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

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Valtonen RI, Kiviniemi A, Hintsala HE, Ryti NR, Kenttä T, Huikuri HV, Perkiömäki J, Crandall C, van Marken Lichtenbelt W, Alen M, Rintamäki H, Mäntysaari M, Hautala A, Jaakkola JJ, Ikäheimo TM. Cardiovascular responses to cold and submaximal exercise in patients with coronary artery disease. *Am J Physiol Regul Integr Comp Physiol* 315: R768–R776, 2018. First published July 5, 2018; doi:10.1152/ajpregu.00069.2018.—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. Sixteen men (59.3 ± 7.0 yr, means ± SD) with stable CAD each underwent 4, 30 min exposures in a randomized order: seated rest and moderate-intensity exercise [walking, 60%–70% of max heart rate (HR)] performed at +22°C and −15°C. Systolic brachial blood pressure (SBP), HR, electrocardiogram (ECG), and skin temperatures were recorded throughout the intervention. Rate pressure product (RPP) and ECG parameters were obtained. 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·beats/min) was 17% higher during exercise in the cold (18,080 ± 3540) compared with neutral (15,490 ± 2,940) 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 postexercise blood pressure was similar regardless of temperature. Whole body exposure to cold during submaximal exercise results in higher cardiac workload compared with 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.

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cold temperature; coronary artery disease; exercise

INTRODUCTION

The benefits of regular physical exercise on well being 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 patients with CAD 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 (8a).

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 a 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, blood pressure (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 patients with CAD 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 individuals and patients with CAD.

However, the smaller vasodilator capacity of the coronary circulation among patients with CAD 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 patients with CAD (40). To our knowledge, none of the previous studies have examined the effects of sustained moderate-intensity exercise performed in a cold environment on cardiovascular responses among patients with CAD. The energy costs (and cardiac work) of submaximal exercise in the cold may be higher because of the need for nonexercise thermogenic mechanisms to balance for the higher heat loss related to movements, as well as simultaneously lowered efficiency (10). This form of exercise is recommended for secondary prevention of CAD, with the results of such research being useful from a perspective of health and safety in these patients. Furthermore, distinct from previous research, the present study investigates a unique population consisting of postinfarction patients with CAD who are asymptomatic and do not demonstrate marked ECG anomalies during exercise. Our approach is also different from previous studies, which have employed graded symptom-limited maximal exercise tests of very short durations (26, 33, 34, 42). In addition, the forms of cold exposure have varied between mild (41, 47) or more severe whole body cold exposure (26, 32, 42, 51) to local cold exposure, such as cold air inhalation (2, 7, 9, 18, 33, 49). Because of the aforementioned varying approaches (22) the results cannot directly be applied for recommendations of exercise-based rehabilitation programs.

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

METHODS

Patients

Sixteen men [age: 59.3 ± 7.0 yr, height: 174.4 ± 4.2 cm, weight: 88.8 ± 15.4 kg, body mass index: 29.2 ± 4.9 kg/m^2 (means ± 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 class I–II) and a non-ST-elevation myocardial infarction at least 3 mo (actual elapsed time was 8–23 mo) before experimentation. The exclusion criteria were the following: Canadian Cardiac Society class III–IV, previous myocardial infarction <3 mo before experimentation, chronic atrial fibrillation, claudication, unstable angina pectoris, left ventricular ejection fraction <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).

Table 1. *Characteristic of study group*

Variables	(*n*) 16
Age, years	59.3 ± 7.0
BMI, kg/m^2	29.2 ± 4.9
BF, %	26.4 ± 7.6
Peak $\dot{V}O_2$, ml·kg^{-1}·min^{-1}	30.0 ± 5.6
SBP, mmHg	126 ± 19
DBP, mmHg	81 ± 10
Hypertension	
Yes	14 (87%)
No	2 (13%)
Medications	
Aspirin	14 (88%)
β-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%)

Values are the number of the patients or means ± SD. ACE, angiotensin-converting enzyme; ADP, adenosine-diphosphate; ATR, angiotensin receptor; BMI, body mass index; BF, body fat percentage; DBP, diastolic blood pressure; Peak $\dot{V}O_2$, estimated (3.5 × MET, where MET is metabolic equivalent of task) symptom-limited maximal oxygen uptake; SBP, systolic blood pressure.

Study Design

Clinical exercise tests were performed approximately 1 mo before 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). Before the test, ECG and heart rate (HR) were measured at rest in the supine position. The test was started from at 30 W and was increased by 15 W 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 crossover 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 1.0 m/s), *2*) 30-min exercise in the neutral environment (+22°C, wind 1.0 m/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 (8a, 14). The exercise consisted of brisk walking for 30 min 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% maximum HR (HR_{max}) where the individual walking speed was adjusted based on target HR and calculated based on the following equation: HR_{rest} + 0.45 × HRR, where HRR (heart rate reserve) = HR_{max} − HR_{rest}. HR_{rest} denotes HR at rest. 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 fewer amount of clothing insulation (0.75 clo) was used during both thermal neutral exposures. The experimental conditions were separated by at least 1 wk. Each patient performed the four trials at the same time of the day.

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

The patients were equipped with 10 skin temperature thermistors, a brachial BP arm cuff, and ECG electrodes. After the instrumentation, the patients moved into the climatic chamber with neutral temperature (+22°C) conditions for 12.5 min of baseline measurements with subjects in the seated position. Following this, the participants moved to the climatic chamber with adjustable temperature and wind speed, which was equipped with a treadmill. The duration of each experimental condition was 30 min during which the patients were either seated (rest) or walking. After the exposure the patients walked back to the neutral temperature chamber for a follow-up of 60 min. A paramedic nurse was monitoring real-time ECG and brachial BP throughout the experiments.

Measured parameters. Brachial BP (BP 200+, Schiller, Baar, Switzerland) was assessed at 5-min intervals during baseline, intervention, and follow-up. RPP was calculated by multiplying brachial SBP with HR. Physical strain was evaluated objectively by HR and subjectively by Borg's perceived of exertion scale (5). HR was monitored continuously, and perceived exertion was asked at 5-min intervals during the intervention.

ECG was recorded and monitored continuously using a 15-lead ECG (Cardiosoft V6.71, GE Healthcare, Freiburg, Germany). The placements of the ECG electrodes at rest followed the standard 12-lead placement and X, Y, Z leads. In the clinical exercise test, and during the interventions, the arm and foot electrode were reset to both shoulders and lower back. Signal analyses were carried out with custom-made software in Matlab (MathWorks, Natick, MA). Ectopic and abnormally shaped beats were removed from the analysis. ECG was used to identify P-wave onset, QRS boundaries, R- and T-wave peak, and T-wave offset, from which 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 HR 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) 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 2 temperature data loggers (SmartReaderPlus, Acr Systems, Surrey, BC, Canada). Mean skin temperature (T_{sk}) was calculated as follows: $T_{sk} = \sum k_i \times T_{sk}i = [(0.07 \times \text{forehead}) + (0.175 \times \text{right scapula}) + (0.175 \times \text{left upper chest}) + (0.07 \times \text{right arm}) + (0.07 \times \text{left arm}) + (0.05 \times \text{left hand}) + (0.19 \times \text{right anterior thigh}) + (0.2 \times \text{left calf})]$, where k_i is the weighting coefficient for that point measurement, and $T_{sk}i$ is local skin temperature at *point i* (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 two-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 were compared with rest at neutral temperature (reference) and their difference compared with interval estimates (95% confidence interval). 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 for windows (Microsoft). Statistical significance was set at $P < 0.05$.

RESULTS

Eight of the patients with CAD were retired from employment, whereas the rest were still a part of working life. The mean physical fitness of the patients (30.0 ± 5.6 $ml \cdot kg^{-1} \cdot min^{-1}$) was moderate when using scales of healthy adults (53), but ~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 mo. 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. 1*D*) by 6.3 ± 1.0°C ($P < 0.001$), whereas exercise in neutral conditions decreased T_{sk} 0.9 ± 0.5°C ($P < 0.001$), both compared with preexposure 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

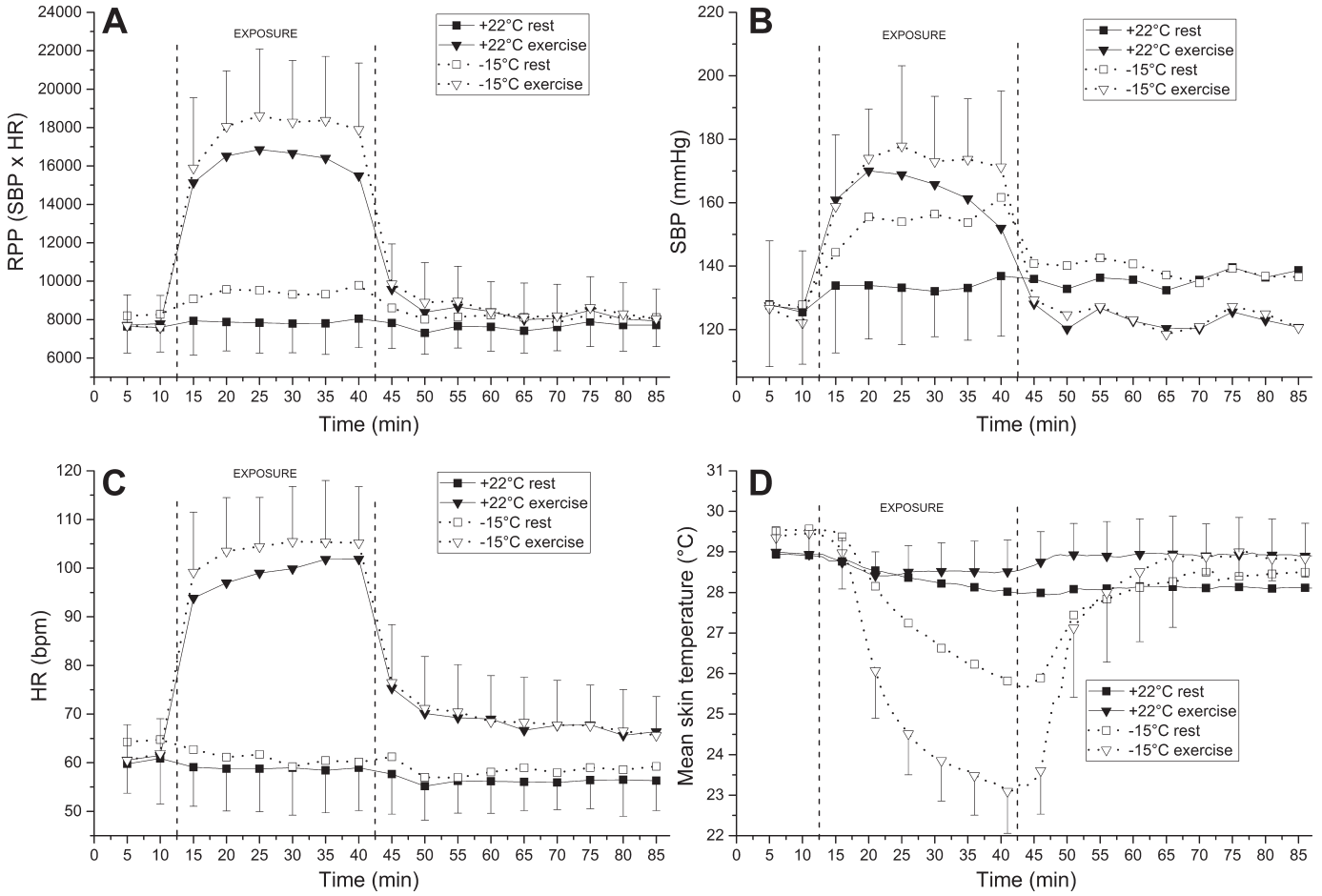

Fig. 1. Rate pressure product (RPP) (*A*), systolic blood pressure (SBP) (*B*), heart rate (HR, in beats/min) (*C*), and mean skin temperature (*D*) at rest and exercise either at +22°C or −15°C (n = 16). The vertical dotted lines represent the start and end of the intervention. Values represent means and their SD. For clarity reasons in *B*, SD bars for recovery are not presented.

measurements sites but to a greater extent in the extremities (forehead, face, calf, finger, and 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 HR_{max} 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.

Cardiovascular Response During Rest and Exercise in a Cold or Neutral Environment

Cardiovascular responses to rest and exercise at 22°C and −15°C are presented in Table 2.

BP, HR and RPP increased similarly in the beginning of exercise (at 2 min) both in cold and neutral environments (Fig. 1). 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). This elevated RPP was primarily driven by SBP, which was 13% (P = 0.001) higher whereas HR was only 3% (P = 0.042) higher in the cold when 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) whereas HR did not appreciably change [2%, not significant (ns); Fig. 1*B*, Table 2]. During the 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).

Independent and Joint Effects of Cold and Exercise

Cold exposure alone increased SBP and RPP but decreased HR compared with rest at neutral conditions (reference). As expected, exercise independently increased SBP, RPP, and HR. The joint effects of cold and exercise on SBP, HR, and RPP were comparable to exercise in a neutral environment in the early phase of the intervention. However, at the end of the intervention for SBP the separate effects of cold were on average +25 (95% confidence interval, 13 to 37) mmHg, exercise +15 (6 to 24) mmHg, and their joint effect +37 (28 to 46) mmHg. Hence, their interaction of −4 (−19 to 12, ns) mmHg indicated an additive effect, i.e., equaled the sum of the individual effects of cold and exercise. For HR the effect of cold was −3 (−5 to −1) beats/min, exercise +42 (36 to 48) beats/min, and their joint effects +45 (39 to 52) beats/min. This indicates a synergistic effect where the sum of cold or

Table 2. *Cardiovascular responses during 30 min of seated rest in a neutral and cold environment, as well as 30 min of exercise in these environments*

	+22°C					−15°C				
	Baseline average	Exposure 2 min	Exposure 27 min	Recovery 13 min	Recovery 33 min	Baseline average	Exposure 2 min	Exposure 27 min	Recovery 13 min	Recovery 33 min
Rest										
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, beats/min	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 × beats/min	7,620 ± 1320	7,940 ± 1840	8,050 ± 1560	7,400 ± 1306	7,720 ± 1710	8,230 ± 1720	9,070 ± 1880	9,880 ± 2,310*	8,169 ± 1640	8,041 ± 1740
Exercise										
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, beats/min	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 × beats/min	7,750 ± 1,230	15,140 ± 2,330	15,490 ± 2,940	8,540 ± 2,150	8,150 ± 1,590	7,630 ± 1,670	15,900 ± 3,790	18,080 ± 3,540*	9,250 ± 2,360	8,480 ± 2,000

Values are means ± SD; $n = 16$ patients. Neutral environment (+22°C); cold environment (−15°C). HR, heart rate; RPP, rate pressure product; SBP, systolic blood pressure; *$P < 0.05$ vs. +22°C for the respective condition.

exercise alone was exceeded by 6 (0 to 12) beats/min. For RPP the effect of cold was +1,218 (355 to 2,080) mmHg·beats/min, for exercise +7,309 (6,088 to 8,530) mmHg·beats/min, and their joint effect +10,017 (8,575 to 11,459) mmHg·beats/min. Therefore, although their interaction of +1,490 (−126 to 3,107, ns) mmHg·beats/min suggests synergistic interaction, the effects are not statistically significant, and the interaction can be considered as additive.

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. The corrected QT (QTc) interval was longer during the first minute of exercising in the cold compared with the first minute of exercise in the neutral environment ($P = 0.023$). This interval was shorter in the beginning of cold rest exposure compared with 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.

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 through a slightly elevated HR during exercise in the cold. The interaction of cold and exercise on SBP and RPP was additive, although 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 postexercise BP compared with 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 is limited to exercise of maximal intensities, short duration, and with varying types 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, 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 noncutaneous vascular beds. Lowered skin temperature, even during exercise, reduces skin blood flow because of both local and reflex mechanisms. In

Table 3. *Cardiovascular responses during 30 min of seated rest in a neutral and cold environment, as well as 30 min of exercise in these environments*

	+22°C					−15°C				
	Baseline	Exposure 1 min	Exposure 25 min	Recovery 1 min	Recovery 3 min	Baseline	Exposure 1 min	Exposure 25 min	Recovery 1 min	Recovery 3 min
Rest										
HR, beats/min	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
Exercise										
HR, beats/min	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 1 min, exposure 25 min, recovery 1 min, and recovery 3 min) ± SD; $n = 16$ patients. Neutral environment (+22°C); cold environment (−15°C). HR, heart rate; QRS; Duration of QRS; QT, QT interval; QTc, corrected; R_{amp}, R peak amplitude; T_{amp}, T peak amplitude. *$P < 0.05$ vs. +22°C.

addition, a low T_{sk} 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 T_{sk} observed at exercise, compared with rest, could be a result of 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 beats/min 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). Finally, wearing winter clothing may increase the energy cost because of 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 because of the use of medications, e.g., β-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 that 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 QTc for rest and exercise in the cold could be related to altered coactivation of the autonomic nervous system (46) and possi-

ble 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 postexercise hypotension among healthy individuals (38), hypertensive individuals (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 postexercise follow-up or involving patients with CAD. Our study showed comparable postexercise 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 interindividual variation. In the present study, SBP of patients with CAD remained elevated for 30 min 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 because of interindividual 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. The main effects of this 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 patients often used more than one type of medication, 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.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.I.P.V., H.E.H., H.V.H., J.P., C.C., W.v.M.-L., M.A., H.R., M.M., A.H., J.J.K.J., and T.M.I. conceived and designed research; R.I.P.V., A.K., H.E.H., N.R.I.R., C.C., M.M., A.H., and T.M.I. performed experiments; R.I.P.V., A.K., H.E.H., T.K., J.J.K.J., and T.M.I. analyzed data; R.I.P.V., A.K., H.E.H., N.R.I.R., T.K., H.V.H., J.P., C.C., W.v.M.-L., H.R., A.H., J.J.K.J., and T.M.I. interpreted results of experiments; R.I.P.V. and T.M.I. prepared figures; R.I.P.V., A.K., H.E.H., N.R.I.R., T.K., H.V.H., J.P., C.C., W.v.M.-L., M.A., H.R., M.M., A.H., J.J.K.J., and T.M.I. drafted manuscript; R.I.P.V., A.K., H.E.H., N.R.I.R., T.K., H.V.H., J.P., C.C., W.v.M.-L., M.A., H.R., M.M., A.H., J.J.K.J., and T.M.I. edited and revised manuscript; R.I.P.V., A.K., H.E.H., N.R.I.R., T.K., H.V.H., J.P., C.C., W.v.M.-L., M.A., H.R., M.M., A.H., J.J.K.J., and T.M.I. approved final version of manuscript.

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