Rasmus Valtonen

CARDIOVASCULAR RESPONSES TO COLD AND EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE
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CARDIOVASCULAR RESPONSES TO COLD AND EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE

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Cardiovascular responses to cold and exercise in patients with coronary artery disease.

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Center for Environmental and Respiratory Health Research; Medical Research Center Oulu; Biocenter Oulu

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

The benefits of regular exercise for wellbeing and health during all stages of life are unambiguous. Physical exercise is therefore crucial for the prevention, treatment, and rehabilitation of coronary artery disease (CAD). A cold environment can induce cardiac symptoms or increase the risk of adverse health events. However, the combined effects of cold and moderate sustained exercise, both known to increase cardiac workload, on cardiovascular responses are not well known.

We conducted two four-period cross-over trials. In the first protocol, we selected 20 CAD patients, who performed moderate-intensity lower-body exercise (walking at 65-70% of HR max) and rested in neutral (+22 °C) and cold (-15 °C) conditions. In the second protocol, CAD patients (n=20) performed static (five 1.5-min work cycles, 10-30% of maximal voluntary contraction) and dynamic (three 5-min workloads, 56-80% of HR max) upper-body exercise at the same temperatures. Both trials consisted of four 30-min exposure periods administered in randomized order. Brachial, central aortic, and continuous blood pressure (BP), as well as electrocardiography (ECG) and skin temperature, were measured.

The combined effects of cold and lower-body dynamic exercise increased rate pressure product (RPP) by 17% compared with neutral conditions (p=0.001). This was primarily due to sustained higher systolic BP, but also a slightly increased heart rate (HR). Dynamic graded upper-body exercise in the cold increased RPP by 18.1-24.4% (p=0.002–0.020), whereas RPP during static exercise remained unaltered due to decreased HR (4.1-7.2%; p=0.009-0.033). Post-exercise central systolic BP decreased by 2-10 mmHg (p<0.001) both after lower- and upper-body dynamic exercise, regardless of temperature. Central systolic BP remained elevated after static upper-body exercise in the cold by 7±6 mmHg (p<0.001). ECG was largely unaltered, regardless of the type of exercise or temperature.

Whole-body exposure to cold during dynamic and static exercise involves higher cardiovascular strain than with a neutral environment among patients with stable CAD. However, no marked changes in ECG indicating myocardial ischemia or other changes were observed. The results support that stable CAD patients probably benefit from year-round regular dynamic exercise, but responses to the following static exercise should be examined further.

Keywords: cold temperature, coronary artery disease, dynamic, exercise, static

Suoritimme kaksi erillistä neljän jakson vaihtovuoroista kokoomista tutkimusta. Ensimmäiseen tutkimukseen valitsimme 20 sepelvaltimotautipotilasta, jotka suorittivat kohtuuukoormitteen alavartaloliikunnan (kävely 65-70 % maksimi sykkeestä) ja lepäsivät sekä lämpimässä (+22 °C) että kylmässä (-15 °C) ympäristössä. Toisessa tutkimuksessa, sepelvaltimotautipotilaat (n=20) suorittivat staattisen (1,5 min työsyklit, 10-30 % maksimi sykkeesä) ja dynaamisen (kolme 5 min työsykliä, 56-80 % maksimi sykkeestä) ylävartaloliikunnan lämpimässä ja kylmässä. Molemmat tutkimukset sisälivät neljä 30 min altistusjaksoa satunnaistetussa järjestyksessä. Olkavarsi, aortan tason ja jatkuva verenpaine sekä sydänsähkökäyrä (EKG) ja iholämpötilat mitattiin.

Kylmän ja alavartaloliikunnan yhteisvaikutukset kohottivat sydämen työmäärää 17 % verrattuna lämpimään ympäristöön (p=0,001). Tämä johti päätösein korkeamman systoliseen verenpaineen, mutta myös osittain kohonneesta sykkeestä. Dynaaminen ylävartalotyö kylmässä kohotti sydämen työmäärää 18,1-24,4 % (p=0,0020-0,020), kun taas sydämen työmäärä ei muutunut staattisen työn aikana matalalleen sykkeen vuoksi (4,1-7,2 %; p=0,009-0,033). Liikunnan jälkeinen aortan tason verenpaine laski 2-10 mmHg sekä dynaamisen ala- ja ylävartaloliikunnan jälkeen riippumatta lämpötilasta. Aortan tason verenpaine pysyi koholla staattisen ylävartalotyön jälkeen 7±6 mmHg (p=0,001). EKG muutoksia ei juurikaan havaittu tutkimuksen kahden lämpötilan ja kahden liikuntatavan määrittämien altistusjaksojen aikana.

Sepelvaltimotautitopilaan koko kehon kylmäaltistus yhdessä dynaamisen ja staattisen liikunnan kanssa lisäsi sydämen kuormitusta verrattuna lepoon lämpimässä. Tästä huolimatta merkittäviä EKG muutoksia ei havaittu. Tulokset viittaavat siihen, että sepelvaltimotautitopilaat todennäköisesti hyötyvät ympäri vuotisesta dynaamisesta liikunnasta, mutta staattista liikuntaa on syytä tutkia tarkemmin.

Asiasanat: dynaaminen, kylmä ilma, liikunta, sepelvaltimotauti, staattinen
To my dad
Acknowledgments

The study was carried out at the Center for Environmental and Respiratory Health Research (CERH), University of Oulu.

I want to express my gratitude to my supervisors. Thank you, docent Tiina Ikäheimo, my principal supervisor, for leading me into the world of science and experimental research. Tiina, without your support and all the guidance, this study would never have been published. I wish to thank my supervisor Professor Jouni Jaakkola for your encouragement, advice on study designs and analyses, and support during my PhD studies.

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Finally, but most of all, I would like to thank my family and friends.

May 2022

Rasmus Valtonen
## Abbreviations

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<th>Description</th>
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<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<td>CBF</td>
<td>coronary blood flow</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian cardiac society</td>
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<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>HRR</td>
<td>heart rate reserve</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MSNA</td>
<td>muscle sympathetic nerve activity</td>
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<tr>
<td>MVC</td>
<td>maximal voluntary contraction</td>
</tr>
<tr>
<td>RPE</td>
<td>rate of perceived exertion</td>
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<tr>
<td>RPP</td>
<td>rate pressure product</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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1 Introduction

There are approximately 200,000 patients in Finland and more than 500 million globally with cardiovascular diseases (CVDs), and even more who have other connected health problems (such as high blood pressure (BP) or cholesterol), further weakening their cardiac function and physical activity and causing mortality (OSF, 2019a; Roth et al., 2020).

Cold weather is an important risk factor for morbidity and mortality (Fares, 2013; Gasparrini et al., 2015), particularly resulting from cardiovascular causes (Fares, 2013; Gasparrini et al., 2015). The elevated risk is mediated both through acute and seasonal (Fares, 2013) effects of a cold environment on cardiovascular function.

The benefits of regular exercise for wellbeing and health during all stages of life are unambiguous. Physical exercise is therefore an important measure in the prevention, treatment, and rehabilitation of many chronic diseases (Kujala, 2009). Exercise is also efficient in the treatment of coronary artery disease (CAD) and in preventing its progress, alleviating its symptoms, as well as reducing the risk of myocardial infarctions or fatal cardiac events (Achttien et al., 2015). Exercise-based cardiac rehabilitation programs have succeeded in reducing mortality related to CAD by as much as 35% according to the systematic review (Heran et al., 2011). Despite the obvious health benefits of exercise, only a few people with CAD perform exercise according to the recommendations. Many also cease being physically active after the onset of CAD despite exercise counseling (Yohannes et al., 2007).

Exercise performed in the winter, such as wood chopping, snow shoveling, and skiing can be particularly strenuous for the cardiovascular system. Experimental studies examining the combined effects of cold exposure and exercise among patients with CAD are scant (Ikäheimo, 2018). Research information is lacking on moderate level endurance exercise in cold environments in people with CAD and how the two stressors, exercise and cold, jointly affect the cardiovascular system. Cold exposure may increase the number of cardiac symptoms (Castellani et al., 2021; Ikäheimo et al., 2014). The effects of cold exposure may be stronger when exercising during the winter. This can elicit fears and prevent CAD patients exercising in the cold season. Yet this increasing aging population would benefit substantially from regular year-round physical activity to maintain their functional ability and independent living. Hence, empirical evidence is needed for how exercise at low temperatures influences cardiovascular responses.
2 Review of the literature

2.1 Human thermal exposure and thermoregulation

People can be exposed to cold temperatures, both at work and during their leisure time. Exposure is usually short term but recurrent. With habitual daily short-term cold exposure, core temperature remains relatively stable, but superficial cooling can occur, depending on the clothing used and the intensity of exposure to cold. Human thermal exposure is determined by the environment, the activity employed, and the clothing used. Maintaining a relatively constant core temperature requires heat production and loss to be balanced. Heat loss from human to the environment occurs through convection, conduction, radiation, and evaporation. Furthermore, the different forms of heat production are shivering and/or non-shivering thermogenesis and external work (Fig. 1.) (Parsons, 2010)

Fig. 1. Human thermal exposure and body heat balance. *Non-shivering thermogenesis.
2.1.1 **Human thermoregulatory system**

Thermoregulation is a complex regulatory process that allows our body to maintain its core temperature within a relatively narrow limit, and it is controlled by the hypothalamus (Fig. 2). Temperature sensitive receptors are free nerve endings that react to a certain level of temperature or its change, and they are located both under the skin and in the inner parts (around major blood vessels and internal organs) of the body. Neural afferent pathways transfer the sensory information to the hypothalamus, where the signals are processed and further conveyed to the sympathetic and somatic neurons. The preoptic area (POA) is thought to be the most important region for processing afferent and efferent neural information. The body can react to changes in heat loss or production, either through the somatic (shivering) and sympathetic nervous system (sweating). The sympathetic nervous system controls heat production or heat loss by activating non-shivering thermogenesis of brown adipose tissue and through cutaneous vasoconstriction and vasodilation. In addition, individual factors such as age, physical fitness, gender, body composition, health, adaptation, and behavioral factors markedly affect the extent of human body heat loss or production. (Parsons, 2010)

![Fig. 2. The thermoregulation system.](image-url)
2.2 Coronary artery disease

2.2.1 Pathophysiology

CAD is a group of diseases that include stable and unstable angina, and myocardial infarction (Willerson & Armstrong, 2015). Stable CAD is characterized by episodes of reversible myocardial demand/supply mismatch related to ischemia and often inducible by exercise or other stressors, for example, cold exposure (Montalescot et al., 2013). CAD manifests when part of the smooth elastic lining inside a coronary artery develops atherosclerosis. The artery’s lining becomes hardened, stiffened, and swollen with calcium and fatty deposits, as well as abnormal inflammatory cells, eventually generating a plaque rupture. The limitation of blood flow to the coronary arteries causes ischemia, which can lead to myocardial infarction, cardiac muscle damage, tissue death, and scarring.

2.2.2 Epidemiology

Cardiovascular diseases (CVDs), including CAD, are the main cause of death globally and a major reason for disability in both developed and developing countries (Malakar et al., 2019; Roth et al., 2020). Based on information from the recent global burden of disease study in 2019, the global burden of CVDs was 523 million, and there were 18.6 million CVD deaths (Roth et al., 2020). The global occurrence of CAD was previously estimated to be 154 million, representing 2.2% of the overall global burden of disease (GBD, 2017). In Finland, a total amount of 173,568 patients received reimbursement for medication for CAD in 2019, 63% men and 37% women (OSF, 2019b). In addition, there were 18,267 CVD deaths in 2019, representing 34% of the overall deaths (OSF, 2019a). CAD was the major cause of CVD deaths, contributing to every sixth death. However, over the last ten years, mortality from CVDs in Finland has decreased by one third in both men and women.

2.2.3 Seasonal variation

Empirical evidence demonstrates that non-optimal weather is related to decreased wellbeing, adverse health effects, and even mortality in the general population, and separately among coronary artery disease patients (Analitis et al., 2008; Gasparrini et al., 2015; Ryti et al., 2016). Seasonal variations in the incidence of acute coronary
syndrome is a well-known phenomenon, and especially the higher mortality rates in the winter months (Spencer et al., 1998; Stewart et al., 2017). The cold season is associated with permanently increased BP (Marti-Soler et al., 2014) and HR (Hopstock et al., 2013) and lower HR variability (Kristal-Boneh et al., 2000). In addition, coagulation factors, e.g., fibrinogen, as well as platelet viscosity and whole blood viscosity, have been reported to increase during the winter months (Mavri et al., 2001), which could contribute to ischemic cardiovascular and cerebrovascular events. Cold spells (prolonged periods with a subnormal temperature) have also been reported to increase the risk of sudden cardiac deaths (Ryti et al., 2017). A recent study also showed that moderate cold exposure during all seasons of the year can be hazardous to health (Ryti et al., 2022).

2.3 Cardiovascular responses to short-term cold exposure

2.3.1 Blood pressure

It is well known that acute cold exposure increases blood pressure in all individuals (Korhonen, 2006). Facial cold exposure alone, without marked whole-body cooling, increases SBP on average by 20–30 mmHg (Hintsala, Kandelberg, et al., 2014; Modesti, 2013) and even up to 60 mmHg (Hintsala, Kandelberg, et al., 2014). Lowering of skin temperature during cold exposure elicits a reflex of activation of sympathetically mediated vasoconstriction (Charkoudian, 2010; J. M. Johnson et al., 2014). This causes vasomotor adjustments mediated by increased sympathetic nerve activity (Greaney et al., 2016), which results in the vasoconstriction of both peripheral and visceral arteries (Wilson et al., 2007). This reduces superficial circulation manifold compared with a neutral environment. Vasoconstriction occurs both in response to reflex and local cooling of skin. A decrease in body core temperature can also activate vasoconstriction (Castellani & Young, 2016). This higher peripheral resistance has been reported to result in 5–30 mmHg higher SBP (Kingma et al., 2011; Mäkinen et al., 2008) and central aortic BP (Edwards et al., 2006; Hess et al., 2009) during whole-body cooling. As with healthy subjects, cold increases SBP in patients with CAD (Manou-Stathopoulou et al., 2015).
2.3.2 Heart rate

HR responses during the whole-body skin cooling with facial exposure result in either unaltered (Mäkinen et al., 2008; Sanchez-Gonzalez & Figueroa, 2013; Wilson et al., 2007) or decreased HR (Hintsala, Kandelberg, et al., 2014; Hintsala, Kentta, et al., 2014; Kingma et al., 2011; Korhonen, 2006). Reduced HR during facial cold exposure is due to the stimulation of the trigeminal nerve, which evokes a non-baroreflex mediated vagal response (Khurana & Wu, 2006). On the other hand, some previous studies have also reported reduced HR during skin surface cooling without facial exposure (Wilson et al., 2010; Yamazaki & Sone, 2000). It should be noted that a possible autonomic conflict can appear due to simultaneous cooling of the face and skin because of the parallel activation of both the sympathetic and parasympathetic nervous systems. This provides conflicting signals to the heart to simultaneously increase and reduce heart rate and can in the worst case provoke arrhythmias (Shatlock & Tipton, 2012).

2.3.3 Myocardial oxygen demand/supply

Whole-body cold exposure at rest increases both cardiac pre- and afterload, but with no marked changes in ventricular contractility, HR, or cardiac output (Wilson & Crandall, 2011). Furthermore, the greater increases in preload and afterload during cooling in older adults contribute to a more considerable increase in the indices of myocardial oxygen demand.

Cold exposure itself can result in higher rate pressure product (RPP) when the cold-induced SBP is augmented, and HR is unaltered or elevated. RPP indicates the stress output on the cardiac muscle by accounting for the number of times it needs to beat per minute (HR) and the arterial blood pressure against which it is pumping (SBP) (Ikäheimo, 2018; Manou-Stathopoulou et al., 2015). It has also been shown that the augmentation index (AI), which is an indicator of systemic arterial stiffness, is elevated during acute cold exposure (Edwards et al., 2006). These further increase afterload and left ventricle work. Cold exposure has been demonstrated to increase coronary blood flow (CBF), as can be expected based on the activation of the sympathetic nervous system and result in a higher cardiac workload. This increases the need for a higher myocardial oxygen supply (Manou-Stathopoulou et al., 2015).
CAD patients

Cold exposure provokes earlier symptoms of angina and results in higher RPP in CAD patients (Hattenhaur & Neill, 1975; Meyer et al., 2010), which can indicate that the higher myocardial oxygen demand cannot be met by increasing coronary blood flow and which leads to myocardial ischemia. CAD patients may also have endothelial dysfunction, which attenuates their vasodilatation response to cold (Zeiher et al., 1991) and further diminishes the increase in coronary blood flow.

Coronary autoregulation

The function of coronary autoregulation is to maintain a steady blood flow despite variations in coronary pressure. The mechanism of autoregulation can be divided into four categories: myogenic; metabolic; endothelial; and neural. Myogenic control adjusts vessel diameter inversely to vascular smooth muscle stretch. The metabolic pathway involves reacting to molecules such as carbon dioxide and adenosine. Endothelial control includes vasoactive factors (e.g., nitric oxide and prostacyclin) produced by the endothelium. Endothelial dysfunction may therefore limit increasing coronary flow in response to elevated myocardial oxygen demands. The neural control of coronary autoregulation includes both parasympathetic and sympathetic activation (N. P. Johnson et al., 2021). During exercise, coronary blood flow increases to match the augmented oxygen demand. In response to increased cardiac workload and shear stress, endothelial factors are released, resulting in the vasodilatation of coronary arteries (Manou-Stathopoulou et al., 2015).

2.4 Cardiovascular responses to short-term exercise

2.4.1 Dynamic exercise

Healthy subjects

Dynamic exercise involves cycles of muscular contraction and relaxation in which perfusion increases considerably during the relaxation phase (e.g., walking and cross-country skiing). Dynamic exercise causes a simultaneous activation of the sympathetic nervous system and withdrawal of vagal control. This augments HR, SBP, and contractility, while DBP remains relatively constant. The blood flow to
the exercising muscles increases, alongside cardiac output, to provide the required oxygen through circulation. The augmented cardiac output increases myocardial oxygen demand, as well as RPP (González-Camarena et al., 2000; Manou-Stathopoulou et al., 2015).

**CAD patients**

Coronary blood flow has also been shown to increase in patients with CAD during dynamic exercise (Okazaki et al., 1993), but less than in healthy subjects. In patients with CAD, the smaller residual vasodilator capacity results in lesser metabolic adaptation during exercise (Duncker & Bache, 2008). When angina occurs during exercise, it is due to the increase in coronary blood flow being insufficient to meet the increased myocardial oxygen demand (Duncker & Bache, 2008; Manou-Stathopoulou et al., 2015). The AI decreases during exercise and indicates a reduction in central SBP wave reflection due to vasodilatation of the systemic muscular arteries, which reduces left ventricle work (Lockie et al., 2012; Manou-Stathopoulou et al., 2015).

### 2.4.2 Static exercise

**Healthy subjects**

Static exercise, e.g., weightlifting (also known as isometric exercise) involves sustained muscle contraction with no change of muscle length. It also differs from dynamic exercise in several ways. Static exercise causes the sustained compression by the contracting muscle fibers, which restricts the local vasodilation occurring during dynamic exercise. The autonomic response to static exercise is related to the simultaneous vagal withdrawal and sympathetic activation (Manou-Stathopoulou et al., 2015). As with dynamic exercise, SBP is also augmented, but primarily because of the elevation in cardiac output. HR increases during static exercise, which with the increased SBP leads to an increased RPP and myocardial workload. It has also been reported that the AI increased during static exercise, inducing greater afterload and left ventricle work (Geleris et al., 2004; Manou-Stathopoulou et al., 2015; Toska, 2010).
CAD patients

HR, MAP, as well as cardiac output and RPP, also increase in the patients with CAD during static exercise. Coronary blood flow is augmented during static exercise, but the response is less than in healthy subjects (Lind, 1970; Manou-Stathopoulou et al., 2015). It should be noted that patients with CAD may have a higher risk of ischemia during exercise when their arms are stretched outwards, and the exercise involves both static and dynamic components.

2.5 Combined effects of exercise and exposure to cold on cardiovascular responses

Examples of the previous studies assessing the effects of cold exposure and physical exercise on cardiovascular responses among cardiovascular disease patients are listed in Table 2 below.

2.5.1 In healthy subjects

Previous studies have shown that systemic vascular resistance, SBP and therefore RPP are higher when exercising in the cold compared with a neutral environment (Muller et al., 2011; Peikert & Smolander, 1991). Some studies also suggest that SBP is the main factor related to the increase in RPP during dynamic exercise in the cold (Epstein et al., 1969; Manou-Stathopoulou et al., 2015; Walsh et al., 1995). On the other hand, others imply that HR is more important (Muller et al., 2011; Peikert & Smolander, 1991). The AI has been reported to be greater when performing isometric handgrip in the cold compared with a neutral environment (Geleris et al., 2004; Koutnik et al., 2014). It should be noted that comparing different studies is difficult because of the various modes of exercise (type and intensity) and forms of cold exposure (air, water, whole-body vs. local) used in the experimental protocols.

2.5.2 In coronary artery disease patients

Experimental studies examining the combined effects of cold exposure and exercise on CAD are scant (Emmett, 1995) and most have employed graded symptom-limited maximal exercise tests of very short durations (Juneau et al., 2002; Lassvik & Areskog, 1979a, 1980; Meyer et al., 2010). In addition, the forms of cold
exposure have varied between mild (Marchant et al., 1994; Peart et al., 1989) or more severe whole-body cold exposure (Juneau et al., 2002; Lassvik & Areskog, 1979b; Meyer et al., 2010; Rosengren et al., 1988) to local cold exposure, such as cold air inhalation (Areskog & Lassvik, 1988; Brown & Oldridge, 1985; Dodds et al., 1995; Hattenhaur & Neill, 1975; Lassvik & Areskog, 1980; Petersen et al., 1994; Williams et al., 2018).

The few studies where submaximal exercise in the cold have been examined among CAD patients demonstrated a slightly higher HR, SBP, and RPP (Emmett, 1995; Juneau et al., 2002). It has further been shown that a modest cold exposure (+15 °C) already increases BP during light exercise, increasing peripheral resistance and attenuating myocardial oxygen delivery (Emmett, 1995). Indeed, CAD patients experience more cold-related angina (Brown & Oldridge, 1985), and their ischemic threshold is reached earlier during exercise in the cold (Juneau et al., 2002; Meyer et al., 2010). Asymptomatic CAD patients, and those who do not experience cold-related angina, also reach the ischemic threshold earlier while exercising in the cold (Meyer et al., 2010).

Upper-body exercise in the cold (e.g., wood chopping, snow shoveling) may be more strenuous for a person with CAD than lower-body exercise (e.g., walking, running). This is largely due to the smaller muscle mass of the arms, where a certain level of exercise increases HR, BP, and the sensation of strain more than with a comparable exercise level performed with the legs (Louhevaara et al., 1990). Furthermore, arm exercise results in a more rapid withdrawal of vagal outflow than dynamic leg exercise (Tulppo et al., 1999), which may be harmful for patients with heart disease. Cold exposure can further increase the physical strain through increased sympathetic activity, peripheral resistance, and increased BP.

Sudden heavy exercise in the cold especially can be dangerous for people with cardiac disease. For example, snow shoveling is physically strenuous, and the energy expenditure of individuals with CAD remains at a lower level compared with healthy individuals (Sheldahl et al., 1992). In addition, this activity increases angina symptoms (Nichols et al., 2012), and may lead in the worst case to myocardial infarction or sudden cardiac death (Anderson & Rochard, 1979).
Table 2. Description of previous study designs for assessing the effects of cold exposure, exercise, and cardiovascular responses among heart disease patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>Type of exercise</th>
<th>Type of cold exposure</th>
</tr>
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<tbody>
<tr>
<td><strong>Whole-body cold exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer et al. 2010</td>
<td>13 men, CAD</td>
<td>max treadmill test</td>
<td>-20 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Schmid et al. 2009</td>
<td>22 men, CHF and CAD</td>
<td>swimming</td>
<td>+22 °C vs. +32 °C (water)</td>
</tr>
<tr>
<td>Blanchet et al. 2003</td>
<td>33 patients, CHF</td>
<td>symptom-limited submaximal exercise</td>
<td>-8 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Juneau et al. 2002</td>
<td>11 patients, CHF</td>
<td>treadmill test</td>
<td>-8 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Marchant et al. 1994</td>
<td>14 patients, CAD</td>
<td>treadmill test</td>
<td>+6 °C vs. +25 °C (air)</td>
</tr>
<tr>
<td>Sheldahl et al. 1992</td>
<td>16 men, CAD</td>
<td>snow shoveling</td>
<td>-1.5 °C (air)</td>
</tr>
<tr>
<td>Peart et al. 1989</td>
<td>15 patients, CAD</td>
<td>treadmill test</td>
<td>0 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Juneau et al. 1989</td>
<td>24 patients, CAD</td>
<td>treadmill test</td>
<td>-8 °C vs. 20 °C (air)</td>
</tr>
<tr>
<td>Rosengren et al. 1988</td>
<td>9 men, AP</td>
<td>bicycle test</td>
<td>-8 °C vs. +22 °C (air)</td>
</tr>
<tr>
<td>Areskog &amp; Lassvik 1988</td>
<td>17 men, AP</td>
<td>bicycle test</td>
<td>-10 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Brown &amp; Oldridge 1985</td>
<td>9 patients, AP</td>
<td>bicycle test</td>
<td>-7.5 °C vs. +24 °C (air)</td>
</tr>
<tr>
<td>Lassvik &amp; Areskog 1980</td>
<td>12 men, AP</td>
<td>bicycle test</td>
<td>-10 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Backman et al. 1979</td>
<td>26 patients, AP</td>
<td>bicycle test</td>
<td>-15 °C vs. +22 °C (air)</td>
</tr>
<tr>
<td>Lassvik &amp; Areskog 1979</td>
<td>11 patients, AP</td>
<td>bicycle test</td>
<td>-30 °C - +20 °C (air)</td>
</tr>
<tr>
<td>Lassvik &amp; Areskog 1979</td>
<td>17 men, AP</td>
<td>bicycle test</td>
<td>-10 °C vs. +20 °C (air)</td>
</tr>
<tr>
<td>Epstein et al. 1969</td>
<td>6 men, CAD</td>
<td>bicycle/treadmill test</td>
<td>+15 °C vs. +25 °C (air)</td>
</tr>
<tr>
<td><strong>Local cold exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams et al. 2018</td>
<td>12, mend CAD</td>
<td>5-min bicycle session</td>
<td>-15 °C vs. +22 °C (inhalation)</td>
</tr>
<tr>
<td>Dodds et al. 1995</td>
<td>12 men, CAD</td>
<td>treadmill test</td>
<td>-15 °C vs. +22 °C (inhalation)</td>
</tr>
<tr>
<td>Petersen et al. 1994</td>
<td>10 Men, previous MI</td>
<td>bicycle test</td>
<td>-22 °C vs. +22 °C (inhalation)</td>
</tr>
<tr>
<td>Hattenhauer &amp; Neill, 1975</td>
<td>17 men, CAD</td>
<td>atrial pacing until angina</td>
<td>-20 °C vs. +20 °C (inhalation)</td>
</tr>
<tr>
<td><strong>Cold pressor test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesto et al. 1989</td>
<td>16 men, CAD</td>
<td>graded maximal test</td>
<td>cold pressor test</td>
</tr>
<tr>
<td>Shea et al. 1987</td>
<td>35 patients, CAD</td>
<td>graded maximal test</td>
<td>cold pressor test</td>
</tr>
<tr>
<td>de Servi et al. 1985</td>
<td>11 patients, CAD</td>
<td>graded maximal test</td>
<td>cold pressor test</td>
</tr>
<tr>
<td>de Servi et al. 1980</td>
<td>8 patients, CAD</td>
<td>isometric exercise</td>
<td>cold pressor test</td>
</tr>
</tbody>
</table>

coronary artery disease (CAD); chronic heart failure (CHF); AP angina pectoris
2.6 Current recommendations for exercise of CAD patients

Exercise is efficient in the treatment of CAD and in preventing its progress, alleviating its symptoms, as well as reducing the risk of myocardial infarctions or a fatal cardiac event. The current international guidelines for stable CAD patients recommend physical activity that includes at least 150 mins a week of moderate intensity or 75 mins a week of vigorous intensity aerobic physical. Exercise training should be prescribed according to the FITT (frequency, intensity, time (duration) and type of exercise) model. Aerobic training is recommended to be performed on most days (at least three days/week and preferably 6–7 days/week) and resistance training two times/week at moderate to vigorous intensity lasting at least 20–30 mins (preferably 45–60 mins) per session. (Ambrosetti et al., 2021). The national exercise training guideline for stable CAD patients in Finland is comparable with the international ones (Hautala et al., 2016).

2.7 Gaps in the knowledge

It is currently unknown whether the exercise currently recommended for people with CAD involves a health risk during the cold season. More specifically, information on the effects of upper- or lower-body and dynamic or static sustained submaximal exercise in the cold are lacking. Because both exercise and cold exposure stimulate cardiac and circulatory functions, it is important to study their combined effect, especially among those with CAD whose myocardial oxygen supply and function are weakened. This research project addresses a large and special population group living in the northern hemisphere, whose symptoms, health events, and mortality are common, and typically provoked during the cold season.
3 Aims and hypotheses of the study

The study’s main aim was to examine how currently recommended health-enhancing exercise in combination with cold exposure affected the cardiac and circulatory functions of people with CAD.

The specific aims of the study were:

1. To assess the separate and combined effects of moderate intensity lower-body dynamic exercise and cold exposure on cardiovascular responses in patients with CAD (I).
2. To examine cardiovascular responses during dynamic and static upper-body exercise in a cold environment (II).
3. To assess the effects of lower- and upper-body dynamic and static exercise in a cold environment on post-exercise central aortic pressure (III).

The hypotheses of the study were:

1. Moderate intensity lower-body exercise causes greater cardiovascular work and signs of myocardial ischemia when performed in the cold compared with a neutral environment (I).
2. Cardiac workload is higher during dynamic and static upper-body exercise in a cold compared with a neutral environment, and myocardial ischemia is observed earlier during exercise in the cold (II).
3. Cold exposure blunts the beneficial effects of aerobic lower-body exercise on central hemodynamics, resulting in a smaller decrease in post-exercise central aortic BP and wave reflection (III).
4. Central aortic blood pressure is reduced less after upper-body dynamic exercise in a cold compared with a neutral environment, and even more so with static exercise (III).
4 Subjects and methods

4.1 Characteristics of the study patients

The inclusion criteria consisted of a diagnosed CAD (Canadian Cardiac Society [CCS] classes I–II) and a non-ST-elevation myocardial infarction at least 3 months (actual elapsed time was 8–49 months) prior to experimentation. The exclusion criteria were CCS classes III–IV, previous myocardial infarction less than 3 months prior to the experiments, chronic atrial fibrillation, claudication, unstable angina pectoris, left ventricular ejection fraction less than 40%, a history of coronary artery bypass grafting, pacemaker, serious complex or electrocardiography (ECG) anomalies during rest, the presence of physician-diagnosed asthma or diabetes, and current smoking.

The recruitment protocol is shown in Fig. 3. An experienced cardiologist evaluated the inclusion and exclusion of each patient based on the criteria described above and contacted them by phone calls. A total of 53 Oulu University Hospital patients were reached by telephone, and 45 of them participated to the physical capacity tests. Eight patients did not meet the inclusion criteria. Five patients were excluded afterwards due to smoking, diabetes, arrhythmia, and/or having a leg infection. A total of 40 patients participated to the actual laboratory measurements, and 38 of them completed all measurements. The total number of patients in Study I was 16, study II 20, and Study III 26 patients.

Fig. 3. Recruitment protocol of the study.
4.2 Study design

We conducted two four-period cross-over trials during the winters of 2016 and 2017 (Fig. 4). During the first trial (2016), each patient participated in four different experimental conditions in random order. These were: 1) a 30 min exercise in the cold environment (-15 °C, wind 1.0m/s); 2) a 30 min exercise in the neutral environment (+22 °C, wind 1.0m/s); 3) a 30 min rest in the aforementioned cold conditions, and 4) a 30 min rest in the neutral conditions. During the second trial (2017) (Fig. 4), each patient experienced the following four different experimental conditions, administered in random order: 1) dynamic upper-body exercise in a cold (-15 °C, wind 1.0m/s) and 2) neutral (+22 °C, wind 1.0m/s) environment, as well as 3) static upper-body exercise in a cold (-15 °C, wind 1.0m/s) or 4) neutral (+22 °C, wind 1.0m/s) environment. The chosen cold environmental temperature (-15 °C) occurs commonly in northern hemisphere countries during the cold season.

![Study design](image)

4.2.1 Physical capacity measurements

Bicycle ergometer tests (Ergoline, ergoselect 100K, Fysioline, Finland) were carried out approximately a month prior to the experiments in both trials to assess the maximal exercise capacity of the patients and to detect possible ECG abnormalities and contraindications for participation. Prior to the test, ECG and HR were measured at rest in the supine position. The test was started from 30W and was increased by 15W each minute until exhaustion. An exercise physiologist carried out the tests, which were monitored by a medical doctor. No abnormalities were detected in the ECGs during exercise in any of the enrolled patients. The
results of the exercise capacity tests were further used to calculate an individually based walking speed for the lower-body experiments that represented moderate intensity exercise (Bubb et al., 1985).

4.2.2 Lower-body dynamic exercise (I)

The types of exercise employed are described in Fig. 5. The selected exercise was chosen to represent health-enhancing exercise recommendations for CAD patients in terms of intensity and duration. It consisted of brisk walking (Fig. 5A) for 30 minutes on a treadmill, with the speed and angle kept constant for each patient while exercising in cold and neutral conditions. The level of exercise was adjusted to correspond to the recommended intensity and duration of health-enhancing aerobic exercise (Secondary prevention 2010, Fletcher 2013). The selected exercise intensity represented 65–70% $\text{HR}_{\text{max}}$, where the individual walking speed was adjusted based on target HR and calculated based on the following equation: $\text{HR}_{\text{rest}} + 0.45\times\text{HR}_{\text{RR}}$, where $\text{HR}_{\text{RR}}$ is heart rate reserve = $\text{HR}_{\text{max}} - \text{HR}_{\text{rest}}$. Resting cold exposure was mainly restricted to the face, as the patients wore full winter clothing consisting of underwear (shirt, pants), insulated trousers, an insulated jacket, over-trousers, an over-jacket, socks, and shoes (insulation value of clothing ensemble 2.13 clo).

During exercise in the cold, clothing insulation was slightly reduced to 1.88 clo (removal of over-trousers and jacket). A smaller amount of clothing insulation (0.75 clo) was also used during exposures occurring in the neutral environment. The experimental conditions were separated from each other by at least one week. Each patient performed the four experiments at the same time of day.

4.2.3 Upper-body dynamic and static exercise

The dynamic upper-body exercise (Fig. 5B) consisted of a 5 min pre-exposure, three 5 min work cycles via an arm crank (Monark 881E, Vansbro, Sweden), each with different intensities, and two 4 min rest periods between the work cycles. The intensity of exercise was adjusted based on subjective judgments of Perceived Exertion to mild (11–12 fairly light), moderate (13–14 somewhat hard), and high (15–16 hard), and kept constant between the different environmental conditions (Borg, 1998).

The level of static upper-body exercise (Fig. 5C) was adjusted based on maximal voluntary contraction (MVC) (Newtest Leg Force [bench press mode],
Newtest, Oulu, Finland). MVC was measured at the beginning of the first visit to the lab, and at least 1 hour before the baseline measurements. The exercise itself consisted of a 5 min pre-exposure and five 1.5 min isometric contractions at the following workloads: 10%, 15%, 20%, 25%, and 30% of MVC. Patients had a 4 min break following each work cycle. They were instructed to avoid heavy exercise for 24 h, alcohol for 48 h, and coffee/caffeine related beverages for 2 h prior to the experiments.

While being exposed to cold, the patients wore full winter clothing consisting of underwear (shirt, pants), insulated trousers, an insulated jacket, over-trousers, an over-jacket, socks, and shoes (insulation value of clothing ensemble 2.13 clo). A smaller amount of insulation (0.75 clo) was used at neutral climate exposures to avoid heat strain.

**Fig. 5.** The different types of exercise employed in the experiments: a) brisk walking; b) arm crank; and c) isometric bench press.
4.3 Measured parameters

4.3.1 Body composition, health and lifestyle questionnaire

Prior to initiating each experiment, body composition was assessed from each patient by bioimpedance measurements (InBody720 Biospace, Seoul, Korea). They also completed a questionnaire about health and lifestyle, which inquired about medication, alcohol consumption, physical fitness, current health status, and exposure to cold at work or during leisure time. The patients were instructed to avoid heavy exercise for 24 h, alcohol for 48 h, and coffee/caffeine related beverages for 2 h prior to the experiments.

4.3.2 Skin temperature, thermal sensations, and rate of perceived exertion

Skin temperature was measured continuously using thermistors (NTC DC95, Digi-Key, Thief River Falls, MN, USA) attached to the right scapula, left cheek, forehead, left calf, right anterior thigh, dorsal side of left index finger (middle phalanx), left hand, left forearm, right shoulder, and left upper chest. Data were recorded at 20 s intervals with two temperature data loggers (SmartReaderPlus; Acr Systems Inc., BC, Canada). Mean skin temperature ($T_{sk}$) was calculated as follows: $T_{sk} = [0.07 \times \text{forehead} + 0.175 \times \text{right scapula} + 0.175 \times \text{left upper chest} + 0.07 \times \text{right arm} + 0.07 \times \text{left arm} + 0.05 \times \text{left hand} + 0.19 \times \text{right anterior thigh} + 0.2 \times \text{left calf}]$ (ISO 9886, 2004). Thermal sensations were investigated using scales of perceptual judgments on personal thermal state (ISO 10551, 1995). Perceived exertion was investigated at 5-minute intervals during exercise using Borg’s scale (Borg, 1998).

4.3.3 Blood pressure and heart rate

Brachial blood pressure (Schiller BP 200+, Switzerland) was assessed at 5-minute intervals during baseline, the intervention, and follow-up during lower-body exercise. During upper-body exercise, blood pressure was assessed at 5-minute intervals (baseline, follow-up, and immediately after the exercise ended).

Central aortic BP was assessed non-invasively via radial artery applanation tonometry (SPC-301; Millari Instruments, Houston TX, USA) by the same operator during baseline before and 25 mins after each intervention. The measurements were performed in a sedentary position at a neutral temperature (+22 °C). Measured
radial artery pressure waves were calibrated with brachial BP values (BP 200+, Schiller, Baar, Switzerland). Thereafter, central aortic BP was computed by using a build-in mathematical algorithm (Chen et al. 1997) (SphygmoCor Px; AtCor Medical, Sydney, Australia).

Central systolic, diastolic, and pulse pressure were defined from the pressure curve. The augmentation index (AI), an index of wave reflection (Laurent et al., 2006), was computed as the difference between second and first systolic pressure peaks, i.e., the augmented pressure, divided by the pulse pressure: (P2−P1)/PP. The augmentation index is inversely dependent on HR and was therefore adjusted to a HR of 75 bpm (Crilly, 2014). Both adjusted and non-adjusted indexes are presented. Reflection time (Tr), the time that the pressure wave needs to reach the main reflection site and return (Laurent et al., 2006), was defined as the time between the onset of the pulse waveform and the onset of the reflected systolic central waveform. Data quality was ensured by rejecting measurements via a built-in quality control operator index (Sphygmocor Px) below 75% (i.e., ensuring low variation for pulse height, diastolic pressure, and shape of the pressure wave during systole). The measured average operator indexes were 94±5% (mean±SD) for the first (lower-body aerobic exercise) and 92±6% for the second (upper-body dynamic and static exercise) study protocol. RPP was calculated by multiplying brachial SBP by HR. MAP was calculated by the following formula: MAP = 1/3 x (SBP – DBP) + DBP.

ECG was recorded and monitored continuously using a 15-lead ECG (Cardiosoft V6.71, GE Healthcare, Freiburg, Germany). The sites of the ECG electrodes at rest followed the standard 12-lead placement of X, Y, Z leads. In the clinical exercise test and during the experiments, the arm and foot electrodes were reset to both the shoulders and lower back. Signal analyses were carried out with custom-made software in Matlab (MathWorks, Inc., Natic, MA, USA). Ectopic and abnormally shaped beats were removed from the analysis. ECG was used to identify P wave onset, QRS boundaries, R and T wave peaks, and T wave offset, from which the QRS and QT interval were calculated. The QRS complex describes ventricular depolarization. A QRS elongation indicates intraventricular conduction disturbances. The T wave reflects ventricular repolarization, and an altered T wave can reflect ischemia. The QT interval describes the repolarization time and is heart-rate-dependent. The QT interval was therefore corrected with the nomogram method (QTc) (Karjalainen et al., 1994). Elongation of the QT-interval could predispose to arrhythmias. An ST segment depression indicates ischemia and was evaluated at 60 ms following the J point.
4.4 Ethics and patient safety

The study follows the Declaration of Helsinki and the legislation and ethical principles concerning medical research on humans in Finland. The study was approved by the Northern Ostrobothnia Hospital Districts Ethical Committee on October 15, 2012. The study’s patients were given both written and oral information about the study and provided informed consent for participation. Separate consent for a blood sample and possible later assessment of genetic susceptibility related to cold and other environmental factors was requested. Patients were selected by a cardiologist and following the agreed exclusion criteria. They were insured for the course of the experiments. The experimental tests were performed by skilled personnel and under the monitoring of a paramedic nurse and supervision of a medical doctor. The employed cold exposure and level of exercise do not deviate from habitual wintertime physical activity and do not cause additional health risks to the patients. Participation in the study was voluntary, and the patient had the right to terminate the experiment at any time (Ikäheimo et al., 2019). The study is registered in the Clinical Trials (NCT02855905).

4.5 Statistical methods

We conducted a sample size estimation and power analysis (G-Power 3.1.0) prior to the study, which was estimated to detect statistically significant differences in BP between a warm and cold environment [Power (1-β err prob), 0.9, Cohen’s effect size 0.8, α err prob 0.05] with 15 patients. Normal distribution of the analyzed parameters was verified with Shapiro-Wilk tests. We used a 3-way ANOVA to assess the global effects of exercise, temperature, and time, using within-subjects factors time (baseline vs. post intervention), temperature (cold vs. neutral), and activity (exercise vs. rest). Based on the observed interaction for temperature and exercise, we conducted separate 2-way ANOVAs for static and dynamic upper-body exercise interventions in which the main effects of temperature (cold vs. neutral) and time (baseline vs. intervention/post-intervention) were compared. For any observed interaction, separate post-hoc analyses were carried out to compare means between the temperature conditions. The results are expressed as means and their standard deviations (SD) or as 95% confidence intervals (CI). Statistical significance was set at p<0.05. Statistical analyses were performed with IBM SPSS for Windows version 23 (IBM Corp, Armonk, NY, USA).
5 Results

5.1 Study patients

The study consisted of 38 male coronary artery disease patients. Twenty-one of the patients were retired, while the rest were still engaged in working life. Their mean exercise capacity was 30.3±5.5 mL/kg/min, which represents moderate physical capacity when using scales of healthy adults (Shvartz & Reibold, 1990). Details of the study patients are in Table 3.

5.2 Skin temperature, thermal sensations, and intensity of exercise

5.2.1 Lower-body dynamic exercise (I, III)

Exercise in the cold decreased $T_{sk}$ (Fig. 6A) by 6.3±1.0 °C ($p<0.001$), while exercise in neutral conditions decreased $T_{sk}$ 0.9±0.5 °C ($p<0.001$), both compared with the pre-exposure baseline. In addition, at the end of the intervention, $T_{sk}$ was lower (+23±1.0 °C) after exercise in the cold compared with rest (+25.6±0.9 °C) in the cold. Facial skin temperature decreased considerably from +31±0.4 °C to +12±1.3 °C ($p<0.001$), both during rest and exercise in a cold environment. It should be noted that skin temperature decreased in the cold at all measurement sites, but to a greater extent in the extremities (forehead, face, calf, finger, hand). At the end of the respective interventions, the average whole-body thermal sensation was: -3/cold (cold rest), -1/slightly cool (cold exercise), 0/neural (neutral rest), and +2/warm (neutral exercise). The achieved exercise intensity represented 69% and 66% of maximum heart rate at cold and neutral temperature respectively. The rate of perceived exertion varied (RPE) from light to somewhat hard (11–14), both while exercising in a neutral and cold environment.
Table 3. Characteristic of the study population (n=38)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.7 ± 7.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.8 ± 4.9</td>
</tr>
<tr>
<td>Body fat. %</td>
<td>24.5 ± 7.4</td>
</tr>
<tr>
<td>Peak oxygen consumption, (ml/kg/min)</td>
<td>30.3 ± 5.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120.4 ± 14.4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76.4 ± 11.1</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>30 (79%)</td>
</tr>
<tr>
<td>Time from myocardial infarction, months</td>
<td>22.6 ± 11.0</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>23 (61%)</td>
</tr>
<tr>
<td>Double vessel disease</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Number of stents</td>
<td>Average 2 (varied 0 to 5)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>61.8% ± 9.4</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid, n</td>
<td>36 (95%)</td>
</tr>
<tr>
<td>Beta blockers, n</td>
<td>26 (68%)</td>
</tr>
<tr>
<td>Statins, n</td>
<td>30 (79%)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors, n</td>
<td>20 (53%)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, n</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Adenosine-diphosphate receptor antagonist, n</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Calcium channel blockers, n</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Pensioner, yes</td>
<td>21 (55%)</td>
</tr>
<tr>
<td>Self-perceived health status, n</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Quite good</td>
<td>13 (34%)</td>
</tr>
<tr>
<td>Average</td>
<td>17 (45%)</td>
</tr>
<tr>
<td>Quite poor</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Use any alcoholic drinks (even occasionally), n</td>
<td>15 (92%)</td>
</tr>
<tr>
<td>Leisure-time physical activity, n</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Rarely</td>
<td>26 (68%)</td>
</tr>
<tr>
<td>Often</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Very often</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Values represent the number of the patients or means ± SD. Peak oxygen consumption, in mL/kg/min, was estimated (3.5*MET, where MET is metabolic equivalent of task) from a symptom limited maximal oxygen uptake test.
5.2.2 Upper-body dynamic exercise (II, III)

Exposure to a cold temperature decreased $T_{sk}$ (Fig. 6B) by 3.7 °C ($p<0.001$), and facial skin temperature decreased considerably from +31 °C to +15 °C ($p<0.001$) during dynamic exercise in the cold environment. At the end of the intervention, the average whole-body thermal sensation of patients was -1/slightly cool (cold dynamic) and +2/warm (neutral dynamic). The achieved exercise intensity represented 56, 62, and 73% of $HR_{max}$ during dynamic exercise in a neutral and 59, 66, and 80% of $HR_{max}$ in a cold environment. The RPE during dynamic exercise varied from somewhat light to hard (11–15) at the neutral temperature and from somewhat hard to very hard (12–16) in the cold environment.

5.2.3 Upper-body static exercise (II, III)

Exposure to cold temperature decreased $T_{sk}$ (Fig. 6B) by 4.1 °C ($p<0.001$) and facial skin temperature from +31 °C to +15 °C ($p<0.001$) by the end of exercise in the cold environment. At the end of the intervention, the average whole-body thermal sensation of patients was -2/cold (cold) and +1/slightly warm (neutral). The achieved exercise intensity represented 46, 47, 48, 52, and 56% of $HR_{max}$ at neutral environment and 42, 43, 44, 47, and 50% in a cold environment. The RPE varied from somewhat light to very hard (10 to 16) at both temperatures.
Fig. 6. Mean skin temperatures during the lower-body (A) and upper-body (B) interventions.
5.3 Cardiovascular responses

5.3.1 Lower-body dynamic exercise (I, III)

BP, HR, and RPP (I) increased similarly at the beginning of exercise (at 2 min), both in cold and neutral environments. However, at the end of exercise (at 27 min) RPP was 17% higher in the cold compared with exercise in neutral conditions ($p=0.001$) (Fig. 7A). This elevated RPP was primarily driven by SBP (Fig. 7B), which was 13% ($p=0.001$) higher, while HR (Fig. 7C) was only 3% ($p=0.042$) higher in the cold compared with neutral conditions. During rest, RPP was 23% higher in the cold compared with rest in the neutral environment ($p=0.018$). This elevated RPP was also primarily driven by an elevation in SBP, which was increased by 19% ($p=0.001$), while HR did not appreciably change (2%, ns). During recovery, SBP remained at a significantly lower level after exercise compared with the experimental resting condition, but with no difference between the environmental temperatures ($p=0.001$).

![Fig. 7. Cardiovascular responses of lower-body dynamic exercise at +22 °C and -15 °C. rate pressure product (RPP), systolic blood pressure (SBP), heart rate (HR), and post-exercise central aortic systolic blood pressure (Central SBP). Modified figure from (I, III).](image-url)
Central hemodynamics after rest and lower-body aerobic exercise in cold and neutral temperatures are presented in Fig. 7D and Tables 4 and 5 (III). Exercise decreased post-exercise central aortic systolic BP compared with rest, independent of the ambient temperature (decrease of -6 to -10 mmHg and increase of 9–10 mmHg after rest from baseline levels, p<0.001). Of note, exercise decreased (p<0.01) central aortic diastolic BP compared with rest, but only when performed at a neutral temperature (p=0.047 for interaction between temperature, activity, and time).

Table 4. Central aortic pressure following lower-body dynamic exercise in +22 °C (n=11).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Rest +22 °C</th>
<th>Exercise +22 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSBP, mmHg</td>
<td>118 (106, 131)</td>
<td>130 (119, 140)</td>
</tr>
<tr>
<td>cDBP, mmHg</td>
<td>81 (73, 88)</td>
<td>88 (80, 96)</td>
</tr>
<tr>
<td>bSBP, mmHg</td>
<td>129 (115, 142)</td>
<td>139 (127, 150)</td>
</tr>
<tr>
<td>bDBP, mmHg</td>
<td>80 (73, 88)</td>
<td>87 (80, 95)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>59 (55, 64)</td>
<td>55 (52, 59)</td>
</tr>
<tr>
<td>AIHR75, %</td>
<td>14 (9, 19)</td>
<td>18 (13, 24)</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>9 (6, 13)</td>
<td>13 (8, 18)</td>
</tr>
<tr>
<td>P1, mmHg</td>
<td>112 (102, 121)</td>
<td>119 (110, 128)</td>
</tr>
<tr>
<td>P2, mmHg</td>
<td>121 (109, 133)</td>
<td>131 (121, 142)</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>149 (140, 158)</td>
<td>146 (139, 154)</td>
</tr>
<tr>
<td>ED, ms</td>
<td>299 (283, 314)</td>
<td>318 (304, 332)</td>
</tr>
</tbody>
</table>

Values are means and 95% confidence intervals. c-SBP central systolic blood pressure; c-DBP central diastolic blood pressure; b-SBP brachial systolic blood pressure; b-DBP, brachial diastolic blood pressure; AIHR75 augmentation index adjusted to heart rate of 75 bpm; AI unadjusted augmentation index; APHR75 augmented pressure adjusted to heart rate of 75 bpm; AP augmentation pressure; P1 and P2 blood pressure at the first and second systolic pressure peak; ED ejection duration; Tr time to reflection.

Brachial systolic and diastolic BP changes were comparable to the changes in central aortic BP. Post-exercise HR was elevated (p<0.001), but with no effect of temperature. Concerning wave reflection, exercise decreased the AI compared with rest, independent of temperature and with or without HR adjustments (ca. 8–40% decrease after exercise compared with the baseline). Augmented pressure decreased, and time to reflection increased, following exercise compared with rest, independent of temperature.
Table 5. Central aortic pressure following lower-body dynamic exercise in -15 °C (n=11). Modified from (III)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest -15 °C</th>
<th>Exercise -15 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-exercise</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
<td>120 (107, 133)</td>
<td>129 (119, 139)</td>
</tr>
<tr>
<td>cDBP, mmHg</td>
<td>83 (76, 91)</td>
<td>87 (81, 93)</td>
</tr>
<tr>
<td>bSBP, mmHg</td>
<td>133 (118, 148)</td>
<td>140 (128, 152)</td>
</tr>
<tr>
<td>bDBP, mmHg</td>
<td>83 (76, 90)</td>
<td>86 (81, 92)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>62 (57, 67)</td>
<td>56 (50, 62)</td>
</tr>
<tr>
<td>AIHR75, %</td>
<td>11 (4, 17)</td>
<td>16 (11, 21)</td>
</tr>
<tr>
<td>AI, %</td>
<td>17 (12, 22)</td>
<td>25 (20, 31)</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>7 (4, 10)</td>
<td>11 (6, 15)</td>
</tr>
<tr>
<td>P1, mmHg</td>
<td>115 (102, 127)</td>
<td>121 (111, 130)</td>
</tr>
<tr>
<td>P2, mmHg</td>
<td>122 (108, 136)</td>
<td>132 (121, 142)</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>153 (144, 162)</td>
<td>146 (141, 152)</td>
</tr>
<tr>
<td>ED, ms</td>
<td>291 (282, 300)</td>
<td>309 (295, 323)</td>
</tr>
</tbody>
</table>

Values are means and 95% confidence intervals. c-SBP central systolic blood pressure; c-DBP central diastolic blood pressure; b-SBP brachial systolic blood pressure; b-DBP, brachial diastolic blood pressure; AIHR75 augmentation index adjusted to heart rate of 75 bpm; AI unadjusted augmentation index; APHR75 augmented pressure adjusted to heart rate of 75 bpm; AP augmentation pressure; P1 and P2 blood pressure at the first and second systolic pressure peak; ED ejection duration; Tr time to reflection.
5.3.2 Upper-body dynamic exercise (II, III)

Dynamic exercise in the cold increased HR by 2.3–4.8% (p=0.002–0.040), MAP by 3.9–5.9% (p=0.038–0.454), and RPP by 18.1–24.4% (p=0.002–0.020) compared with a neutral temperature (Fig. 8 A, B, C). Post-exercise recovery of RPP after cold exposure was delayed by 10 minutes compared with a neutral environment.

Fig. 8. Cardiovascular responses of upper-body dynamic exercise at +22 °C or -15 °C. Rate pressure product (RPP), systolic blood pressure (SBP), heart rate (HR), and central aortic systolic blood pressure (Central SBP). Modified figure from (II, III).

Dynamic upper-body exercise decreased post-exercise central aortic systolic BP by approximately 2–4 mmHg (p=0.01) from the baseline (Fig. 8D, Table 6). Brachial BP was not altered. A higher post-exercise HR (7 bpm) was observed (p<0.001), which was not temperature related. Concerning wave reflection, the AI (Table 6) decreased after exercise, but the changes were not significant after adjusting for HR. P2 also decreased (p<0.01) following exercise, but with no temperature effect.
Table 6. Central aortic pressure following upper-body dynamic exercise (n=15). Modified from (III).

<table>
<thead>
<tr>
<th>Variable</th>
<th>+22 °C upper-body dynamic exercise</th>
<th>-15 °C upper-body dynamic exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-exercise</td>
</tr>
<tr>
<td>c-SBP, mmHg</td>
<td>107 (99, 115)</td>
<td>105 (98, 112)</td>
</tr>
<tr>
<td>c-DBP, mmHg</td>
<td>78 (72, 83)</td>
<td>79 (74, 84)</td>
</tr>
<tr>
<td>b-SBP, mmHg</td>
<td>119 (110, 128)</td>
<td>118 (109, 127)</td>
</tr>
<tr>
<td>b-DBP, mmHg</td>
<td>77 (72, 82)</td>
<td>78 (73, 83)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>61 (58, 65)</td>
<td>68 (64, 73)</td>
</tr>
<tr>
<td>AI ren, %</td>
<td>9 (6, 13)</td>
<td>8 (5, 10)</td>
</tr>
<tr>
<td>AI, %</td>
<td>16 (12, 20)</td>
<td>11 (7, 15)</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>5 (3, 6)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>P1, mmHg</td>
<td>101 (94, 107)</td>
<td>101 (94, 107)</td>
</tr>
<tr>
<td>P2, mmHg</td>
<td>105 (98, 113)</td>
<td>104 (97, 110)</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>151 (144, 157)</td>
<td>149 (143, 155)</td>
</tr>
<tr>
<td>ED, ms</td>
<td>292 (284, 300)</td>
<td>274 (262, 287)</td>
</tr>
</tbody>
</table>

Values are means and 95% confidence intervals. c-SBP central systolic blood pressure; c-DBP central diastolic blood pressure; b-SBP brachial systolic blood pressure; b-DBP, brachial diastolic blood pressure; AI ren augmentation index adjusted to heart rate of 75 bpm; AI unadjusted augmentation index; AP ren augmented pressure adjusted to heart rate of 75 bpm; AP unadjusted augmentation pressure; P1 and P2 blood pressure at the first and second systolic pressure peak; ED ejection duration; Tr time to reflection.

5.3.3 Upper-body static exercise (II, III)

Static exercise in the cold resulted in higher MAP (6.3–9.1%; p=0.000–0.014), lower HR (4.1–7.2%; p=0.009–0.033), and unaltered RPP compared with a neutral environment (Fig. 9 A, B, C). The recovery of RPP following static exercise was delayed and reached the same level as the neutral exercise intervention 10 mins after the end of the exposure.
Fig. 9. Cardiovascular responses of upper-body static exercise at +22 °C or -15 °C. Rate pressure product (RPP), systolic blood pressure (SBP), heart rate (HR) and central aortic systolic blood pressure (Central SBP). Modified figure from (II, III).

Central aortic (p<0.001) and brachial (p=0.002) systolic BP increased following static exercise in cold conditions (Fig. 9D, Table 7). In neutral conditions, systolic BP remained unaltered. Post-exercise central and brachial DBP increased, but with no temperature effect. HR was lowered after static exercise, regardless of thermal condition. Concerning pulse wave reflection, both P1 (p=0.001) and P2 (p<0.001) were higher after exercising in the cold, and AI_{HR75} did not change.
Table 7. Central aortic pressure following upper-body static exercise (n=15). Modified from (III).

<table>
<thead>
<tr>
<th>Variable</th>
<th>+22 °C upper-body static exercise</th>
<th>-15 °C upper-body static exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
<td>107 (100, 114)</td>
<td>109 (102, 117)</td>
</tr>
<tr>
<td>cDBP, mmHg</td>
<td>77 (72, 83)</td>
<td>80 (75, 85)</td>
</tr>
<tr>
<td>bSBP, mmHg</td>
<td>118 (111, 126)</td>
<td>120 (111, 130)</td>
</tr>
<tr>
<td>bDBP, mmHg</td>
<td>77 (71, 82)</td>
<td>79 (74, 85)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>64 (57, 71)</td>
<td>61 (55, 67)</td>
</tr>
<tr>
<td>AIHR75, %</td>
<td>11 (8, 14)</td>
<td>11 (7, 15)</td>
</tr>
<tr>
<td>AI, %</td>
<td>18 (13, 22)</td>
<td>19 (14, 23)</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>6 (4, 7)</td>
<td>6 (4, 8)</td>
</tr>
<tr>
<td>P1, mmHg</td>
<td>101 (95, 108)</td>
<td>104 (96, 111)</td>
</tr>
<tr>
<td>P2, mmHg</td>
<td>107 (100, 114)</td>
<td>110 (101, 118)</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>146 (139, 153)</td>
<td>145 (141, 150)</td>
</tr>
<tr>
<td>ED, ms</td>
<td>290 (281, 298)</td>
<td>292 (278, 305)</td>
</tr>
</tbody>
</table>

Values are means and 95% confidence intervals. c-SBP central systolic blood pressure; c-DBP central diastolic blood pressure; b-SBP brachial systolic blood pressure; b-DBP, brachial diastolic blood pressure; AIHR75 augmentation index adjusted to heart rate of 75 bpm; AI unadjusted augmentation index; APHR75 augmented pressure adjusted to heart rate of 75 bpm; AP augmentation pressure; P1 and P2 blood pressure at the first and second systolic pressure peak; ED ejection duration; Tr time to reflection.

5.4 Electrocardiography findings

5.4.1 Lower-body dynamic exercise (I)

In general, the effects of the different experimental conditions on ECG changes were modest. The QTc interval was longer during the first minute of exercise in the cold compared with the neutral environment (p=0.023). This interval was shorter at the beginning of resting in the cold compared with a neutral environment (p=0.010). Six patients demonstrated a few ST depressions (leads V1 to V5) exceeding 1 mm during exercise but with no difference between the environmental conditions. None of the patients experienced angina and/or arrhythmias during the experiments.

5.4.2 Upper-body exercise (II)

Changes in recorded and calculated ECG parameters during dynamic upper-body exercise at either +22 °C or -15 °C were modest. The QT interval was shorter at all
the different levels of dynamic exercise in the cold compared with the neutral environment (p<0.020). Eleven patients had ST segment depression over 1 mm from baseline during the last dynamic work cycle in the neutral environment and twelve patients in the cold environment (channels II, V2–V5). The maximum ST segment depression was 1.2 mm in the neutral environment and 1.5 mm in the cold. ECG parameters during static exercise in the neutral environment were unaltered compared with the cold environment, except for heart rate.
6 Discussion

In summary, our results demonstrate that whole-body exposure to cold during submaximal lower-body exercise (I) and graded dynamic and static upper-body exercise (II) resulted in higher cardiovascular strain compared with a neutral environment. Dynamic lower- and upper-body exercise mainly lowers post-exercise central SBP, irrespective of the environmental temperature (III). In contrast, central SBP was elevated after static exercise in a cold environment (III). Despite the higher cardiovascular strain during exercise in the cold, no marked changes in electric cardiac function were observed for either lower- or upper-body exercise, although ST depressions were detected for heavy dynamic upper-body exercise in both thermal conditions. The measured parameters and their responses to cold and different exercise modes is summarized in Table 7.

Table 8. Measured cardiovascular responses of the different experimental studies to different modes of exercise and whole-body cold exposure. Rest at neutral temperature (+22 °C) as the reference.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rest at -15 °C</th>
<th>Walk at -15 °C</th>
<th>Arm crank at -15 °C</th>
<th>Static exercise at -15 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SBP</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>MAP</td>
<td>(NM)</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CBP</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>RPP</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

NM= not measured; ↔=unaltered; ↑=increase; ↓=decrease.

6.1 Cardiovascular responses to dynamic lower-body exercise in the cold (I)

There is strong experimental evidence that both exposure to cold (Neill et al., 1974; Zeiher et al., 1989) and physical exercise (Hirzel et al., 1985; Kerber et al., 1975) independently increase cardiac workload in patients with CAD (Ikäheimo, 2018; Manou-Stathopoulou et al., 2015). However, current knowledge of their combined effects is limited to exercise of maximal intensities, short duration, and with varying types of cold exposure (Juneau et al., 2002; Lassvik & Areskog, 1979b; Meyer et al., 2010). The novelty of the present study is that none of the previous studies focused on submaximal exercise of longer duration or aimed to mimic natural exposure or protection. Our results in Study I show that cardiac workload (RPP) was higher during exercise in the cold compared with a neutral environment.
This finding is in accordance with previous studies involving whole-body cold exposure performed during symptom-limited maximal exercise, where RPP was either higher (Areskog & Lassvik, 1988; Juneau et al., 2002; Lassvik & Areskog, 1979a; Rosengren et al., 1988) or unaltered (Juneau et al., 1989; Lassvik & Areskog, 1979b; Marchant et al., 1994; Meyer et al., 2010; Peart et al., 1989) than in exercise in neutral conditions. Equally, inhalation of cold air while exercising also resulted in either increased (Dodds et al., 1995; Hattenhauer & Neill, 1975; Lassvik & Areskog, 1980) or unaltered (Petersen et al., 1994; Williams et al., 2018) RPP. The higher RPP observed during exercise in the cold was mostly due to augmented SBP.

We also detected an increased SBP when cold exposure and exercise were combined. The higher SBP observed at the end of exercise probably reflects sustained vasoconstriction to cutaneous and non-cutaneous vascular beds. A lowered skin temperature, even during exercise, sustains vasoconstriction and reduces skin blood flow due to both local and reflex mechanisms. In addition, a low Tsk itself shifts the onset of active vasodilation to higher internal temperature, thereby delaying heat-induced vasodilation (Pergola et al., 1996). As we did not measure core temperature, its increase during exercise and effect on the regulation of skin blood flow remains speculative. The lower mean skin temperature observed in exercise, compared with rest, could be due to both insufficient clothing insulation for the conditions, as well as higher forced convective heat transfer caused by movement. Such a response would further constrict the cutaneous vasculature relative to cold exposure in the absence of exercise.

We observed that HR decreased during rest but increased during exercise in the cold. As HR was only ~3 bpm higher during exercise in the cold, its physiological significance is rather minor. An augmented HR while exercising in the cold may be a response to higher sympathetic nervous activity because of both exercise and cooling of the skin. Submaximal exercise in the cold could also involve a higher energy cost, related to the need for thermoregulatory responses to balance the higher heat loss. Cooling of the tissues could also reduce performance efficiency (Doubt, 1991). Finally, wearing winter clothing may increase the energy cost due to the additional weight and friction of the garments (Rintamäki, 2007). Ultimately, the reasons for the higher HR during exercise in the cold remain speculative. It is noteworthy that our study succeeded in reaching a moderate intensity of exercise, as judged by patients achieving ~70% of HRmax and subjective ratings of somewhat “hard” exercise in the cold. Although the calculated RPP suggested a low to intermediate cardiac workload, a comparison with healthy populations is not
meaningful due to the use of medications, e.g., beta blockers restricting HR responses (Gobel et al., 1978).

6.2 Cardiovascular responses to upper-body exercise in the cold

6.2.1 Dynamic upper-body exercise in the cold

In accordance with our hypothesis, we detected 18–24% higher cardiac workload (RPP) during graded dynamic upper-body exercise in the cold compared with a neutral condition. The subjective ratings for the exercise intensities in the cold ranged from relatively light to hard, representing 59–80% of HRmax. The observed higher RPP was related both to an increase in MAP and HR.

Consistently with our hypothesis, we detected a higher cardiac workload during upper-body exercise in the cold compared with a neutral condition, which can be explained by a few mechanisms. Dynamic exercise is itself related to increased blood flow to the working muscles, vasodilation, and related cardiac volume loading (Manou-Stathopoulou et al., 2015). As a result of upper-body dynamic exercise, BP and HR increases, and cardiac workload and myocardial oxygen demand therefore also increases (Calbet et al., 2015; Miles et al., 1989). In addition, whole-body cold exposure, which causes cooling of the skin, results in peripheral and visceral vasoconstriction (Charkoudian, 2010; J. M. Johnson et al., 2014; Wilson et al., 2007) and elevates BP further (Castellani & Young, 2016). Indeed, we also demonstrated a constantly decreasing Tsk at the highest exercise intensities, which indicates whole-body superficial cooling. At the same time, an increased HR during dynamic upper-body exercise in the cold may be related to higher sympathetic activity and the withdrawal of parasympathetic activity related to exercise itself (González-Camarena et al., 2000; Tulppo et al., 1999).

Previous studies examining cardiovascular responses to dynamic upper-body exercise in a cold condition are scarce. These studies have mainly examined the energy expenditure of habitual chores such as snow shoveling among healthy people (Franklin et al., 1995; Smolander et al., 1995) and CAD patients (Sheldahl et al., 1992), but did not separately examine the effect of a cold environmental temperature on cardiovascular responses. Upper-body dynamic exercise has also been examined in relation to double-poling performance during skiing in healthy
athletes (Ø. N. Wiggen et al., 2013; O. N. Wiggen et al., 2016), but these studies did not examine cardiovascular responses.

### 6.2.2 Static upper-body exercise in the cold

We hypothesized that a cold environment would increase cardiovascular strain during upper-body static exercise compared with the corresponding exercise in a neutral condition. In accordance with our hypothesis, we observed higher MAP during graded static exercise in a cold condition.

The mechanisms for the higher MAP during exercise in a cold environment could be due to several factors. Static exercise itself is related to increased sympathetic activity (Machado-Vidotti et al., 2014) and a pressor response due to mechanical compression, reduced perfusion, an accumulation of metabolites, and muscle chemoreflex activation (Osada et al., 2015; Tanaka et al., 2014). Furthermore, the concurrent cooling of the skin increases sympathetic activation and vascular resistance (Charkoudian, 2010; J. M. Johnson et al., 2014). Their combination can further increase cardiac workload, both among healthy individuals and CAD patients (Manou-Stathopoulou et al., 2015). Indeed, we observed that the decrease in Tsk persisted throughout the graded exercise in this thermal condition.

A difference with dynamic exercise was that we observed a lower HR when individuals exercised in the cold, which was sustained at all exercise intensities. Despite a reduced HR while exercising in the cold, the magnitude of its increase toward bouts of graded static exercise remained the same at both environmental temperatures (Fig. 7C). The observed bradycardic response to isometric exercise in the cold is consistent with previous findings among healthy individuals (Mäkinen et al., 2008). Static exercise itself is known to augment both sympathetic and vagal activity (González-Camarena et al., 2000). It is further possible that the increased vagal activity related to facial cold exposure stimulates the trigeminal nerve and evokes a non-baroreflex mediated vagal response (Khurana & Wu, 2006) that reduces HR further compared with exercise in a neutral environment. Such a response is apparently maintained during the rest cycles for static (Fig. 7C), but not dynamic, exercise (Fig. 6C).

To our knowledge, only a few studies have examined cardiovascular responses to upper-body static exercise in the cold. Those studies employed the isometric handgrip test (3 mins at 30% of maximal voluntary contraction) and involved only healthy subjects (Greaney et al., 2014; Koutnik et al., 2014; Mäkinen et al., 2008). Consistent with the study’s findings (Mäkinen et al., 2008), they demonstrated
higher SBP and a decrease in HR when the isometric handgrip exercise was performed at +10 °C (whole-body cold exposure) compared with +25 °C. In the study of (Koutnik et al., 2014), they detected a higher aortic BP during isometric handgrip exercise in the cold at +4 °C, but unaltered brachial SBP, DBP, and HR compared with exercise at +20 °C. These somewhat deviating findings could be due to differences in the study populations, as well as the intensity, forms, and duration of cold exposure and exercise.

6.3 Post-exercise central aortic blood pressure in relation to lower-body and upper-body exercise in the cold (III)

We hypothesized that cold exposure blunts the beneficial effects of aerobic lower-body exercise on central hemodynamics, resulting in a lesser decrease in post-exercise central aortic BP and wave reflection. We further assumed that central aortic blood pressure is reduced less after upper-body dynamic exercise in the cold compared with a neutral environment, and even more following static exercise. In contrast with our hypothesis, we detected a lowering of central SBP and wave reflection after dynamic lower- and upper-body exercise, irrespective of temperature. To our knowledge, study III is the first to have examined the combined effects of cold exposure and exercise on post-exercise central BP in CAD patients. Previous studies have assessed central aortic BP with cold exposure in resting conditions (Edwards et al., 2006, 2008; Hess et al., 2009; Hintsala, Kandelberg, et al., 2014; King et al., 2013; Prodel et al., 2017) or cycling combined with cold air inhalation (Williams et al., 2018). Our results of a lowered post-exercise central SBP in CAD patients after exercise is in line with research concerning healthy individuals and prehypertensive and hypertensive patients (Carpio-Rivera et al., 2016; Compton et al., 2019; Millen et al., 2016). We also observed comparable post-exercise BP responses for central aortic and brachial BP (study III) to those in a study of a hypertensive subject resting in a cold environment during (Hintsala, Kandelberg, et al., 2014).

There may be several reasons for the similar post-exercise reduction in central aortic SBP after exercise, regardless of environmental temperature. Dynamic exercise itself involves vasodilation and increased blood flow to the activated muscles (MacDonald, 2002). This response may counteract peripheral cold-induced vasoconstriction during exercise in a cold environment and enhance post-exercise recovery. However, Study I showed that brachial SBP remained higher during the exercise in the cold compared with a neutral environment. Instead, we
suggest that the similar post-exercise response could be due to a rapid withdrawal of sympathetic activity and an increase in cardiac vagal activity immediately after exercise at both temperatures (Kiviniemi et al., 2015), quickly reducing BP to comparable post-exercise levels. In addition, the lowered Tsk during exercise in the cold had almost returned to the baseline 25 minutes after exercise. However, the elevated post-exercise HR implies that some sympathetic activity prevailed.

In Study III, we found a higher post-exercise central systolic and diastolic BP after static upper-body exercise in the cold compared with a neutral environment, which was in line with our hypothesis. The observed higher central BP and arterial stiffness are consistent with other studies involving static exercise conducted at neutral environmental temperatures (Pierce et al., 2018). Some studies have also reported post-exercise hypotension (Casonatto et al., 2016; Rezk et al., 2006), but the different findings are related to the intensity of exercise and activated muscle groups. To our understanding, one previous study has assessed the effects of whole-body cold exposure and static exercise on central aortic BP in healthy men (Koutnik et al., 2014). They reported elevated central aortic BP and wave reflection when static handgrip was applied in the cold compared with neutral conditions. However, their follow-up after the intervention was 3 minutes, which is probably not long enough to detect recovery responses (de Brito et al., 2019).

There may be several reasons for the higher central BP after static exercise in a cold environment. Static exercise is itself related to increased sympathetic activity and pressor response due to mechanical compression, reduced perfusion, an accumulation of metabolites, and muscle chemoreflex activation (Osada et al., 2015; Tanaka et al., 2014). Whole-body cold exposure also increases sympathetic activation and vascular resistance (Ikäheimo, 2018; Manou-Stathopoulou et al., 2015). Their combination can further increase cardiac workload among CAD patients (Manou-Stathopoulou et al., 2015) and affect post-exercise recovery of BP. With a higher post-exercise central BP, we also observed a lowered HR. This response is consistent with previous reports and is related to the coactivation of both sympathetic and vagal activity during static exercise (González-Camarena et al., 2000). Facial exposure to cold also increases vagal activity (Hintsala et al., 2016; Ikäheimo, 2018) and could further reduce post-exercise HR.

Exercise of certain intensity and duration may result in post-exercise hypotension among healthy (MacDonald, 2002) and hypertensive (S. Liu et al., 2012) individuals and those with CAD (Kiviniemi et al., 2015). This recovery response could be further affected by cold-related effects on autonomic nervous function (Greaney et al., 2017). Our study suggests that acute dynamic lower- and
upper-body exercise reduces systolic BP and wave reflection to a similar extent for exercise at cold and neutral ambient temperatures. Second, systolic BP recovers normally after moderate intensity lower-body aerobic exercise in the cold. Third, we observed an increased systolic BP after acute static upper-body exercise in the cold, indicating a slower recovery of post-exercise BP. It therefore remains to be established whether static exercise in the cold is beneficial in long-term BP management. In line with previous studies conducted at neutral environment temperatures (Kiviniemi et al., 2015; C. Liu et al., 2015), our study also demonstrated large inter-individual variation.

6.4 Electrocardiogram responses

An ECG-detected ST depression equaling or exceeding 1 mm during exercise is considered an indicator of myocardial ischemia (Laukkonen et al., 2001). In Studies I and II, we found that temperature did not affect the onset or occurrence of ST depressions during moderate intensity exercise. We only detected an ST depression exceeding 1 mm during upper-body dynamic exercise at the highest exercise intensity that was not related to temperature. In addition, none of the patients reported angina pectoris. This finding differs from the few previous studies employing maximal exercise intensities which demonstrated higher occurrence (Backman et al., 1979), greater maximal ST depression (Williams et al., 2018), and an earlier onset of ST depressions in cold conditions among patients with CAD (Juneau et al., 1989; Meyer et al., 2010). It should be noted that the present study would have excluded patients that demonstrated ST depressions during the preselection maximal exercise testing. Contrasting results have also shown that the occurrence of ST depressions during cold exposure (whole-body and/or inhalation, or cold pressor test) and symptom-limited exercise were not different at the onset of angina or maximal workload compared with exercise in a neutral environment (Lassvik & Areskog, 1979b, 1980; Nesto et al., 1989). Overall, myocardial ischemia among patients with CAD during exercise in the cold may arise from increased cardiac oxygen demand, with simultaneous blunting of the metabolic adaptation (coronary autoregulation) that would ordinarily increase myocardial oxygen supply (Manou-Stathopoulou et al., 2015). For example, both the cold pressor tests (Böttcher et al., 2002; Zeiher et al., 1989) and exercise (Duncker & Bache, 2008) separately impaired myocardial perfusion among patients with CAD. On the other hand, inhalation of cold air during exercise in a neutral environment did not affect coronary blood flow (Hattenhaur & Neill, 1975).
Cardiac electrical function may be altered, both because of cold exposure and exercise. Although ECG anomalies are usually only detected following cold exposure that considerably decrease body temperature (Aslam et al., 2006), superficial cooling alone may result in altered cardiac repolarization at rest (Hintsala, Kentta, et al., 2014). Overall, most of the ECG parameters during lower- or upper-body exercise were not affected by temperature; the exception was a prolonged QTc interval occurring during lower-body dynamic exercise in the cold, compared with a neutral environment. A prolonged QTc interval has been reported to occur with healthy subjects during exercise (Kligfield et al., 1996). On the other hand, excessive QTc prolongation during dynamic exercise may cause cardiovascular events such as arrhythmias (Maebuchi et al., 2010). We detected that QTc interval was shorter at rest in the cold, which is in accordance with a study examining whole-body cold exposure among mildly hypertensive individuals (Hintsala, Kentta, et al., 2014). Although speculative, the differential effects on QTc for rest and exercise in the cold could be related to altered co-activation of the autonomic nervous system (Nesto et al., 1989) and a possible shift from vagal dominance at rest to augmented sympathetic activity while exercising in the cold.

6.5 Strengths and limitations

A major strength of this study is our comprehensive a priori study design, in which both the level of exposure and exercise were strictly controlled. Each patient served as his own control by participating in each of the experimental conditions of the two protocols, which eliminates confounding related to inter-individual variation. Confounding due to circadian rhythms was reduced by performing the experiments at the same time of day for everyone. Each experiment was performed meticulously and within a relatively narrow time frame. In addition, randomization of the experiments reduces any possible order effect. Finally, the strict selection of patients reduces confounding from causes other than those related to cardiovascular disease.

For safety reasons, we did not cease medication of the patients during the experiments. The main effects of this would be a lowering of the HR and BP, which is also probably reflected in the observed responses to the intervention. However, for individual patients, the effect of the experimental intervention remains the same, because the medication was unaltered during the trials. Furthermore, as each of the patients often used more than one type of medication, the effects of any single agent on the observed cardiovascular responses cannot be distinguished. Hence, we
evaluated cardiovascular responses of individuals who are being treated for CAD, rather than examining the disease in the absence of medical treatment.

6.6 Applications and public health implications

The produced research information enables us to find a means to motivate and activate a population of people whose cardiac and physical condition is weakened. They are a special population of often elderly and relatively inactive people, who need information and support for their year-round physical activity, as regular exercise is beneficial for maintaining their functional ability and independence. Knowledge about appropriate and safe exercise in a cold climate may reduce or prevent cold-related coronary symptoms, myocardial infarctions, and morbidity and mortality. Examining the joint effects of exercise and cold exposure on cardiovascular responses among patients with an ischemic heart disease helps understand their benefits and potential health risks (Janardhanan et al., 2010; Toukola et al., 2015)

The present research project provides novel information on the impacts of lower- and upper-body dynamic and static exercise in a cold environment on the cardiovascular response of CAD patients. Individuals can utilize the research information of safe forms of activity to employ appropriate physical activity related to the self-treatment of their disease. Healthcare professionals and rehabilitation experts can use the information produced to advise their patients about healthy and safe winter exercise. The expected benefits for the patients include maintaining and improving their functional and working ability during the cold season.

The importance of the present results is emphasized because of the expected higher variability of weather with the changing climate, as well as due to the aging of populations and the higher prevalence of cardiovascular diseases. CVD is a major global health concern that is largely both preventable and treatable. Related to this regular exercise is an effective method in the prevention, treatment, and rehabilitation of CAD. Despite the obvious health benefits, only some of the people with CAD pursue physical exercise according to recommendations because of a passive lifestyle or fear related to having a myocardial infarction. According to this research, year-round health-enhancing submaximal exercise may also be an applicable treatment for patients with stable CAD in climates involving recurrent exposure to low environmental temperatures. Further studies are suggested that consider the role of disease severity, comorbidity, and medication related to CAD where environmental temperature must also be considered.
7 Conclusions

The aim of this thesis was to examine how different types of physical exercise in combination with cold exposure affected the cardiac and circulatory functions of patients with CAD. The forms and intensity of exercise, clothing, and cold exposure resembled an ordinary exercise occasion in a northern climate.

We found that whole-body exposure to cold during submaximal lower- and upper-body dynamic exercise increased cardiovascular strain (blood pressure and RPP during dynamic exercise) in stable CAD patients but did not markedly alter their cardiac electrical function. These results also show that post-exercise lowering of central aortic BP among stable CAD patients is largely unaffected by the environmental temperature when dynamic exercise is performed. In contrast, systolic BP was elevated after static upper-body exercise in cold conditions, which provides a foundation for further investigations into the mechanisms of this response.

Overall, this information encourages stable CAD patients to continue performing exercise such as walking throughout the year. Future studies should explore the use of exercise as a potential adjunct treatment in CAD when environmental temperature must also be considered. Further studies are also suggested that consider the role of disease severity, comorbidity, and medication related to CAD.
List of references


Original publications


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