Coronary responses to cold air inhalation following afferent and efferent blockade

Matthew D. Muller, Zhaohui Gao, Patrick M. McQuillan, Urs A. Leuenberger, and Lawrence I. Sinoway
Pennsylvania State University College of Medicine, Penn State Hershey Heart and Vascular Institute, Hershey, Pennsylvania

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Coronary responses to cold air inhalation following afferent and efferent blockade. Am J Physiol Heart Circ Physiol 307: H228–H235, 2014. First published May 9, 2014; doi:10.1152/ajpheart.00174.2014.—Cardiac ischemia and angina pectoris are commonly experienced during exertion in a cold environment. In the current study we tested the hypotheses that oropharyngeal afferent blockade (i.e., local anesthesia of the upper airway with lidocaine) as well as systemic β-adrenergic receptor blockade (i.e., intravenous propranolol) would improve the balance between myocardial oxygen supply and demand in response to the combined stimulus of cold air inhalation (−15 to −30°C) and isometric handgrip exercise (Cold + Grip). Young healthy subjects underwent Cold + Grip following lidocaine, propranolol, and control (no drug). Heart rate, blood pressure, and coronary blood flow velocity (CBV, from Doppler echocardiography) were continuously measured. Rate-pressure product (RPP) was calculated, and changes from baseline were compared between treatments. The change in RPP at the end of Cold + Grip was not different between lidocaine (2,441 ± 376) and control conditions (3,159 ± 626); CBV responses were also not different between treatments. With propranolol, heart rate (8 ± 1 vs. 14 ± 3 beats/min) and RPP responses to Cold + Grip were significantly attenuated. However, at peak exercise propranolol also resulted in a smaller ΔCBV (1.4 ± 0.8 vs. 5.3 ± 1.4 cm/s, P = 0.035), such that the relationship between coronary flow and cardiac metabolism was impaired under propranolol (0.43 ± 0.37 vs. 2.1 ± 0.63 arbitrary units). These data suggest that cold air breathing and isometric exercise significantly influence efferent control of coronary blood flow. Additionally, β-adrenergic vasodilation may play a significant role in coronary regulation during exercise.

Angina pectoris and acute myocardial infarction can be triggered by physical exertion in a cold environment. Indeed, numerous studies indicate that snow shoveling (13, 40, 66), downhill skiing (10, 46, 77), and deer hunting in winter (30) are associated with cardiovascular morbidity and mortality. The reason(s) why cold temperature has a negative effect on the human heart is not entirely clear. One concept is that surges in sympathetic nerve activity can restrain metabolic coronary vasodilation, thereby impairing the balance between myocardial oxygen supply and demand (2, 3, 38, 44); this scenario could potentially provoke symptoms of angina during exposure to cold temperatures. It has been established that coronary vasodilator responses to various stimuli (e.g., adenosine infusion, handgrip exercise, cold pressor test) have both diagnostic and prognostic value (14, 31, 34, 53, 65, 73, 75). If coronary vasodilation in response to exercise is restrained by sympathethic vasoconstriction (because of cold air inhalation), this could be a mechanistic link explaining why exertion in the cold is associated with poor outcomes. By using transthoracic Doppler echocardiography to measure coronary blood flow velocity (CBV) along with beat-by-beat measures of heart rate (HR) and arterial blood pressure (BP), our laboratory has begun to study the balance between myocardial oxygen supply and demand in vivo (22–24, 56, 58).

Because the mouth and face are most likely to be exposed to cold ambient conditions in daily life, we believe that studying how cold air inhalation influences coronary blood flow is clinically valuable. We recently established that cold air inhalation (−15 to −25°C) impairs the coronary supply-to-demand ratio compared with inhalation of neutral temperature air (20 to 25°C) in healthy subjects (60, 61). This impairment was also noted when cold air breathing was combined with isometric handgrip exercise, a laboratory intervention known to raise myocardial oxygen demand as well as sympathetic nerve activity (8, 19, 68). In our previous studies, we observed that rate-pressure product (RPP) increased to a greater extent in response to the combined stimulus of cold air inhalation and isometric handgrip (Cold + Grip) compared with handgrip under neutral air conditions. This augmented RPP response should signal metabolic vasodilatation, but we consistently observed less coronary hyperemia compared with control (i.e., neutral air) conditions (60, 61). Taken together, it appears that cold air inhalation impairs metabolic coronary vasodilatation when experienced alone or in combination with isometric work.

The purpose of the current study was to determine the effect of autonomic blockade on the coronary blood flow responses to Cold + Grip. In experiment 1, we tested the hypothesis that oropharyngeal afferent blockade (i.e., local anesthesia of the upper airway with 4% topical lidocaine) would attenuate the rise in RPP and enhance the CBV response to the Cold + Grip stimulus compared with control conditions (Cold + Grip without lidocaine). In experiment 2, we tested the hypothesis that systemic β-adrenergic receptor blockade (i.e., intravenous propranolol) would attenuate the rise in RPP in response to the Cold + Grip protocol. The current studies in healthy humans provide several unexpected findings and support the concept that vascular β-adrenergic receptors play an important role in coronary regulation during times of increased RPP.

METHODS

Design and subjects. The overall study used a within-subjects, repeated-measures design whereby physiological parameters were continuously measured during baseline, 5 min of cold air inhalation at rest, and 2 min of isometric handgrip while continuing to breathe cold air (Fig. 1, timeline). The comparison for experiment 1 was between lidocaine and control (no lidocaine); the comparison for experiment 2 was between propranolol and control (no propranolol). All study
protocols were approved in advance by the Institutional Review Board of the Penn State Milton S. Hershey Medical Center and confirmed to the Declaration of Helsinki. All volunteers provided written informed consent.

Thirteen young subjects (7 men and 6 women, 26 ± 1 yr, 1.77 ± 0.04 m, 77.3 ± 5.4 kg, and 24.7 ± 1.1 kg/m²) participated in experiment 1. Nine young subjects (4 men and 5 women, 27 ± 1 yr, 1.79 ± 0.05 m, 78.4 ± 4.7 kg, and 24.4 ± 1.2 kg/m²) participated in experiment 2. Three subjects participated in both experiments 1 and 2. We did not specifically control for menstrual cycle phase in young women. The sample size for experiment 2 was determined after the first six subjects had completed testing. Specifically, we determined that if the difference in the CBV-to-RPP ratio between propranolol and control conditions was 1.7 arbitrary units (AU) and had a standard deviation of 1.5 AU, we would be able to reject the null hypothesis with probability (power) of 0.92 and a type 1 error of 0.05.

All subjects had supine resting BPs below 120/80 mmHg and were nonasthmatic, nonobese, nonsmokers, not taking any prescription or vasoactive medication, and were in good health as determined by history and physical examination. All subjects reported being physically active, but none were competitive athletes. Subjects refrained from caffeine, alcohol, and exercise for 24 h before the study and arrived to the laboratory following an overnight fast.

Physiological and perceptual measurements used in both experiments. All imaging protocols were conducted in the supine or left lateral position in a dimly lit thermostatically controlled laboratory (22–25°C) in the morning hours (7:30 AM to 12:00 PM). Upon arrival at the laboratory, subjects were outfitted with a three-lead EKG (Cardiocap/5, GE Healthcare) to monitor HR, a finger BP cuff (Finometer, FMS), and a pneumotrace to monitor respiratory movement. Before echocardiography imaging, resting BPs were obtained in triplicate by automated oscillometry of the left brachial artery (Philips Sure Signs VS3) after 15 min of quiet rest. The average baseline brachial artery pressures [systolic BP, diastolic BP, and mean arterial BP (MAP)] were used to adjust the Finometer values during offline analysis. For example, if brachial MAP was 90 mmHg at baseline and the Finometer value for MAP was 85 mmHg, then 5 mmHg was added to all Finometer values in subsequent minutes. By doing this, we ensured that RPP and coronary vascular resistance (CVR) were calculated with the brachial systolic BP and MAP values, respectively. Arterial oxygen saturation was monitored by pulse oximetry on the earlobe (Respiratory Gas Monitor 5250, Ohmeda). All of the variables listed above were collected at 200 Hz by a PowerLab (ADInstruments).

Rating of thermal sensation of the body (where 1 = cold and 7 = hot) (20), perception of mouth coldness (where 0 = neutral or no sensation of cold and 11 = unbearable cold) (27), perception of mouth pain (where 0 = no pain and 10 = unbearable pain) (64), and perceived exertion in the hand and forearm (where 0 = very, very light and 20 = maximal exertion) (7) were also quantified.

Basic pulmonary function was determined with a MiniSpir device (Medical International Research) in both the seated and left lateral positions. The variables of interest included forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC).

CBV, an index of myocardial O₂ supply, was obtained from the adjusted apical four-chamber view using a GE Vivid 7 echocardiography system. The specific procedures used in our laboratory have been previously described (23–25, 58). Briefly, a variable frequency phased-array transducer (7S) was positioned to explore the left ventricular apex. The imaging depth was set at ~2 to 3 cm. Color flow mapping was used, and the two-dimensional gain was adjusted to obtain the best blood flow signal of the left anterior descending coronary artery. Once this was obtained, a 2.0-mm sample volume was placed over the color signal, and CBV was recorded at end expiration. The transducer was held still throughout the protocol, and care was taken to obtain at least one three-beat clip during the last 10 s of each minute. The Doppler tracking of the diastolic portion of each cardiac cycle was analyzed using ProSolv 3.0 to obtain peak diastolic CBV, as previously described (60, 61). Because of the limited spatial resolution and small vessel size, we did not attempt to measure the diameter of the left anterior descending coronary artery. However, our laboratory has documented that the percent increase in peak diastolic CBV measured via transthoracic Doppler echocardiography is similar to the percent increase in peak diastolic CBV measured by an intracoronary Doppler guidewire (57). Other studies have demonstrated strong correlations between CBV and coronary blood flow in response to vasodilator stimuli (51, 69).

Cold air inhalation plus handgrip protocol. A custom system was used to deliver cold air to the subjects, as previously described (60). Briefly, a closed loop of copper coil was placed in an insulated container that was filled with liquid nitrogen. Compressed medical air was attached to the distal end of the copper coil system, and subjects were instructed to breathe normally through a Hans Rudolph 2700B mouthpiece. Breathing rate and air temperature were measured in real time using thermistors (TC-2000, Sable Systems) situated in the mouthpiece. Because breathing cold air is a novel laboratory stimulus, at least two familiarization trials always occurred during an initial visit to the laboratory. During the familiarization trial, pulmonary function was determined in the seated upright position before and after cold air breathing. Additionally, maximum voluntary contraction (MVC) of the hand and forearm was also obtained using a handgrip dynamometer. Thirty percent of the MVC was calculated and used in subsequent trials; this workload is known to raise sympathetic nerve activity (52) and RPP (i.e., needed to elicit metabolic coronary vasodilation). For both experiments 1 and 2, the protocol always included 3 min of baseline, 5 min of cold air inhalation and rest, and 2 min of 30% isometric handgrip while continuing to breathe cold air. Contrary to our previous publications (60, 61) in which inspired air temperature was the independent variable (cold vs. neutral), in the current report, drug was the independent variable (lidocaine vs. no lidocaine; propranolol vs. no propranolol).
Experiment 1: effect of lidocaine. The procedures for upper airway anesthesia have been previously described for our laboratory (63). Briefly, participants were seated on an examination table and received 6 ml of 4% topical lidocaine via nebulizer. Compressed medical air was supplied at 4–8 l/min, and subjects breathed until the entire solution was gone (~15 min). Subjects were then situated in the left lateral position and breathed an additional 2 ml of nebulized lidocaine while coronary baseline measurements were obtained. Throughout lidocaine administration, suction was allowed ad libitum (Alliance K86 Medi-Vac Yankauer Suction). Cold air inhalation then occurred for a total of 7 min; the last 2 min also included isometric handgrip at 30% MVC (Fig. 1). Within 15 s of the end of exercise, the gag reflex was tested. If the gag reflex was absent at this time point, we considered the upper airway anesthesia to be effective. Subjects were not allowed to leave the laboratory until the gag reflex returned (typically 20–40 min). In four subjects, the gag reflex was present at the end of exercise, so all their data were excluded (i.e., afferent blockade ineffective in these people, so n = 9 in RESULTS). Control trials (without lidocaine) were performed on a separate day and were conducted in a counterbalanced fashion.

Experiment 2: effect of propranolol. For experiment 2, subjects dressed in a high-density, tube-lined suit (Med-Eng Systems, Ottawa, ON, Canada) that covered the entire body except for the feet, hands, and head. Neutral water (34–35°C) was perfused through the suit to maintain mean skin temperature at a constant level. Two intravenous catheters were placed (one in a left antecubital vein and one in a right antecubital vein). Following baseline measurements in the supine position, an intravenous infusion of isoproterenol, a nonselective β-adrenergic agonist, occurred in the left arm (Fig. 1). This infusion was based on previous human experiments (5, 70, 72) and began at a rate of 0.5 μg/min for 1 min and increased by 0.5 μg/min each minute until HR increased by 25–30 beats/min. After a 30-min washout period, a loading dose of propranolol was infused in the right arm over 15 min (0.25 mg/kg at a rate of 4 ml/min), followed by a maintenance infusion (0.006 mg·kg⁻¹·min⁻¹ at a rate of 1.45 ml/min) for the remainder of the study (11, 71). Pulmonary function was measured in the left lateral position before the start of propranolol infusion and after the loading dose of propranolol to ensure that β-adrenergic receptor blockade did not influence lung function (42). Baseline measurements were obtained, and then Cold + Grip occurred as described above. At the end of the study, the same duration and volume of isoproterenol was again infused into the left arm while the maintenance dose of propranolol continued in the right arm. Quantifying the tachycardia in response to isoproterenol before and after propranolol allowed us to determine the effectiveness of our systemic β-adrenergic blockade. Because of the high dose of propranolol given, orthostatic vital signs were recorded before the participants were released from the laboratory. Control trials (without propranolol) were performed on a separate day and were conducted in a counterbalanced fashion.

Data collection and statistical analysis. All variables were continuously measured and were analyzed off-line. An average of the last 15 s of each minute is presented. RPP (the product of HR and systolic BP) was used as a noninvasive index of myocardial oxygen demand (28). Both CBV and the ratio of ΔCBV to ΔRPP (i.e., the slope of the relationship between coronary flow and cardiac metabolism at peak exercise) were used as indexes of myocardial oxygen supply (22, 25). We also calculated CVR (the quotient of MAP and CBV) in an effort to compare with a previous study (59). For all variables, a two-treatment (drug, control) by nine-time point repeated-measures ANOVA was conducted using the raw physiological parameters. Paired t-tests were used when a significant drug by time interaction was found. Planned comparisons were also used to compare physiological parameters at baseline and at the end of exercise (i.e., when it was expected that treatment effects would be most prominent). Changes from baseline (Δ) were also compared between treatments.

RESULTS

Experiment 1: effect of lidocaine. Lidocaine inhalation was generally well tolerated, but several subjects reported that it was difficult to talk following lidocaine treatment. At baseline before cold air breathing, CBV (22.7 ± 2.7 vs. 21.8 ± 2.7 cm/s, P = 0.621) and CVR (3.6 ± 0.3 vs. 3.7 ± 0.4 mmHg·cm⁻¹·s⁻¹, P =
Table 1. Thermal and perceptual response to the Cold + Grip protocol

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<td>Lidocaine</td>
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<td>Tair °C</td>
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<td>Tmouth °C</td>
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<td>TS mouth AU</td>
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<td>Pain mouth AU</td>
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<td>Workload kg</td>
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Nine subjects completed experiment 1 and eight subjects completed experiment 2. Temperatures are average values taken during the exercise part of the protocol. All perceptual variables were obtained by verbal report immediately after the protocol ended. Tair, air temperature; Tmouth, mouth temperature; TS, thermal sensation; RPE, rating of perceived exertion (where 13 = somewhat hard, 15 = hard, and 17 = very hard). Data are means ± SE, *P < 0.05 compared with control.

0.592) were not altered by lidocaine compared with control conditions. In response to Cold + Grip, lidocaine did not have an effect on any of the measured variables compared with control (Fig. 2). The change in CBV at the end of exercise was not different between lidocaine (6.6 ± 2.1 cm/s) and control (4.1 ± 1.6 cm/s, P = 0.441). In a similar way, the change in CVR at the end of exercise was not different between lidocaine (−0.21 ± 0.21 mmHg·cm⁻¹·s⁻¹) and control (0.19 ± 0.33 mmHg·cm⁻¹·s⁻¹, P = 0.354). Thus upper airway afferent blockade (i.e., at a level that blocked the gag reflex) did not influence the hemodynamic and coronary responses to Cold + Grip. Thermal and perceptual variables are presented in Table 1.

Experiment 2: effect of propranolol. The average dose of propranolol received was 51 ± 3 mg. Consistent with our previous report, which gave the same dose of propranolol in different subjects (62), the tachycardia in response to intravenous isoproterenol was completely blocked by intravenous propranolol (ΔHR pre = 29 ± 3 beats/min vs. post 1 ± 1 beats/min). Thus β-adrenergic blockade was effective. Pulmonary function was reduced in the left lateral position compared with the seated position (FEV1 from 3.75 ± 0.21 to 3.45 ± 0.17 liters and FVC from 4.93 ± 0.28 to 4.59 ± 0.23 liters, P < 0.001). However, there was no further reduction in FEV1 (to 3.41 ± 0.16 liters, P = 0.137) or FVC (to 4.51 ± 0.20 liters, P = 0.265) following the infusion of propranolol. Thus propranolol did not significantly influence lung function in these young healthy subjects. Importantly, orthostatic vital signs were clinically acceptable at the completion of the study (i.e., appropriate tachycardia upon sitting and standing, no hypotension, and no dizziness).

Technical difficulty in coronary imaging resulted in one young woman being excluded from analysis. As depicted in Fig. 3, the Cold + Grip protocol significantly raised all variables across time. For the variable MAP, there was no main effect for drug or drug by time interaction. For both HR and RPP, there was a significant drug by time interaction such that propranolol lowered these variables at baseline and also attenuated the reflex increase in response to the Cold + Grip protocol. Indeed, ΔHR at peak exercise was blunted by propranolol (8 ± 1 beats/min compared with control (14 ± 3 beats/min, P = 0.025), and a similar effect was observed for RPP (2,393 ± 376 vs. 3,357 ± 660 beats·min⁻¹·mmHg, P = 0.049). Moreover, the ΔHR (0 ± 1 vs. 5 ± 1 beats/min, P = 0.006) and ΔRPP (114 ± 128 vs. 895 ± 160 beats·min⁻¹·mmHg, P < 0.001) in response to 5 min of cold air at rest (before exercise) were also significantly attenuated by propranolol compared with control; this effect was observed in 9 of the 10 subjects studied.

As shown in Fig. 3, CBV revealed a drug × time interaction. While none of the specific time points were different between

Fig. 3. Hemodynamic and coronary response to experiment 2 (n = 8). Propranolol trials (dashed line with white diamonds) and control trials (solid line with black squares) were performed on separate days. In response to the Cold + Grip protocol, propranolol had no effect on MAP but lowered the HR and RPP response compared with control. Propranolol also impaired the coronary vasodilator response at peak exercise (i.e., the change in CBV was significantly less with propranolol than control). Data are means ± SE. *Difference between treatments at the specific time point.
treatments, the ΔCBV was significantly impaired (i.e., less coronary hyperemia) under propranolol (1.4 ± 0.8 cm/s) compared with control (5.3 ± 1.4 cm/s, \( P = 0.035 \), Fig. 4). The derived quantities ΔCVR (propranolol, 1.3 ± 0.41 vs. control, 0.16 ± 0.38 mmHg·cm\(^{-1}\)·s\(^{-1}\), \( P = 0.015 \)) and ΔCBV/ΔRPP (propranolol, 0.43 ± 0.37 vs. control, 2.1 ± 0.63 AU, \( P = 0.041 \)) were also impaired under β-adrenergic receptor blockade. Individual data plotting CBV and RPP are displayed in Fig. 4. In total, the relationship between coronary flow and cardiac metabolism was impaired under propranolol such that less hyperemia occurred in response to the Cold Grip protocol (i.e., a stimulus that raises myocardial O\(_2\) demand as well as sympathetic tone). Thermal and perceptual variables are presented in Table 1. It is interesting to note that rating of perceived exertion of the hand and forearm was significantly higher with propranolol (\( P = 0.028 \)).

**DISCUSSION**

In the current study we hypothesized that local afferent blockade of the oropharynx (experiment 1) and systemic efferent blockade of β-adrenergic receptors (experiment 2) would improve the balance between myocardial oxygen supply (CBV) and demand (RPP) during the combined stimulus of cold air inhalation and isometric handgrip. The current data do not support these hypotheses. Nevertheless, herein we provide two key findings. First, lidocaine administration in the oropharynx did not attenuate the rise in RPP in response to the Cold + Grip protocol, and it also did not facilitate a larger coronary hyperemic response. Second, intravenous propranolol attenuated the HR and RPP response to the Cold + Grip protocol but actually impaired coronary hyperemia (presumably due to blockade of vascular \( \beta_2 \)-receptors in the coronary microcirculation). These data are novel on a physiological level and also may benefit patients with cardiovascular disease who undergo exertion in a cold environment.

We previously reported that cold air inhalation attenuated the coronary hyperemia in response to a 2-min bout of isometric handgrip compared with neutral air despite a significantly greater rise in RPP (i.e., a situation that should elicit a larger metabolic coronary vasodilation) (60, 61). These acute laboratory studies were consistent with previous experiments that used cold air inhalation alone (15, 33, 35, 47, 49, 67) or in combination with dynamic exercise in a whole body environmental chamber (9, 18, 43, 48, 50, 54). Additionally, the clinical observation that angina pectoris, arrhythmia, and sudden cardiac death are more prevalent following a heavy snowstorm (26, 32, 39, 74) suggests that synergistic effects between cold temperature and vigorous exertion exist. Based on a recent publication from our group (63), it is clear that tactile stimulation of the oropharynx raises both sympathetic nerve activity and myocardial O\(_2\) demand; this effect can be blocked by pretreating the upper airway with 4% lidocaine (i.e., local afferent blockade). In the current study, we used this same anesthetic procedure to evaluate how cold stimulation influences CBV and RPP. The data in Fig. 2 indicate that afferent blockade had no effect on the balance between myocardial oxygen supply and demand during Cold + Grip. This was contrary to our hypothesis. It should be noted that breathing lidocaine through a nebulizer anesthetizes the oropharynx, the back of the tongue, and possibly the larynx in some subjects but not the teeth, gums, or bronchioles (12, 45, 76). The possibility that the teeth and/or lower airway contribute to sympathetic reflex pathways remains to be prospectively tested.

In experiment 2, we tested the hypothesis that intravenous propranolol would attenuate the rise in RPP in response to the Cold + Grip protocol. We chose propranolol (as opposed to an \( \alpha \)-blocker such as phentolamine) because our previous studies have shown that the HR response to Cold + Grip was augmented, whereas the MAP response was similar to handgrip under neutral air breathing (60, 61). Additionally, propranolol is commonly used in patients with cardiovascular disease (i.e., the people most at risk for adverse events in the winter months) (78). Consistent with our hypothesis, the HR and RPP response to both cold air inhalation at rest and also the Cold + Grip protocol were significantly attenuated by propranolol (Fig. 3). This might indicate that β-blockers are useful for people who undergo exertion in the cold because the metabolic demand of
the heart would be lower. However, when considering the coronary blood flow data, we found that propranolol actually impaired myocardial oxygen supply. Indeed, both CBV and the CBV-to-RPP ratio were impaired under propranolol, indicating a smaller coronary hyperemia when normalizing for the metabolic stimulus (Fig. 4). While this was an unexpected finding, it suggests that under normal conditions (i.e., no drug), young healthy people experience a significant amount of β-adrenergic coronary vasodilation in response to the Cold + Grip stimulus (i.e., a physiological stimulus that raises myocardial metabolism as well as sympathetic nerve activity). We speculate this is also true for exercise under neutral air conditions, but the current study was not designed to test this concept directly. In general, our findings are consistent with previous coronary studies in exercising dogs (29, 55) and pigs (16, 17, 21). Under nonselective β-adrenergic receptor blockade, α-adrenergic constriction is unchecked and circulating catecholamines elicit a net vasoconstriction (36, 41).

When comparing the data from experiment 2 with those of previous studies, there are several factors that must be considered. First, we used local cooling of the upper airway combined with isometric handgrip in the supine posture, whereas dynamic exercise such as snow shoveling is conducted outdoors in the upright position. Second, the changes in HR and RPP due to propranolol were small in magnitude and may have limited clinical significance. However, higher exercise intensities (i.e., greater sympathetic activation) conducted in a cold environment would likely magnify the effects of propranolol rather than diminish them. Third, vagal withdrawal and baroreflex buffering also occur when undergoing isometric handgrip at 30% MVC so the net effect of propranolol on coronary blood flow is an integrated response of several different inputs. Fourth, propranolol is a nonselective β-blocker and using an intravenous route of administration results in the entire body (both heart and blood vessels) being β-blocked. In this study, we chose propranolol to ensure a complete blockade of the β-adrenergic receptors. Had we chosen a different β-blocker we may not have observed the surprising finding that the CBV-to-RPP ratio was impaired at peak exercise (Fig. 3, bottom, and Fig. 4). Fifth, our subjects were young and did not have other cardiovascular disease risk factors. Young subjects presumably have higher coronary β-adrenergic vasodilatory capacity compared with older people or patients with overt cardiovascular disease (although this speculation is not known for certain). From a clinical perspective, young subjects typically do not experience chest pain when shoveling snow. Sixth, we did not use a systemic α-blocker in this study and it should be noted that systemic propranolol not only impairs β-adrenergic coronary vasodilation but also enhances α-adrenergic coronary vasoconstriction. Despite these six caveats listed above, we are the first to evaluate coronary responses to cold air breathing and isometric exercise. It is also clear that acutely stressful situations (e.g., exposure to cold and exercise) are linked with adverse cardiovascular events (13, 40, 66) and that heightened sympathetic tone can impair coronary vasodilation (2, 3, 37, 38, 44). In the current study we used transthoracic Doppler echocardiography along with pharmacological blockade to understand how cold air inhalation and isometric exercise influence the balance between myocardial oxygen supply and demand. In experiment 1, we determined that afferent blockade of the oropharynx had no effect on RPP and CBV in response to the Cold + Grip protocol. In experiment 2, we found that intravenous propranolol lowered the HR and RPP responses to both cold air inhalation at rest and also the Cold + Grip protocol but also impaired coronary blood flow at peak exercise. These data in young healthy people support the concept that cold air breathing and isometric exercise significantly influence efferent control of coronary blood flow. Additionally, the data suggest that β-adrenergic vasodilation plays a significant role in coronary regulation during times of increased myocardial oxygen demand.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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CORONARY BLOOD FLOW WITH COLD AIR BREATHING


