environments. J Sports Med Phys Fitness 30: 235–240.

Mitchell R, Blane D & Bartley M (2002.) Elevated risk of high blood pressure: climate and the inverse housing law. Int J Epidemiol 31: 831–838.

Modesti PA, Morabito M, Bertolozzi I, Massetti L, Panci G, Lumachi C, Giglio A, Bilo G, Caldara G, Lonati L, Orlandini S, Maracchi G, Mancia G, Gensini GF & Parati G (2006) Weather-related changes in 24-hour blood pressure profile: effects of age and implications for hypertension management. Hypertension 47(2): 155–161.

Moore MV, Jeffcoate WJ & Macdonald IA (1987) Apperent improvement in diabetic autonomic neuropathy induced by captopril. J Hum Hypertens 1: 161–165.

Mori H, Ukai H, Yamamoto H, Saitou S, Hirao K, Yamauchi M & Umemura S (2006) Current status of antihypertensive prescription and associated blood pressure control in Japan. Hypertens Res 29: 143–151.

Moschos N, Christoforaki M & Antonatos P (2004) Seasonal distribution of acute myocardial infarction and its relation to acute infections in a mild climate. Int J Cardiol 93: 39–44.

Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E & Erikssen J (1997) Seasonal covariation in physical fitness and blood pressure at rest and during exercise in healthy middle-aged men. Blood Press 6(5): 269–273.

Nakajima J, Kawamura M, Fujiwara T & Hiramori K (2000) Body height is a determinant of seasonal variation in patients with essential hypertension. Hypertens Res 23(6): 587–592.

Narang R & Wasir H (1996) Seasonal variation in the incidence of hypertension and coronary artery disease. Int J Cardiol 1996; 56: 90–92.

Näyhä S (2005) Environmental temperature and mortality. Int J Circumpolar Health. 64(5): 451–458.

Näyhä S (2000) Seasonal variation of deaths in Finland- is it still diminishing? Int J Circumpolar Health 59: 182–187.

Näyhä S (1985) Adjustment of blood pressure data by season. Scand J Prim Health Care 3: 99–105.

Nyquist P, Brown RD Jr, Wiebers D, Crowson C & O'Fallon W (2001) Circadian and seasonal occurrence of subarachnoid and intracerebral hemorrhage. Neurology 56: 190–193.

O'Connor DT & Preston RA (1982) Propranolol effects on autonomic function in hypertensive men. Clin Cardiol 5(5): 340–346.

O'Malley BP, Cook N, Richardson A, Barnett DB & Rosenthal FD (1984) Circulating catecholamine, thyrotrophin, thyroid hormone and prolactin responses of normal subjects to acute cold exposure. Clin Endocrinol 21(3): 285–291.

Ornato JP, Peberdy MA, Chandra NC & Bush DE (1996) Seasonal pattern of acute myocardial infarction in the National Registry of Myocardial Infarction J Am Coll Cardiol 28: 1684–1688.

Pääkkönen T & Leppäluoto J (2002) Cold exposure and hormonal secretion: a review. Int J Circumpolar Health 61(3): 265–276.

Pandhi P & Sharma PL (1987) Comparative effects of beta-, alpha- and combined beta-plus alpha-adrenoceptor blocking agents in stress–induced increase in arterial blood pressure. Int J Clin Pharm Ther Toxicol 25(6): 297–300.

Pandhi P, Sharma PL, Sharma BK & Wahi PL (1986) Comparative effect of propranolol and labetalol on isometric exercise and cold stress induced increase in arterial blood pressure. Int J Clin Pharmac Ther Toxicol 24: 249–253.

Passero S, Reale F, Ciacci G & Zei E (2000) Differing temporal patterns of onset in subgroups of patients with intracerebral hemorrhage. Stroke 31: 1538–1544.

Peikert D & Smolander J (1991) The combined effect of the cold pressor test and isometric exercise on heart rate and blood pressure. Eur J Appl Physiol Occup Physiol 62(6): 445–449.

Perez-Lloret S, Toblli JE, Vigo DE, Cardinali DP & Milei J (2006) Infradian awake and asleep systolic and diastolic blood pressure rhythms in humans. J Hypertens 24(7): 1273–1279.

Polat M, Akil I, Yuksel H, Coskun S, Yilmaz D, Erguder I & Onag A (2006) The effect of seasonal changes on blood pressure and urine specific gravity in children living in Mediterranean climate. Med Sci Monit 12(4): CR186–190.

Pool JL (2000) α-Adrenoceptor blockers. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 595–599.

Pörsti I, Arvola P, Säynävälammi P, Nurmi AK, Metsä-Ketelä T, Koskenvuo K, Laitinen LA, Manninen V & Vapaatalo H (1990) Effects of single doses of quinapril and atenolol on autonomic nervous function and exercise capacity in healthy volunteers. Eur J Clin Pharmacol 38: 541–546.

Prineas RJ, Gillum RF, Horibe H & Hannan PJ (1980) The Minneapolis children's blood pressure study. Part 2: multiple determinants of children's blood pressure. Hypertension 2(4 Pt 2): I24–I28.

Puybasset L, Lacolley P, Laurent S, Mignon F, Billaud E, Cuche JL, Comoy E & Safar M (1993) Effects of clonidine on plasma catecholamines and neuropeptide Y in hypertensive patients at rest and during stress. J Cardiovasc Pharmacol 21(6): 912–919.

Raatikka VP, Rytkönen M, Näyhä S & Hassi J (2007) Prevalence of cold-related complaints, symptoms and injuries in the general population: the FINRISK 2002 cold substudy. Int J Biometerol 51(5): 441–448.

Radomski MW & Boutelier C (1982) Hormone response of normal and intermittent cold-preadapted humans to continuous cold. J Appl Physiol 53(3): 610–616.

Raven P, Niki I, Dahms T & Horvath S (1970) Compensatory cardiovascular responses during an environmental cold stress, 5°C. J Appl Physiol 29: 417–421.

Reed HL, Kowalski KR, D´Alesandro MM, Robertson R & Lewis SB (1991) Propranolol fails to lower the increased blood pressure caused by cold air exposure. Aviat Space Environ Med 62: 111–115.

Riggs CE Jr, Johnson DJ, Kilgour RD & Konopka BJ (1983) Metabolic effects of facial cooling in exercise. Aviat Space Environ Med 54(1): 22–26.

Ringqvist A, Leppert J, Myrdal U, Ahlner J, Ringqvist I & Wennmalm A (1997) Plasma nitric oxide metabolite in women with primary Raynaud's phenomenon and healthy subjects. Clin Physiol 17(3): 269–277.

Roca-Cusachs A, Gomez-Gerique JA, Bou F & Homs R (1991) (Seasonal variations of lipids and arterial pressure.) (in Spanish) Med Clin 97(19): 721–725.

Rogot E & Padgett SJ (1976) Association of coronary and stroke mortality with temperature and snowfall selected areas of the United States, 1962–1966. Am J Epidemiol 103: 565–575.

Rose G (1966) Cold weather and ischaemic heart disease Br J Prev Soc Med 20(2): 97–100.

Rose G (1961) Seasonal variations in blood pressure in man. Nature 189: 235–239.

Rosenthal T (2004) Seasonal variations in blood pressure. Am J Geriatr Cardiol 13(5): 267–272.

Rowell LB (1986) Human circulation. Regulation during physical stress. New York: Oxford University press.

Ruddy MC & Kostis JB (2000) Angiotensin II receptor antagonists. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 621–636.

Savino EA & Varela A (1999) Influence of moderate cooling (37ºC - 25ºC) on the reactivity of isolated rat tail artery. Acta Physiol Pharmacol Ther Latinoam 49(3): 141–148.

Sayer J, Wilkinson P, Ranjadayalan K, Ray S, Marchant B & Timmis A (1997) Attenuation or absence of circadian and seasonal rhythms of acute myocardial infarction. Heart 77: 325–329.

Schiffrin EL (2005) Vascular endothelin in hypertension. Vascul Pharmacol 43(1): 19–29.

Scholander PF (1958) Studies on man exposed to cold. Fed Proc 17(4): 1054–1057.

Sega R, Cesana G, Bombelli M, Grassi G, Stella ML, Zanchetti A & Mancia G. (1998) Seasonal variations in home and ambulatory blood pressure in the PAMELA population. Pressione Arteriose Monitorate E Loro Associazioni. J Hypertens 16: 1585–1592.

Seguro C, Siddi PP, Sau F, Giardina G, Scano G, Mura O, Arru A, Zedda N & Cherchi A (1992) (The effect of antihypertensive therapy on the seasonal variations in arterial pressure in hypertensive patients.) (in Italian) Cardiologia 37: 51–58.

Shah SU, Anjum S & Littler WA (2004) Use of diuretics in cardiovascular disease: (2) hypertension. Postgrad Med J 80: 271–276.

Sharma BK, Sagar S, Sood GK, Varma S & Kalra OP (1990) Seasonal variations of arterial blood pressure in normotensive and essential hypertensives. Indian Heart J 42(1): 66–72.

Sharovsky R & Ce sar LA (2002) Increase in mortality due to myocardial infarction in the Brazilian city of Sao Paolo during winter. Arq Bras Cardiol 78: 106–109.

Sheth T, Nair C, Muller J & Yusuf S (1999) Increased winter mortality from acute myocardial infarction and stroke: effect of age. J Am Coll Cardiol 33: 1916–1919.

Sica DA & Gehr TWB (2000) Angiotensin-converting enzyme inhibitors. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 599–608.

Sipilä R, Hiltunen TP & Näveri H (2005) **(**Acute myocardial infarction after snow removal.**)** (in Finnish) Duodecim 121: 181–183

Smith PA, Graham LN, Mackintosh AF, Stoker JB & Mary DA (2002) Sympathetic neural mechanisms in white-coat hypertension. J Am Coll Cardiol 40: 126–132.

Spencer FA, Goldberger RJ, Becker RC & Gore JM (1998) Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. J Am Coll Cardiol 31: 1226–1233.

Sposito M, Nieto FJ & Ventura JE (2000) Seasonal variations of blood pressure and overhydration in patients on chronic hemodialysis. Am J Kidney Dis 35(5): 812–818.

Stewart S, Mcintyre K, Capewell S & McMurray J (2002) Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. J Am Coll Cardiol 39: 760–766.

Stout RW & Crawford V (1991) Seasonal variations in fibrinogen concentrations among elderly people. Lancet 338: 9–13.

Sugimoto K, Kumagai Y, Tateishi T, Seguchi H & Ebihara A (1989) Effects on autonomic function of a new angiotensin converting enzyme inhibitor, ramipril. J Cardiovasc Pharmacol 13 (Suppl 3): S40–S45.

Tanaka S, Konno A, Hashimoto A, Hayase A, Takagi Y, Kondo S, Nakamura Y & Iimura O (1989) The influence of cold temperatures on the progression of hypertension: an epidemiological study. J Hypertens 7(Suppl 1): S49–S51.

The Eurowinter Group (1997) Cold exposure and winter mortality from ischemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 349: 1341–1346.

Thomas JR, Ahlers ST, House JF, Schrot J, Van Orden KF, Winsborough MM, Hesslink RL Jr & Lewis SB (1990) Adrenergic responses to cognitive activity in a cold environment. J Appl Physiol 68(3): 962–966.

Timberlake DS, O'Connor DT & Parmer RJ (2001) Molecular genetics of essential hypertension: recent results and emerging strategies. Curr Opin Nephrol Hypertens 10: 71–79.

Tozawa M, Iseki K, Iseki C, Morita O, Yoshi S & Fukiyama K (1999) Seasonal blood pressure and body weight variation in patients on chronic hemodialysis. Am J Nephrol 19(6): 660–667.

Tsementzis SA, Kennet RP, Hitchcock ER, Gill JS & Beevers DG (1991) Seasonal variation of cerebrovascular diseases. Acta Neurochir 111(3–4): 80–83.

Tsuchihashi T, Uezono K, Abe I, Matsuoka M & Kawasaki T (1995) Seasonal variation in 24-h blood pressure pattern of young normotensive women. Hypertens Res 18(3): 209–214.

Ulmer H, Kelleher C, Diem G, Concin H & Ruttmann E (2004) Estimation of seasonal variations in risk factor profiles and mortality from coronary heart disease. Wien Klin Wochenschr 116(19–20): 662–668.

van Rossum C, Shipley M, Hemingway H, Grobbee D, Mackenbach J & Marmot M (2001) Seasonal variation in cause-spesific mortality: Are there high-risk groups? 25-year follow-up of civil servants from the first Whitewall study. Int J Epidemiol 30: 1109–1116.

Verdon F, Bountry JF, Chuat M, Studer JP, Truong CB & Jacot E (1993) (Seasonal variations in arterial pressure in hypertensive patients.) (in French) Schweiz Med Wochenschr 123: 2363–2369.

Victor RG, Leimbach WN Jr, Seals DR, Wallin BG & Mark AL (1987) Effects of the cold pressor test on muscle sympathetic nerve activity in humans. Hypertension 9(5): 429–436.

Wagner JA & Horvath SM (1985) Cardiovascular reactions to cold exposures differ age and gender. J Appl Physiol 58 (1): 187–192.

Wang Y, Levi CR, Attia JR, D'Este CA, Spratt N & Fisher J (2003) Seasonal variation in stroke in the Hunter Region, Australia: a 5-year hospital-based study, 1995–2000. Stroke 34(5): 1144–1150.

Wang H, Sekine M, Chen X & Kagamimori S (2002) A study of weekly and seasonal variation of stroke onset. Int J Biometeorol 47: 13–20.

Weber K, Bohmeke T, van der Does R & Taylor SH (1998) Hemodynamic differences between metoprolol and carvedilol in hypertensive patients. Am J Hypertens 11: 614–617.

Weder AB, Takiyyuddin M, Sekkarie MA & Julius S (1989) Behaviour and hypertension: a pathophysiological puzzle. J Hypertens 7(Suppl 1): S13–S17.

Westerterp-Plantenga MS, van Marken Lichtenbelt WD, Strobbe H & Schrauwen P (2002) Energy metabolism in humans at a lowered ambient temperature. Eur J Clin Nutr 56(4): 288–296.

Winnicki M, Canali C, Accurso V, Dorigatti F, Giovinazzo P & Palatini P (1996) Relation of 24-hour ambulatory blood pressure and short-term blood pressure variability to seasonal changes in environmental temperature in stage I hypertensive subjects. Results of the Harvest study. Clin Exp Hypertens 18(8): 995–1012.

Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D & Vescio F (2003) Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 289(18): 2363–2369.

Woodhouse PR, Khaw KT & Plummer M (1993) Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. J Hypertens 11(11): 1267–1274.

World Health Organization (2002) The World Health Report 2002: Risks for health 2002. Geneve. World Health Organization.

Wu RA, Kailasam MT, Cervenka JH, Palmer RJ, Kennedy BP, Ziegler MG & O'Connor DT (1994) Does lipophilicity of angiotensin converting enzyme inhibitors selectively influence autonomic neural function in human hypertension? J Hypertens 12: 1243–1247.

Zeisberger E (1998) Biogenic amines and thermoregulatory changes. Prog Brain Res 115: 159–176.

Zelis R (1983) Mechanisms of vasodilation. Am J Med 74: 3–12.

Zwieten PA (2000) Calcium antagonists as antihypertensives. In: Oparil S & Weber MA (eds) Hypertension: Companion to Brenner's and Rector's the kidney. W.B. Saunders Company, London, 609–620.

Yamasaki F, Seo H, Furuno T, Hamashige N, Kawai K, Owaki T, Hujinaga H & KAMI Study Group. Kochi Acute Myocardial Infarction (2002) Effect of age on chronological variation of acute myocardial infarction onset: study in Japan. Clin Exp Hypertens 24(1–2): 1–9.

Young AJ (1996) Homeostatic responses to prolonged cold exposure: human cold acclimatization. In: Fregly MJ, Blatteis CM (eds), Section 4: Environmental Physiology, vol 1, Handbook of Physiology. Oxford University Press, New York, 419–438.

Appendices

Table 12. Data collected from studies about seasonal variation in mortality of cardiovascular diseases

Disease	Place and time	Type of study	Number	Seasonal effect (higher in winter)	Author (year)
IHD	England and Wales 1950–1962	Register	Deaths in England and Wales	Yes, winter mortality 20–70% higher than in summer	Rose 1966
Myocardial infarction	Ontario, Canada England and Wales; Great Britain 1958–1962	Register	4953	Yes, England and Wales: Peak in January (RR 1.3), lowest in July (RR 0.8) Ontario: Peak in January (RR 1.09), lowest in August (RR 0.9)	Anderson & Le Riche 1970
Stroke Coronary heart disease	USA 1962–1966	Register	Data from 32 metropolitan statistical areas	Yes, mortality was higher in lower temperature	Rogot & Padgett 1976
Sudden death from IHD	Toronto, Canada 1960–1974	Register	Toronto area	Yes, 4.4°C drop in mean temperature → 16% increase in sudden death and 8.3°C drop → 25% increase in sudden death	Anderson & Rochard 1979
Myocardial infarction (old and new)	Minneapolis, USA 1973–1977	Register	Minneapolis-St Paul Standard metropolitan Statistical area	Yes, 13% increase in old myocardial infarction if snow occurred compared no snow in winter	Baker-Blocker 1982
Myocardial infarction	Brisbane, Australia and Montreal, Canada	Register		Yes, higher number of deaths in cooler times	Frost *et al*. 1992
Cardiovascular diseases	Norway and Ireland	Register		Yes, during a 10-year period 22% higher in Norway and 35% higher in Ireland during winters	Eng & Mercer 1998
IHD Cerebrovascular diseases	Yakutsk, eastern Siberia	Register	All people (50–59 y, 65–74 y), who live within 400 km from Yakutsk	No	Donaldson *et al*. 1998a
IHD Cerebrovascular diseases	Yekaterinburg, Russia	Register	All people (50–59, 65–74 live within 140 km from Yekaterinburg	Yes, mortality increased, when temperature fell below 0°C	Donaldson *et al*. 1998b
Acute myocardial infarction	USA, 1994–1996	Register	259 891	Yes, 9% more in winter than summer (hospital)	Spencer *et al*. 1998
Chronic heart failure	France 1992–1996	Register	138 602	Yes, higher in winter than in summer. Peak in January and lowest in August.	Boulay *et al*. 1999

Table 12 (Continued)

Disease	Place and time	Type of study	Number	Seasonal effect (higher in winter)	Author (year)
Coronary deaths	North district of France 1985–1994	Register	38.3% of 3314 fatal	Yes, a 10°C decrease in temperature increased deaths by 11%	Danet *et al.* 1999
Acute myocardial infarction Stroke	Canada 1980–1982, 1990–1992	Register (Canadian Mortality database)	300 000	aMI:RR 1.09, relative risk difference 18.6% stroke: RR 1.11, relative risk difference 19.9% Peak in January and lowest in September	Sheth *et al.* 1999
IHD Cerebrovascular diseases	Emily-Romagna, Italy	Register		Yes P=< 0.01–0.001. Peak in January and lowest in August	Cordioli *et al.* 2000
IHD Stroke	Finland 1961–1995	Register		1.33 1.42 Peak in December and lowest in August	Näyhä 2000
Coronary heart disease Stroke	Great Britain 1986–1996	Register	2 825 223 > 65 years	Higher in winter than in summer. OR 1.15–1.22 (95% CI >1) OR 1.12–1.18 (95% CI >1)	Aylin *et al*. 2001
IHD Cerebrovascular disease & others	Great Britain 1967–1970	Follow up study Whitehall study	19 019	Yes, peak in January, lowest in August, In other diseases peak in December and lowest in June	van Rossum *et al*. 2001
Cerebrovascular diseases Myocardial infarction	USA 1986–1993	Register	Deaths from 22 cities	Yes, higher on cold days MI: higher on hot days and in summer	Braga *et al.* 2002
Myocardial infarction	Sao Paolo, Brazil 1996–1997	Register	5615	30% higher in winter than summer (p< 0.01)	Sharovsky & Ce sar 2002
Heart failure	Scotland, Great Britain	Register		Yes, peak in December, lowest in July	Stewart *et al.* 2002
Myocardial infarction	Northern Ireland 1979–1998	Register	68 683	Yes, higher in winter. Peak in February	Crawford *et al.* 2003
Sudden cardiac death	North of Sweden	Cohort study	1139	Yes, but statistically significant in men	Messner & Lundberg 2003
Chronic heart failure after myocardial infarction	New York City, USA	Prospective study	517	Yes, higher in winter and summer compared to spring and autumm	Aranow & Ahn 2004
Cardiovascular diseases	London, Great Britain 1900–1996	Register		Yes, e.g RR 1.25, 95% CI 1.1–1.38 during the period 1986–1996	Carson *et al.* 2006

Table 13. Data collected from studies about seasonal variation in morbidity of ischemic heart diseases

Disease	Place and time	Type of the study	Number of patients	Seasonal effect (higher in winter)	Author (year)
Heart failure atherosclerotic	Cincinnati, Ohio, USA 1922–1936	Hospital based	8673	Yes, peak in March (February), lowest in August	Bean & Mills 1938
Myocardial infarction	Los Angeles, USA	Hospital admission based	501	Yes	Hoxie 1940
Myocardial infarction	Belfast Ireland	Hospital admission based	2348	Yes.	Bull 1973
Myocardial infarction	Great Britain 1988–1991	Hospital admission based	633	Yes	Marchant *et al.* 1993
Coronary artery disease	North India 1991–1995	Hospital based	73873	Yes	Narang & Wasir 1996
Acute myocardial infarction	USA 1990–1993	Register	83 541	Yes, 10% higher in winter than in summer ($p<0.05$)	Ornato *et al.* 1997
Acute myocardial infarction	London; Great Britain 1988–1994	Hospital admission based	1225	Yes, higher in winter than in summer ($p=0.009$)	Sayer *et al.* 1997
Acute myocardial infarction	USA, second national registry of myocardial infarction, 1994–1996	Register	259 891	Yes, 53% more in winter than summer. Peak in January, lowest In July	Spencer *et al.* 1998
Chronic heart failure	France 1995–1997	Hospital based	324 013	Yes, peak in April, lowest in August	Boulay *et al.* 1999
Myocardial infarction	North district of France 1985–1994	Hospital based	3314	Yes, an increase of 13% by a 10°C decrease in temperature	Danet *et al.* 1999
Acute myocardial infarction	Malta 1994–1998	Hospital admission based	2157	Yes, $P<0.0001$. Peak in January, lowest in August	Grech *et al.* 2001
Heart failure	Scotland, Great Britain	Register	75 452 men 81269 women	Yes, peak in December, lowest in July	Stewart *et al.* 2002
Acute myocardial infarction	Southern Japan	Hospital based	725	No, only middle-aged peak in spring	Yamasaki *et al.* 2002
Acute myocardial infarction	Rhodes 1988–1998	Hospital based	1196	Yes, peak in March, lowest in October	Moschos *et al*. 2004
Coronary heart disease	Japan 1992–2002	Hospital based	101	Yes, older patients in winter and younger in summer	Azegami *et al*. 2005
Acute myocardial infarction	Italy 1998–2004	Hospital based	4014	Yes, peak in December, lowest in September	Manfredini *et al.* 2005

Table 14. Data collected from studies about seasonal variation in morbidity of cerebrovascular diseases

Disease	Place and time	Type of the study	Number of patients	Seasonal effect (higher in winter)	Author (year)
CI	Belfast Ireland	Hospital admission based	1016	Yes.	Bull 1973
Cerebrovascular diseases	England West midland region 1973–1980	Hospital admission based		Yes, peak from October to April	Tsementzis *et al.* 1991
Cerebral haemorrhage	Belgium 1983–1990	Hospital based	236	Yes, peak (23%) in November–December and lowest (10%) in July–August	Capon *et al.* 1992
	Finland 1982–1992	Register	15 449	Yes.	Jakovljevic *et al.* 1996
Stroke				Stroke: peak in January, lowest in August.	
SAH				SAH: peak in February, lowest in June.	
ICH				ICH: peak in March, lowest in July	
ICH	Siena, Italy	Hospital-admission	1018		Passero *et al.* 2000
Subgroups:					
All				Yes, peak in December, lowest in August–July	
Hypertensive				Yes, peak in December, lowest in August	
Secondary				No, peak in November, lowest in January	
undetermined				No.	
SAH	Adelaide, Hobart, Perth Australia 1995–1998 Auckland, New Zealand 1981–1983, 1991–1993	Hospital based	783	Yes (winter and spring RR 1.3 95% CI 1.1–1.5)	Feigin *et al*. 2001
SAH	Rochester, MN, USA	Hospital based	155	Yes, the occurrence of hemorrhage increased in winter,	Nyquist *et al*. 2001
ICH	SAH 1960 to 1989 and ICH 1975 to 1989		137	limited only to SAH	
Stroke	Calgary, Canada 1996–2000	Hospital based	3075	No	Field & Hill 2002
Stroke	Japan	Hospital based	10729	Yes, RR 1.21	Wang *et al.* 2002
CI	1991–1998			RR 1.17	
CH				RR 1.33	
SAH				RR 1.23	
Other				RR 0.91	
SAH	Turkey, Istanbul 1994–2000	Hospital based	761	No, 9.7% in January and 7.3% in September	Hakan *et al.* 2003
ICH	Izumo city, Japan 1991–1998	Hospital admission based	350	No seasonal variation in women Seasonal variation with haematomas larger than 5 ml, also younger than 69 years	Inagawa *et al.* 2003
stroke	Hunter region, Australia 1995–2000	Hospital based	3803	Yes, RR 1.07, 95% CI 1.05–1.10 Peak in July (winter), lowest in February (summer)	Wang *et al.* 2003

Table 15. Data collected from studies about seasonal variations in blood pressure

Subjects	Number	Place	Measurement methods of BP	Seasonal effect (higher in winter)		Author (year)
				Yes/No	Winter–summer differences in SBP/DBP(Δ) or other results	
IHD	56	Great Britain	Office	Yea		Rose 1961
NT	8397	Great Britain	Office	Yes	High room temperature decreased the blood pressure	Heller *et al*. 1978
HT	17 282	Great Britain	Office	Yes		Brennan *et al*. 1982
NT	14	Japan	Office	Yes	Δ 4/3 mmHg (NS) in normotensive	Hata *et al*. 1982
HT	20				Δ 9/8 mmHg ($p<0.05$) in borderline hypertensive Δ 9/10 mmHg ($p<0.05$) in hypertensive	
HT	39	USA Milwaukee	Office	No		Kochar *et al.* 1985
Population based	801	Finland	Office	Yes	Δ 8–9/5 mmHg	Näyhä 1985
HT	22	Italy	24 h ABPM	Yes	Δ 5/4 mmhg higher in cold season	Giaconi *et al.* 1988
HT	22	Italy	24 h ABPM	Yes	mean daytime: Δ 2–12/5–10 mmHg higher in winter	Giaconi *et al.* 1989
Population based	909	Japan	Office	Yes	Winter/summer difference is higher in hypertensive than normotensive	Tanaka *et al.* 1989
NT	5	USA	Office	Yes	Δ 3 mmHg higher in winter	Izzo *et al*. 1990
HT	21	northern				
HT	157	USA New York	24 h ABPM	No	Men: Δ 6/4 mmHg higher in summer Women: Δ −1/6 mmHg higher in summer	James *et al*. 1990
NT	15	India	Office	Yes	Δ 17.1/7.4 mmHg higher in NT and Δ 23.1/12.6 higher in HT	Sharma *et al.* 1990
HT	15					
HT	2 000	Canada Montreal	Office	Yes	7/3 mmHg between −24 °C and 27 °C	Kunes *et al*. 1991
Older than 75 years	100	Great Britain	Office	No	No difference between six cold months and six warm months	Stout & Crawford 1991
NT	36	Spain	Office	No		Roca-Cusachs *et al.* 1991
HT	145	Spain	Office	Yes	Δ 5/5 mmHg	Seguro *et al.* 1992
HT	80	France	Office	Yes	Δ 6.7/3.5 mmHg	Verdon *et al.* 1993
Elderly, 65–74 years	96	Great Britain	Office	Yes	Δ 14.2/6.5 mmHg in men and 9.9/4.9 mmHg in women higher in winter	Woodhouse *et al*. 1993
HT	25	Japan	24 h ABPM	Yes	Δ 7.5 /4.1 mmHg in the morning and 8.2/4.5 mmHg at night higher in winter	Fujiwara *et al.* 1995
NT	101	Israel	24 h ABPM	Yes	Δ 3.4/3.3 mmHg	Kristal Boneh *et al*. 1995
NT	10	Japan	24 h ABPM	No	Δ all day 1/1.0 mmHg, daytime 0.5/0.5 mmHg and nighttime 2.2/1.9 mmHg	Tsuchihashi *et al*. 1995

Table 15 (Continued)

Subjects	Number	Place	Measurement methods of BP	Seasonal effect (higher in winter)		Author (year)
				Yes/No	Winter–summer differences in SBP/DBP(Δ) or other results	
NT	16	Japan	Home Office	Yes.	Δ Home BP 2.0/2.6 mmHg	Imai *et al.* 1996
NT	101	Israel	24 h ABPM	Yes		Kristal Boneh *et al.* 1996
HT	8 769	India	Office	Yes	New cases of hypertension is higher in winter	Narang & Wasir 1996
HT	1 000/ 46	Italy	24 h ABPM Office	Yes and no	SBP: Office 2.4 mmHg and ambulatory daytime 3.8 mmHg higher in winter and DBP not	Winnicki *et al.* 1996
NT Nonsmokers smokers	93 73 24	Israel	24 h ABPM	Yes and no	Daytime: non-smokers 2.7/3.1 mmHg and smokers 7.3/4.4 mmHg higher in winter Nighttime: non-smokers −4.2/0.7 and smokers −4/−1.1 mmHg higher in winter	Kristal Boneh *et al.* 1997
HT	47	Holland	24 h ABPM	Yes and No	Δ Daytime SBP 3 mmHg, others ranged 0–3 mmHg	Brueren *et al.* 1998
HT	315	Japan	Home and office	Yes.	Δ Office men 4.1/2.5 mmHg, women 1.0/2.5 mmHg Δ Home: men 3.9/1.7 mmHg, women 4.6/2.4 mmHg	Minami *et al.* 1998
NT HT	2051	Italy	Office Home 24 h ABPM	Yes	Office, home and 24 h abpm higher in winter	Sega *et al.* 1998
NT	1 574	Norway	Office	Yes	Δ At rest SBP 2.8 and during exercise 4.2 mmHg higher	Mundal *et al.* 1997
HT	119	Japan	24 h a ABPM	Yes	Δ Daytime: 8/4 mmHg in men and 5/2 mmHg in women	Nakajima *et al.* 2000
NT young NT elderly	21 25		24 h ABPM	Yes	In elderly subjects, BP higher in winter and higher in both seasons than in younger.	Goodwin *et al.* 2001
HT	43	Spain	24 h ABPM	Yes		Miquel *et al.* 2001
HT older than 64 years	4 487	Italy	Office		In September–October period outcomes in recognised hypertension were higher than in May–June	Corsonello *et al.* 2003
HT	1 006	Spain	48 h ABPM	Yes		Hermida *et al.* 2003
Population based	149 650	Australia	Office	Yes		Ulmer et al. 2004
Population based study	18 770	Oslo citizens, Norway		Yes.	Men: Δ 3.3/1.4 mmHg, women Δ 3.2/1.3 mmHg A 10 °C reduction in outdoor temperature increased SBP/DBP 1.5/1.3 mmHg in men and 2.4/1.8 mmHg in women	Madsen & Nafstad 2006
NT HT	6404	Italy	24 h ABPM Office	Yes.	Office and mean 24-hour systolic higher in cold	Modesti *et al.* 2006
Population	1649	Argentina	24 h ABPM	Yes.	Peak in July (winter). Δ 6.2/4.2 mmHg	Perez-Floret *et al.* 2006

Table 16. Data have been collected from studies about how antihypertensive drugs affect on seasonal variation of blood pressure

Number	Place	Measurement methods of BP	Drug treatment	Seasonal effect (higher in winter) Yes/No Difference in SBP/DBP (Δ)	Author (year)
17 282	Great Britain	Office	Bentofluazide	Yes	Brennan *et al*. 1992
			Propranolol	Yes	
			Placebo	Yes	
145	Spain	Office		Yes, treated HT have higher BP in winter than in summer	Seguro *et al.* 1992
			Beta-blockers	Δ 4/3 mmHg	
			Diuretics	Δ 0/0 mmHg	
			Calcium channel blocker	Δ 5/3 mmHg	
			Betablocker and diuretics	Δ 3/3 mmHg	
80	France	Office		Yes	Verdon *et al.* 1993
			Diuretics	Δ 7.7/3.5 mmHg	
			Vasodilating drugs (calcium channel blockers and ACE inhibitor)	Δ 7.9/1.7 mmHg	
			Diuretics and vasodilating drugs	Δ 9.7/4.7 mmHg	
			Beta-blockers and diuretic/vasodilating drugs	Δ 3.7/2.1 mmHg	
315	Japan	Home and office	88% of subjects	Yes. No differences between no drug, one drug, two drug or more (Δ 2–3.1/2.3–2.8 in office measurements) Calcium antagonist: Δ 4/1.9 mmHg and other drugs Δ 4.4/2.1 mmHg	Minami *et al.* 1998
2051	Italy	Office, Home 24 h ABPM		Office, home and 24 h ABPM. Higher in winter also in treated HT	Sega *et al*. 1998
119	Japan	24 h ABPM	Calcium channel blockers	Day time: Δ 8/4 mmHg in men and Δ 5/2 mmHg in women	Nakajima *et al.* 2000
6 404	Italy	24 h ABPM Office	Not defined	> 65years number of antihypertensive drugs is higher on cold days than on hot, but no < 50 years. On hot nights higher BP than in untreated.	Modesti *et al.* 2006

Original papers

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

I Tähtinen T, Määttä S, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (1999) Effect of amlodipine on blood pressure responses in local and whole-body cooling in normotensive men. Arzneimittel-Forschung 49: 494–499.

II Komulainen S, Tähtinen T, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2000) Blood pressure responses to whole body cold exposure: effect of carvedilol. Eur J Clin Pharmacol 56 (9–10): 637–642.

III Komulainen S, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2004) Blood pressure responses to whole-body cold exposure: effect of metoprolol. J Hum Hypertens 18: 905–906.

IV Komulainen S, Oja T, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2004) Blood pressure and thermal responses to whole-body cold exposure in mildly hypertensive subjects. J Thermal Biol 29: 851–856.

V Komulainen S, Rintamäki H, Virokannas H & Keinänen-Kiukaanniemi S (2007) Blood pressure responses to whole-body cold exposure in mildly hypertensive subjects: effects of ACE-inhibitor and AT II receptor blocker agent. Manuscript.

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

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