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

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ABSTRACT:

Introduction: Regular year-round exercise is recommended for patients with coronary artery disease (CAD). However, the combined effects of cold and moderate sustained exercise, both known to increase cardiac workload, on cardiovascular responses are not known. We tested the hypothesis that cardiac workload is increased and evidence of ischemia would be observed during exercise in the cold in patients with CAD. **Methods:** Sixteen men (59.3±7.0 years, mean±SD), with stable CAD underwent each four 30 min exposures in a randomized order: seated rest and moderate-intensity exercise (walking, 60-70% of HR_{max}) performed at +22°C and -15°C. Systolic brachial blood pressure (SBP), heart rate (HR), electrocardiogram (ECG), and skin temperatures were recorded throughout the intervention. Rate pressure product (RPP) and ECG-parameters were obtained. **Results:** The combined effects of cold and submaximal exercise were additive for SBP and RPP and synergistic for HR when compared with rest in a neutral environment. RPP (mmHg · bpm) was 17% higher during exercise in the cold (18,080±3540) compared with neutral (15,490±2940) conditions (p=0.001). Only a few ST-depressions were detected during exercise, but without an effect of ambient temperature. The corrected QT interval increased while exercising in the cold compared with neutral temperature (p=0.023). Recovery of post-exercise BP was similar regardless of temperature. **Conclusions:** Whole-body exposure to cold during submaximal exercise results in higher cardiac workload compared to a neutral environment. Despite the higher RPP, no signs of myocardial ischemia, or abnormal ECG responses were observed. The results of this study are useful for planning year-round exercise-based rehabilitation programs for stable CAD patients.

Keywords: coronary artery disease, cold temperature, exercise

INTRODUCTION:

The benefits of regular physical exercise on wellbeing and health during all stages of life are unambiguous. Regular exercise is crucial in the prevention, treatment and rehabilitation of many chronic diseases (31). For example, exercise is effective 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 (1). It is especially important that physical activity in CAD patients is consistently performed, and the current guidelines suggest moderate intensity exercise to be performed 3-5 times per week for at least 30 min per session, together with resistance training (12).

Cold weather is an important risk factor for morbidity and mortality (13, 15), particularly from cardiovascular causes (13, 36). The elevated risk is mediated both through acute and seasonal (13) effects of cold environment on cardiovascular function. Facial cold exposure alone, without marked whole-body cooling, increases cardiac strain by elevating systolic blood pressure (SBP) an average of 20-30 mmHg (19, 43), and even up to 60 mmHg (19). In addition to these acute effects, BP is higher throughout the cold season (54). It is known that cold exposure increases cardiovascular strain in all individuals. However, myocardial oxygen supply may be insufficient in response to cold among CAD patients whose coronary autoregulation might be impaired and myocardial blood flow attenuated (22, 40). The subsequent myocardial ischemia induces angina pectoris, which may progress to myocardial infarction, fatal arrhythmias, and sudden cardiac death (52). Equally to cold exposure, exercise increases cardiac workload in both healthy and CAD patients. However, the smaller vasodilator capacity of the coronary circulation among CAD patients may result in myocardial ischemia and angina pectoris during exercise (40).

It is possible that the increased cardiac workload, as a result of combined cold exposure and exercise, may lead to a mismatch between myocardial oxygen demand and supply in CAD patients (40). To our knowledge, none of the previous studies have examined the effects of sustained

74 moderate-intensity exercise performed in a cold environment on cardiovascular responses among
75 CAD patients. The energy costs (and cardiac work) of submaximal exercise in the cold may be higher
76 due to the need for nonexercise thermogenic mechanisms to balance for the higher heat loss related
77 to movements, as well as simultaneously lowered efficiency (10). This form of exercise is
78 recommended for secondary prevention of CAD, with the results of such research being useful from
79 a perspective of health and safety in these patients. Furthermore, distinct from previous research, the
80 present study investigates a unique population consisting of post-infarction CAD patients, but who
81 are asymptomatic, and do not demonstrate marked ECG anomalies during exercise. Our approach is
82 also different from previous studies which have employed graded symptom-limited maximal exercise
83 tests of very short durations (26, 33, 34, 42). In addition, the forms of cold exposure have varied
84 between mild (41, 47) or more severe whole-body cold exposure (26, 32, 42, 51) to local cold
85 exposure, such as cold air inhalation (2, 7, 9, 18, 33, 49). Due to the aforementioned varying
86 approaches (22) the results cannot directly be applied for recommendations of exercise-based
87 rehabilitation programs.

88 Therefore, the aim of this study was to examine the independent and joint effects of moderate-
89 intensity aerobic exercise and cold exposure on cardiac and circulatory functions in patients with
90 CAD. We hypothesized a priori that moderate-intensity exercise causes greater cardiovascular work
91 and signs of myocardial ischemia when performed in the cold compared to exercise in a neutral
92 environment.
93

METHODS:

Patients: Sixteen men (aged 59.3±7.0 years, height: 174.4±4.2 cm, weight 88.8±15.4 kg, BMI: 29.2±4.9 kg/m^2 [mean±SD]) were identified from the hospital records of the Oulu University Hospital (Table 1). All agreed to participate in the study. The inclusion criteria consisted of a diagnosed CAD (Canadian Cardiac Society [CCS] class I-II) and a non-ST-elevation myocardial infarction at least 3 months (actual elapsed time was 8-23 months) prior to experimentation. The exclusion criteria were: CCS class III-IV, previous myocardial infarction less than 3 months prior to experimentation, 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 ECG anomalies during rest, presence of physician-diagnosed asthma or diabetes and current smoking. An experienced cardiologist evaluated the inclusion and exclusion of each subject based on the aforementioned criteria. The participants received both oral and written information of the study and a signed informed consent was required for participation. The study was approved by the Ethics Committee of Oulu University Hospital District. The study is registered in the Clinical Trials (NCT02855905).

(Place Table 1 approximately here)

Study design: Clinical exercise tests were performed approximately a month prior to the experiments to assess maximal exercise capacity of the patients and to detect possible ECG abnormalities, indicating cardiac ischemia, during a bicycle ergometer test (Ergoline, ergoselect 100K, Fysioline, Finland). Prior to the test ECG and HR were measured at rest in the supine position. The test was started from at 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 subjects. The results of the exercise capacity tests were used to calculate an individually based walking speed for the experiments that represented moderate-intensity exercise (8).

We conducted a cross-over trial where each subject participated in four different experimental conditions in random order. These were: 1) 30 min exercise in the cold environment (-15°C, wind 1.0m/s); 2) 30 min exercise in the neutral environment (+22°C, wind 1.0m/s); 3) 30 min rest in the aforementioned cold conditions and 4) 30 min rest in the aforementioned neutral conditions. The level of exercise was adjusted to correspond to the recommended intensity and duration of health-enhancing aerobic exercise (12, 14). The exercise consisted of brisk walking for 30 minutes on a treadmill, with the speed and grade of the treadmill remaining constant for each subject while exercising in cold and neutral conditions. The selected exercise intensity represented 65-70 % HR max where the individual walking speed was adjusted based on target HR and calculated based on the following equation: HRrest+0.45xHRR, where HRR is heart rate reserve = HRmax-HRrest. The chosen cold environmental temperature (-15°C) occurs commonly in countries of the northern hemisphere during the cold season. Resting cold exposure was mainly restricted to the face, as the participants wore full winter clothing consisting of underwear (shirt, pants), insulated trousers, insulated jacket, overtrousers, overjacket, socks and shoes (insulation value of clothing ensemble 2.13 clo). During exercise in the cold, clothing insulation was reduced to 1.88 clo (removal of overtrousers and jacket). A lesser amount of clothing insulation (0.75 clo) was used during both thermal neutral exposures. The experimental conditions were separated by at least one week. Each patient performed the four trials at the same time of the day.

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

142 The patients were equipped with ten skin temperature thermistors, a brachial BP arm cuff and
143 ECG electrodes. After the instrumentation, the patients moved into the climatic chamber with neutral
144 temperature (+22°C) conditions for 12.5 min of baseline measurements with subjects in the seated
145 position. Following this, the participants moved to the climatic chamber with adjustable temperature,
146 wind speed and equipped with a treadmill. The duration of each experimental condition was 30
147 minutes during which the patients were either seated (rest) or walking. After the exposure the patients
148 walked back to the neutral temperature chamber for a follow-up of 60 minutes. A paramedic nurse
149 was monitoring real time ECG and brachial BP throughout the experiments.
150
151 ***Measured parameters***
152 Brachial blood pressure (Schiller BP 200+, Switzerland) was assessed at 5 minutes intervals
153 during baseline, intervention and follow-up. RPP was calculated by multiplying brachial systolic BP
154 with HR. Physical strain was evaluated objectively by HR and subjectively by Borg's perceived of
155 exertion scale (5). HR was monitored continuously and perceived exertion was asked at 5 minutes
156 interval during the intervention.
157 ECG was recorded and monitored continuously using a 15-lead ECG (Cardiosoft V6.71, GE
158 Healthcare, Freiburg, Germany). The placements of the ECG electrodes at rest followed the standard
159 12 lead placement and X, Y, Z leads. In the clinical exercise test, and during the interventions, the
160 arm and foot electrode were reset to both shoulders and lower back. Signal analyses were carried out
161 with custom-made software in Matlab (MathWorks, inc., Natic, MA, USA). Ectopic and abnormally
162 shaped beats were removed from the analysis. ECG was used to identify P-wave onset, QRS
163 boundaries, R- and T-wave peak and T-wave offset, from which QRS, QT interval were calculated.
164 The QRS-complex describes ventricular depolarization. A QRS elongation indicates intraventricular
165 conduction disturbances. The T-wave reflects ventricular repolarization and an altered T-wave can
166 reflect ischemia. The QT interval describes the repolarization time and is heart rate dependent.

Therefore, the QT interval was corrected with the nomogram method (QTc) (27). Elongation of the QT-interval could predispose to arrhythmias. An ST-segment depression indicates ischemia and was evaluated 60 ms following the J-point.

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, left upper chest. Data were recorded at 20 s intervals with two temperature data loggers (SmartReaderPlus; Acr Systems Inc., BC, Canada). Mean skin temperature (Tsk) was calculated as follows: $tsk=\sum k_i*tsk_i$=[0.07*forehead+0.175*right scapula+0.175*left upper chest+0.07*right arm+0.07*left arm+0.05*left hand+0.19*right anterior thigh+0.2*left calf] (24). Thermal sensations were inquired using scales of perceptual judgements on personal thermal state (23).

Statistical Methods

We compared mean differences in cardiovascular parameters over time (baseline, intervention, recovery) within and between the different conditions (neutral or cold at rest or exercise) with a repeated measures 2-way ANOVA. When detecting a significant main or interaction effect, corresponding contrast tests (simple) were used to compare individual data points with baseline (prior exposure), as well as between conditions. We further analyzed for each individual the independent and joint effects and their interaction of SBP, HR and ECG at the beginning (2 min) and end of the intervention (27 min). The effects of the experimental condition was compared with rest at neutral temperature (reference) and their difference compared with interval estimates (95% CI). The joint effect or interaction were calculated by subtracting the mean differences in cardiovascular parameters during exercise in the cold with that of cold exposure or exercise in a neutral environment. All parameters were normally distributed. Statistical analyses were performed with IBM SPSS version

23 (SPSS, Inc., USA) for windows (Microsoft Corporation, USA). Statistical significance was set at $p<0.05$.

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RESULTS:

Eight of the patients with CAD were retired from employment, while the rest were still a part of working life. The mean physical fitness of the patients (30.0±5.6 mL/kg/min) was moderate when using scales of healthy adults (53), but approximately 70% rated their physical fitness as being quite good. In addition, 63% reported being rarely physically active during their leisure time. All the patients rated their health status as being moderate or better (Table 1). The average time elapsed from the myocardial infarction was 15±5 months. Of the patients 69% had a single-vessel, 25% a double-vessel and 6% a triple-vessel disease. The number of stents was on average two, but varied from 1 to 5. The ejection fraction of the patients was on average 61±10%.

Skin temperature, thermal sensation and level of exercise

Exercise in the cold decreased T_{sk} (Fig. 1D) 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 pre-exposure baseline. In addition, at the end of the intervention T_{sk} was lower (23±1.0°C) during exercise in the cold when compared with rest (25.5±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 cold at all measurements 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/neutral (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 from light to somewhat hard (11-14), both while exercising in a neutral and cold environment.

220 ***Cardiovascular response during rest and exercise in a cold or neutral environment***

221 Cardiovascular responses to rest and exercise at 22 °C and -15 °C are presented in Table 2.
222 BP, HR and RPP, increased similarly in the beginning of exercise (at 2 min) both in cold and neutral
223 environments (Fig 1.). However, at the end of exercise (at 27 min) RPP was 17 % higher in the cold
224 compared to exercise in neutral conditions (p=0.001). This elevated RPP was primarily driven by
225 SBP, which was 13% (p=0.001) higher while HR was only 3% (p=0.042) higher in the cold when
226 compared to neutral conditions. During rest, RPP was 23 % higher in the cold compared to rest in the
227 neutral environment (p=0.018). This elevated RPP was also primarily driven by an elevation in SBP,
228 which was increased by 19% (p=0.001) while HR didn't appreciably change (2%, ns) (Table 2). (Fig
229 1B, Table 2). During the recovery, SBP remained at a significantly lower level after exercise
230 compared with the experimental resting condition, but with no difference between the environmental
231 temperatures (p=0.001).

232

233 ***Independent and joint effects of cold and exercise***

234 Cold exposure alone increased SBP and RPP but decreased HR compared with rest at neutral
235 conditions (reference). As expected, exercise independently increased SBP, RPP and HR. The joint
236 effects of cold and exercise on SBP, HR and RPP were comparable to exercise in a neutral
237 environment in the early phase of the intervention. However, at the end of the intervention for SBP
238 the separate effects of cold were on average +25 (95% CI 13 to 37) mmHg, exercise +15 (6 to 24)
239 mmHg and their joint effect +37 (28 to 46) mmHg. Hence, their interaction of -4 (-19 to 12, ns.)
240 mmHg indicated an additive effect, i.e. equaled the sum of the individual effects of cold and exercise.
241 For HR the effect of cold was -3 (-5 to -1) bpm, exercise +42 (36 to 48) bpm and their joint effects
242 +45 (39 to 52) bpm. This indicates a synergistic effect where the sum of cold or exercise alone was
243 exceeded by 6 (0 to 12) bpm. For RPP the effect of cold was +1218 (355 to 2080) mmHg · bpm, for
244 exercise +7309 (6088 to 8530) mmHg · bpm and their joint effect +10017 (8575 to 11459) mmHg ·

bpm. Hence, although their interaction of+1490 (-126 to 3107, ns.) mmHg · bpm suggests synergistic interaction, the effects is not statistically significant and the interaction can be considered as additive.

(Place Figure 1 approximately here)

Recorded and calculated ECG parameters during rest and exercise in either a cold or warm environment are presented in Table 3. In general, the effects of the different experimental conditions on ECG changes were modest. QTc interval was longer during the first minute of exercising in the cold compared to the first minute of exercise in the neutral environment (p=0.023). This interval was shorter in the beginning of cold rest exposure compared to rest in a neutral environment (p=0.010). Six study 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.

(Place Table 2 approximately here)

(Place Table 3 approximately here)

DISCUSSION:

Our novel results show that submaximal exercise in the cold increases cardiac workload in patients with stable CAD compared with a neutral environment. This response was achieved mainly through a sustained higher SBP, but also slightly elevated HR during exercise in the cold. The interaction of cold and exercise on SBP and RPP was additive, while this was synergistic for HR. The observed higher cardiac workload did not cause adverse electrocardiographic changes, evidenced by the largely unaltered ECG. In addition, no myocardial ischemia was detected during exercise in the cold, as judged by the lack of ST-depressions. Exercise resulted in comparable lowering of post-exercise BP compared to rest irrespective of environmental temperature.

It is well known that both exposure to cold (44, 55) and physical exercise (21, 28) independently increase cardiac workload among patients with CAD (40). However, current knowledge of their combined effects are limited to exercise of maximal intensities, short duration and with varying type of cold exposure and protection (26, 33, 42). The unique aspect of the present study is that none of the prior studies focused on submaximal exercise of longer duration, or aimed to mimic natural exposure or protection. We found an additive effect on RPP when exercise and cold exposure were combined. This finding is in accordance with previous studies involving whole body cold exposure performed during symptom-limited maximal exercise where RPP was either higher (2, 26, 34, 51) or unaltered (25, 32, 41, 42, 47) compared with exercise at neutral conditions. Equally, also inhalation of cold air while exercising, resulted in either increased (9, 18, 33) or unaltered (49) RPP. The higher RPP observed during exercise in the cold is mostly due to a higher SBP.

We also detected a heightened effect on SBP when cold exposure and exercise were combined. This higher SBP observed at the end of exercise probably reflects sustained vasoconstriction to cutaneous and non-cutaneous vascular beds. Lowered skin temperature, even during exercise, reduces skin blood flow due to both local and reflex mechanisms. In addition, a low mean skin temperature itself shifts the onset of active vasodilation to higher internal temperature, thereby delaying heat-

induced vasodilation (48). As we did not measure core temperature, its increase during exercise and effect on regulation of skin blood flow remains speculative. The lower mean skin temperature observed at exercise, compared with rest, could be due to both insufficient clothing insulation for the condition, as well as higher forced convective heat transfer of movements. Such a response would further constrict the cutaneous vasculature relative to cold exposure in the absence of exercise.

We observed a synergistic effect on HR when cold exposure and exercise were combined. This was largely due to the fact 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 related to higher sympathetic nervous activity, as a result 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 for the higher heat loss. Cooling of the tissues could also reduce performance efficiency (10). Lastly, wearing winter clothing may increase the energy cost due to the additional weight and friction of the garments (50). In the end, the reasons for the higher HR during exercise in the cold remain speculative. Of note, our study succeeded in reaching a moderate intensity of exercise, as judged by subjects achieving ~70% of HR_{max} 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 less meaningful due to the use of medications, e.g. beta-blockers restricting HR responses (16).

An ECG detected ST-depression during exercise equaling or exceeding 1 mm is considered an indicator of myocardial ischemia (35). Our study showed that temperature did not affect the onset or occurrence of ST-depressions during moderate intensity exercise. 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 (4) and earlier onset of ST-depressions in cold conditions among patients with CAD (25, 42). However, if in the present study prospective

subjects demonstrated ST-depression during the preselection exercise testing, each have been excluded from the study. 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 (32, 33, 45). When it occurs, 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 (40). As an example, both the cold pressor tests (6, 55) and exercise (11) separately impair 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 (18). To conclude, in our study submaximal exercise in a cold environment did not cause myocardial ischemia, despite of the higher cardiac workload.

Cardiac electrical function may be altered both as a result of cold exposure and exercise. Although ECG anomalies are usually detected during cold exposure involving a considerable decrease in body temperature (3), superficial cooling alone may result in altered cardiac repolarization at rest (20). Overall in our study, most of the ECG parameters while exercising were not affected by temperature; the exception being a prolonged QTc interval during exercise in the cold when compared with exercise in a neutral environment. A prolonged QTc interval has been reported to occur with normal healthy subjects during exercise (30). On the other hand, excessive QTc prolongation during dynamic exercise may cause cardiovascular events like arrhythmias (39). QTc interval was shorter at rest in the cold, which is in accordance with a study examining whole-body cold exposure among mildly hypertensive persons (20). Although speculative, the differential effects on QT_c for rest and exercise in the cold could be related to altered co-activation of the autonomic nervous system (46) and possible shift from vagal dominance at rest to augmented sympathetic activity while exercising

in the cold. In summary, the findings of only a slightly higher RPP, but mainly unaltered ECG indices are consistent with each other.

Exercise of certain intensity and duration may result in post-exercise hypotension among healthy (38), hypertensive (37), and individuals with CAD (29). This recovery response could be further affected by cold-related effects on autonomic nervous function (17). To our knowledge, there are no cold-related studies assessing BP involving longer post-exercise follow-up, or involving patients with CAD. Our study showed comparable post-exercise BP responses when followed for 45 min regardless of prior exposure-temperature. In line with previous research conducted at neutral environment temperatures (29, 37), our study also demonstrated large inter-individual variation. In the present study SBP of patients with CAD remained elevated for 30 minutes following rest in cold. This is probably due to sustained vasoconstriction and supported by the detected lower skin temperatures.

Strength and limitations

The strengths of this study include a comprehensive study design where both the level of thermal exposure and exercise were strictly controlled. Furthermore, each subject served as his own control, through participating in all of the four different experiments conditions. Such a design improves accuracy of the statistical analyses by eliminating any potential confounding effects due to inter-individual variation. In addition, randomization of the trials reduces any possible order effect. Finally, strict selection of participants helps reducing confounding from other causes than those related to cardiovascular diseases (CAD and hypertension).

For safety reasons we did not cease medication during the experiments. Hence, the main effects of these would be lowering of HR and BP, which is also likely reflected in the observed responses to the intervention. However, for individual patients the effect of the experimental intervention remains the same, as medication was unaltered during the experiments. Furthermore, as each of the patient

often used more than one type of medications, the effects of any single agent on the observed cardiovascular responses cannot be distinguished. By not withholding medication, we were able to evaluate cardiovascular responses to individuals who are being treated for CAD, rather than evaluating the direct effects of CAD in the absence of medical treatment.

PERSPECTIVES AND SIGNIFICANCE:

The current guidelines for health-enhancing exercise for patients with CAD suggest regular aerobic exercise to be performed for a sufficient duration at a time. Despite a slightly higher cardiac workload observed in the present study during exercise in the cold, no significant signs of impaired cardiac function were observed. The obtained results are applicable to a relatively healthy population of patients with stable CAD, who are asymptomatic and do not demonstrate marked ECG alterations during exercise. The observation suggests that year-round health enhancing submaximal exercise may be an applicable treatment for patients with stable CAD, also in climates involving recurrent exposures to low environmental temperatures. However, given the substantial evidence on the adverse cardiovascular outcomes associated with cold weather (13), we would suggest further research involving different types of exercise (in terms of form and intensity) and taking into account issues, such as disease severity, comorbidity and medication related to CAD. The produced research information can be useful for health care professionals and rehabilitation experts in advising their clients of healthy and safe wintertime exercise as a way to promote health of cardiac patients. The expected benefits for the patients include maintaining and improving their functional and working ability during the cold season.

DISCLOSURES

The authors declared no conflict of interest.

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FIGURE LEGENDS

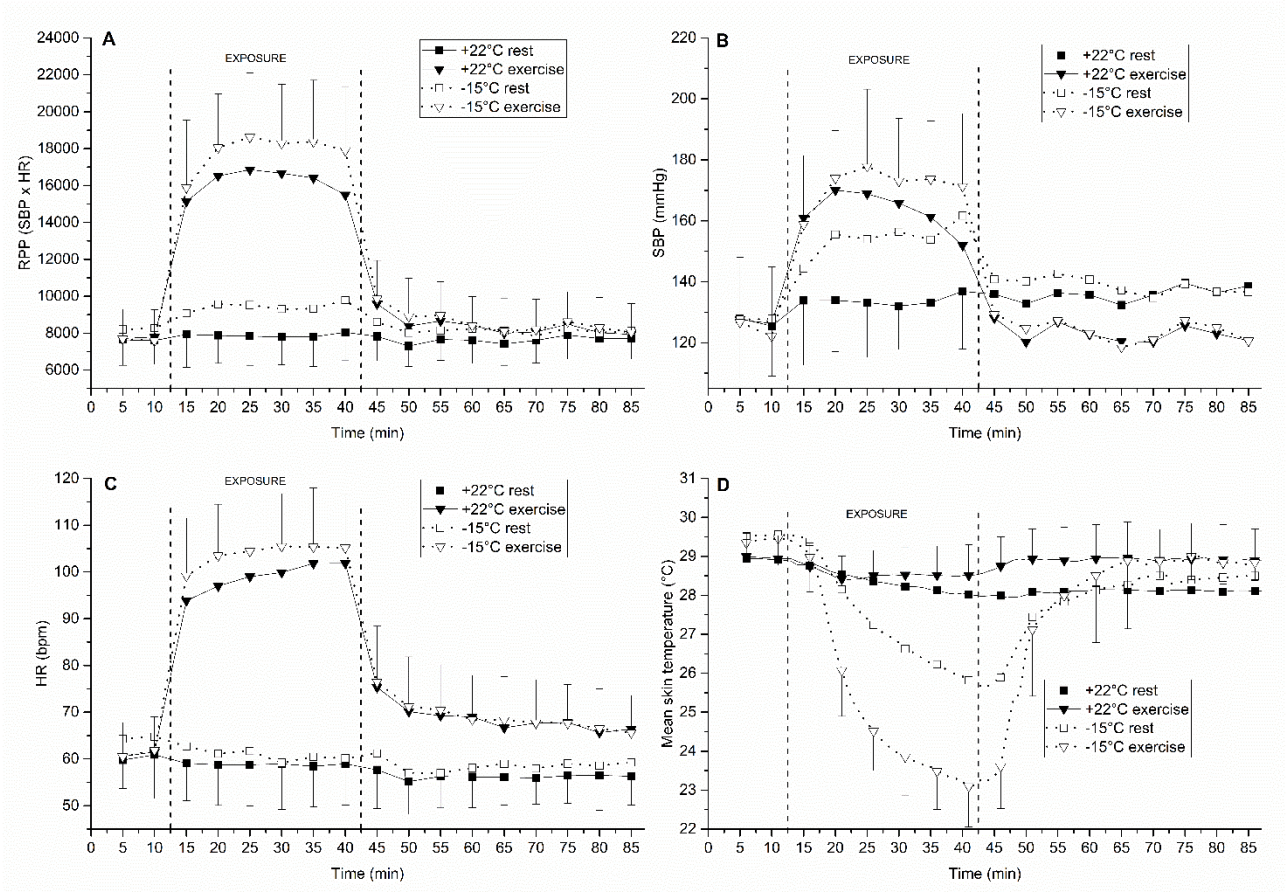

Figure 1: (A) Rate pressure product (RPP), (B) systolic blood pressure (SBP), (C) heart rate (HR) and (D) mean skin temperature (T_{sk}) at rest and exercise either at +22°C or -15°C (n=16). The

vertical dotted lines represent start and the end of the intervention. The values represent means and their standard deviation (SD). For clarity reasons in Fig B, SD bars for recovery are not presented.

Table 1. Characteristic of the study group (n=16).

Variables	N=16
Age, years	59.3±7.0
BMI, kg/m2	29.2±4.9
BF, %	26.4±7.6
Peak VO2, mL/kg/min	30.0±5.6
SBP, mmHg	126±19
DBP, mmHg	81±10
Hypertension	
Yes	14 (87%)
No	2 (13%)
Medications	
Aspirin	14 (88 %)
Beta-blockers	9 (56 %)
Statins	12 (75 %)
ADP receptor antagonist	5 (31 %)
ACE-inhibitors	10 (62 %)
ATR-blocker	3 (19 %)
Calcium channel blocker	2 (13 %)
How do you find your current health status?	
Excellent	3 (19 %)
Quite good	5 (31 %)
Average	8 (50 %)
Quite poor	0 (0 %)
Very poor	0 (0 %)
Do you use any alcoholic drinks, even occasionally	

Yes	14 (88 %)
No	2 (13 %)
How demanding is your work physically?	
My work is mainly done sitting	7 (44 %)
I walk quite much in my work	4 (25 %)
I have to walk and lift much	4 (25 %)
My work represents heavy manual labor	1 (6 %)
How much do you exercise and stress yourself physically in your leisure time?	
Never	2 (13 %)
Rarely	10 (63 %)
Often	3 (19 %)
Very often	1 (6%)
How do you find your current physical fitness status?	
Excellent	1 (6 %)
Quite good	11 (69 %)
Average	4 (25 %)
Quite poor	0 (0 %)
Very poor	0 (0 %)

563 Values are the number of the patients or means ± standard deviation. BMI, body mass index; BF, Body fat
564 percentage; Peak VO2, estimated (3.5 x MET) symptom-limited maximal oxygen uptake; SBP, resting
565 systolic blood pressure; DBP, resting diastolic blood pressure.

Table 2. Cardiovascular responses during 30 min of seated rest in a neutral (+22°C) and cold (-15°C) environment, as well as 30 min of exercise in these environments.

	+ 22 °C					-15°C				
REST N=16	**Baseline average**	**Exposure 2'**	**Exposure 27'**	**Recovery 13'**	**Recovery 33'**	**Baseline average**	**Exposure 2'**	**Exposure 27'**	**Recovery 13'**	**Recovery 33'**
SBP, mmHg	127 ± 18	134 ± 22	137 ± 20	133 ± 17.9	135 ± 19.8	128 ± 21	144 ±20*	163 ± 22*	143 ± 20.2	138 ±20.3
HR, bpm	60 ± 8	59 ± 8	59 ± 9	56 ± 6.9	57 ± 6.6	65 ± 9	62 ± 8	60 ± 10	57 ± 6.8	58 ± 6.7
RPP, mmHg x bpm	7620±1320	7940 ±1840	8050 ± 1560	7400 ±1306	7720 ±1710	8230±1720	9070±1880	9880±2310*	8169±1640	8041±1740
EXERCISE	**Baseline average**	**Exposure 2'**	**Exposure 27'**	**Recovery 13'**	**Recovery 33'**	**Baseline average**	**Exposure 2'**	**Exposure 27'**	**Recovery 13'**	**Recovery 33'**
SBP, mmHg	127 ± 15	161 ± 17	152 ± 21	122 ±26.9	120 ± 23.4	124 ± 22	159 ± 23	171 ± 24*	127 ± 20.9	123 ± 20.5
HR, bpm	61 ± 6	94 ± 9	102 ± 14	71 ±10.9	68 ± 7.4	61 ± 7	99 ±13	105 ± 12.0*	73 ± 10.9	68 ± 9.1
RPP, mmHg x bpm	7750 ± 1230	15140 ± 2330	15490 ± 2940	8540 ± 2150	8150 ± 1590	7630 ± 1670	15900 ± 3790	18080 ± 3540*	9250 ± 2360	8480 ± 2000

Values are mean ± standard deviation; N, number of patients; SBP, systolic blood pressure; HR, heart rate; RPP, rate pressure product; *, $p<0.05$ vs. +22°C for the respective condition.

Table 3. Cardiovascular responses during 30 min of seated rest in a neutral (+22°C) and cold (-15°C) environment, as well as 30 min of exercise in these environments.

	+ 22 °C					-15°C				
REST N=16	**Baseline**	**Exposure 1'**	**Exposure 25'**	**Recovery 1'**	**Recovery 3'**	**Baseline**	**Exposure 1'**	**Exposure 25'**	**Recovery 1'**	**Recovery 3'**
HR, bpm	60 ± 8	60 ± 8	58 ± 8	68 ± 10	59 ± 8	64 ± 7	65 ± 9	60 ± 9	79 ± 10	62 ± 8
QRS, ms	91 ± 11	92 ± 11	90 ± 10	91 ± 11	91 ± 11	92 ± 11	93 ± 12	92 ± 11	93 ± 12	92 ± 12
QT, ms	433 ± 24	425 ± 22	435 ± 25	424 ± 30	433 ± 25	421 ± 21	401 ± 20*	427 ± 19	413 ± 22	416 ± 22
QTc, ms	433 ± 17	424 ± 19	430 ± 24	440 ± 22	430 ± 19	431 ± 17	411 ± 15*	426 ± 19	448 ± 22	420 ± 15
R-amp, mV	3.2 ± 0.9	3.1 ± 0.8	3.1 ± 0.9	3.1 ± 0.8	3.1 ± 0.8	3.2 ± 1	3.3 ± 0.8	3.2 ± 0.9	3.4 ± 0.9	3.3 ± 0.8
T-amp, mV	1.1 ± 0.6	1.2 ± 0.6	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.6	1 ± 0.5	1.1 ± 0.6	1.1 ± 0.6	1 ± 0.6	1.2 ± 0.6
	+ 22 °C					-15°C				
EXERCISE N=16	**Baseline**	**Exposure 1'**	**Exposure 25'**	**Recovery 1'**	**Recovery 3'**	**Baseline**	**Exposure 1'**	**Exposure 25'**	**Recovery 1'**	**Recovery 3'**
HR, bpm	61 ± 6	88 ± 8	101 ± 12	90 ± 16	79 ± 11	62 ± 9	95 ± 10*	105 ± 11	98 ± 11	80 ± 11
QRS, ms	91 ± 11	92 ± 12	95 ± 11	93 ± 13	93 ± 13	91 ± 12	93 ± 13	94 ± 11	93 ± 10	93 ± 11
QT, ms	431 ± 23	396 ± 25	345 ± 22	349 ± 28	382 ± 28	429 ± 22	392 ± 35	336 ± 21	348 ± 20	376 ± 26
QTc, ms	433 ± 18	444 ± 17	464 ± 54	418 ± 41	422 ± 27	433 ± 20	479 ± 67*	473 ± 43	450 ± 51	412 ± 19
R-amp, mV	3.2 ± 0.9	3.3 ± 0.8	3.3 ± 0.8	3.1 ± 0.8	3.1 ± 0.8	3.2 ± 0.8	3.3 ± 0.7	3.4 ± 0.7	3.3 ± 0.8	3.2 ± 0.7
T-amp, mV	1 ± 0.5	1 ± 0.5	1.1 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	1.1 ± 0.5	0.9 ± 0.5	1.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.5

Values are group means over each phase (baseline, exposure 1min, exposure 25 min, recovery 1 min and recovery 3min) ± standard deviations. N, number of patients; HR, heart rate; QRS; Duration of QRS; QT, QT interval; QTc, QT adjusted to HR; R-amp, R peak amplitude; T-amp, T peak amplitude; *, $p<0.05$ vs. +22°C