Beta-adrenergic blockade enhances coronary vasoconstrictor response to forehead cooling

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AUTHOR CONTRIBUTIONS

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Running Head: Forehead cooling and coronary vasoconstriction

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ABSTRACT

Forehead cooling activates the sympathetic nervous system and can trigger angina pectoris in susceptible individuals. However, the effect of forehead cooling on coronary blood flow velocity (CBV) is not well understood. In this human experiment, we tested the hypotheses 1) that forehead cooling reduces CBV (i.e., coronary vasoconstriction); and 2) this vasoconstrictor effect would be enhanced under systemic beta-adrenergic blockade. A total of 30 healthy subjects (age range 23-79 years) underwent Doppler echocardiography evaluation of CBV in response to 60 seconds of forehead cooling (1°C ice bag on forehead). A subset of subjects (n = 10) also underwent the procedures following an intravenous infusion of propranolol. Rate pressure product (RPP) was used as an index of myocardial oxygen demand. Consistent with our first hypothesis, forehead cooling reduced CBV from 19.5 ± 0.7 to 17.5 ± 0.8 cm/sec (P < 0.001) while MAP increased by 11 ± 2 mmHg (P < 0.001). Consistent with our second hypothesis, forehead cooling reduced CBV under propranolol despite a significant rise in RPP. The current studies indicate that forehead cooling elicits a sympathetically-mediated pressor response and a reduction in CBV and this effect is augmented under beta-blockade. The results are consistent with sympathetic activation of beta-receptor coronary vasodilation in humans, as has been demonstrated in animals.

Keywords: sympathetic nervous system, blood flow, cold temperature, myocardium, phenylephrine, isoproterenol
INTRODUCTION

Exposure to cold ambient temperature is a commonly reported trigger for angina pectoris (12, 22, 31, 37, 38). Moreover, cardiovascular morbidity and mortality are highest in the cold winter months compared to any other time of year (1, 2, 44). Thus, continued investigation into how and why cold exposure influences coronary vascular regulation in human subjects is needed.

Forehead cooling is a unique stimulus that activates the sympathetic nervous system, increases limb vascular resistance, and elicits an acute rise in arterial blood pressure (BP) (8, 11, 13, 18, 24, 26, 50, 51, 64). Recent studies from our laboratory demonstrated that local cooling of the forehead (1°C) also caused renal vasoconstriction in healthy subjects (52). Currently, the effect of forehead cooling on coronary blood flow velocity (CBV) is unknown. Because forehead cooling raises sympathetic tone (13, 26) and because elevated sympathetic tone can decrease CBV (and/or increase coronary resistance) via activation of alpha-adrenergic receptors (54, 63, 67, 70, 71), it is possible that forehead cooling would also reduce CBV. However, sympathetic stimulation also elicits beta-adrenergic vasodilation so the coronary vasoconstrictor response to forehead cooling (i.e., a reduction in CBV) is likely to be more pronounced under beta-blockade. This concept remains to be experimentally tested in humans.

With this background in mind, the purpose of this investigation was to determine the interactive effects of: 1) forehead cooling; 2) aging; and 3) systemic beta-adrenergic blockade on CBV in healthy humans. We hypothesized that: 1) forehead cooling would reduce CBV across time; 2) CBV responses to forehead cooling would be augmented in older adults; and 3) intravenous beta-adrenergic receptor blockade would lower CBV at
rest and augment the reflex reduction in CBV in response to forehead cooling. The current studies indicate that forehead cooling elicits a potent sympathetically-mediated coronary vasoconstriction that (under normal circumstances) is dampened by parallel beta-adrenergic vasodilation.

METHODS

Subjects and Design

The overall study used a repeated measures design whereby physiological parameters were continuously measured during baseline and forehead cooling. Age group (young versus older) served as a between-subjects factor. All study protocols were approved in advance by the Institutional Review Board of the Penn State Milton S. Hershey Medical Center and conformed to the Declaration of Helsinki. A total of 17 young (8 women, 26 ± 2 yr) and 13 older (5 women, 66 ± 2 yr) subjects volunteered to participate and provided written informed consent. All subjects had supine resting blood pressures below 125/80 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. All older subjects underwent a Bruce treadmill protocol with 12 lead EKG monitoring that was read by a cardiologist to rule out myocardial ischemia. Subjects refrained from caffeine, alcohol, and exercise for 24 h before the study and arrived to the laboratory in a semi fasted state (i.e., 4-6 h after their last meal).
Measurements

All experiments were conducted in the supine or left lateral position in a dimly lit thermoneutral laboratory (22-25°C). Upon arrival at the laboratory, subjects were outfitted with a 3-lead EKG (Cardiocap/5, GE Healthcare) to monitor HR, a finger blood pressure cuff (Finometer, FMS), and a pneumotrace to monitor respiratory movement. Water temperature of the forehead ice bag was measured via thermistors (TC-2000, Sable Systems International). Prior to the forehead cooling protocol, resting blood pressures were obtained in triplicate by automated oscillometry of the left brachial artery (Philips Sure Signs VS3) after 15 minutes of quiet rest. The average baseline brachial artery pressures (SBP, DBP, and 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. Thermal sensation (0 = neutral/no sensation of cold and 11= unbearable cold) and pain perception of the forehead (0 = no pain and 10 = unbearable pain) were obtained immediately after each stimulus (47).

CBV, an index of myocardial O₂ supply, was obtained from the apical four-chamber view using a GE Vivid 7 echocardiography system. The specific procedures used in our laboratory have been previously described (15-17, 40). Briefly, a variable frequency phased-array transducer (7S) was positioned to explore the left ventricular apex. The imaging depth was set at 5 cm, and the focal zones were set at ~2-3 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 (LAD). 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 3-beat clip during the last 10 seconds of forehead cooling. The Doppler tracing of the diastolic portion of each cardiac cycle was analyzed using Pro Solv 3.0 to obtain CBVpeak, as previously described (45, 46). Because of the limited spatial resolution and small vessel size, we did not attempt to measure LAD diameter. However, our laboratory documented that the percent increase in CBV measured via transthoracic Doppler echocardiography is similar to the percent increase in CBV measured by an intracoronary Doppler guidewire (39). Furthermore, intracoronary Doppler guidewire measurements of the percent increase in CBV significantly correlate with the percent increase in coronary blood flow (58).

Experiment 1: Effect of Forehead Cooling on CBV

Consistent with prior published studies from our laboratory (52), subjects underwent familiarization trials during a prescreening visit. These familiarization studies attempted to minimize subject anxiety during subsequent coronary blood flow experiments. Following baseline hemodynamic and coronary measurements, local forehead cooling was conducted for 60 seconds, as previously described (25, 32, 34). Briefly, a plastic bag filled with ~250 mL of ice and water (1°C) was placed on the forehead. Care was taken to avoid contact with the eyes (i.e. to avoid the oculocardiac reflex) and subjects were monitored to ensure normal breathing. This forehead cooling procedure is thought to stimulate trigeminal afferents that are involved in the diving reflex (i.e., bradycardia and peripheral vasoconstriction) but bradycardia is not universally observed in healthy subjects (11, 26, 65). MAP, HR, and CBV were measured continuously.
In a subset of subjects (n = 4 young men), MSNA was measured during forehead cooling to confirm that peak sympathetic activation occurred during the last 10 seconds of forehead cooling (i.e., when peak coronary vasoconstriction was measured) (13, 26). Multifiber recordings of MSNA were obtained with a tungsten microelectrode (Frederick Haer Company, Bowdoin, ME) inserted in the peroneal nerve of a leg. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria (69). Briefly, MSNA was distinguished from other nerve signals when there was increased burst activity in response to maximal voluntary end-expiratory apnea and/or passive muscle stretch but not with skin stroking of the innervated area, rapid inspiration, or arousal stimuli (69). The nerve signal was amplified, band-pass filtered with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Model 662C-3, Iowa Bioengineering, Iowa City, IA). The nerve signal was also routed to a loudspeaker and a computer for monitoring throughout the study.

The effects of aging (young subjects versus older subjects) was determined once all data were collected.

**Experiment 2: Effect of Beta-Adrenergic Receptor Blockade on CBV Response to Forehead Cooling**

Ten male subjects participated in Experiment 2, which occurred chronologically after Experiment 1 (i.e., once all data collection was complete). Five of the ten subjects had also participated in Experiment 1 and the control trials (without drug) were repeated in these individuals on a separate day. Upon arrival at the laboratory, two intravenous
catheters were placed (one in a left antecubital vein and one in a right antecubital vein). Following baseline measurements in the supine posture, an intravenous infusion of isoproterenol, a nonselective beta-adrenergic agonist, occurred in the left arm. This infusion was based on previous human experiments (4, 59, 61) and began at a rate of 0.5 μg/min for one minute and increased by 0.5 μg/min each minute until HR increased by 25-30 beats/min. Because of this infusion paradigm, the duration and volume of infusion was different for each subject. After a 30-minute washout period, a loading dose of propranolol was infused in the right arm over 15 minutes (0.25 mg/kg at a rate of 4 mL/min) followed by a maintenance infusion (0.006 mg/kg/min at a rate of 1.45 ml/min) for the remainder of the study (6, 60). A baseline period was obtained and then forehead cooling 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 beta-adrenergic blockade.

**Experiment 3: Effect of Alpha-Adrenergic Stimulation on CBV**

To determine if a pharmacological stimulus would also elicit coronary vasoconstriction, in four young men, we systemically injected a bolus of phenylephrine (an alpha-1 adrenergic agonist) at dosages of 50-150 μg (41, 43). Our goal was to increase MAP by ~8 mmHg, since forehead cooling raises MAP by an average of 6-10 mmHg in young subjects (26, 52). A bolus injection was chosen as opposed to a steady state infusion to elicit a short duration coronary vasoconstriction (i.e., similar to forehead cooling) (62, 66). Two trials were conducted and were separated by 20 minutes; average CBV responses are reported in text and individual data are presented in Figure 2.
Data Collection and Statistical Analysis

Physiological variables were collected continuously at 200 Hz by a PowerLab (ADInstruments) and were analyzed offline in 10-second bins. Consistent with previous publications, the last 10 seconds of forehead cooling was considered to be the peak response (14, 33, 52) and we ensured that coronary images were acquired during this bin.

Rate pressure product (RPP), an index of myocardial oxygen demand (19, 30) was calculated as HR * systolic blood pressure (SBP) (42). We also compared changes in CBV to changes in RPP, which is a ratio of coronary supply to demand (46). For Experiment 1, the peak response (in physiological units) obtained during the last 10 seconds of forehead cooling was compared to baseline with a paired t-test. Also for Experiment 1, changes from baseline between groups (young versus older adults were compared with independent t-tests. Experiment 2 utilized a within-subjects, crossover design whereby 2 treatments (control, propranolol) were compared between two time points (baseline, peak forehead cooling) with a repeated measures ANOVA. Paired t-tests were utilized when a drug by time interaction was observed. For Experiment 3, coronary variables were analyzed at two specific time points with paired t-tests: 1) the highest MAP following infusion of phenylephrine; and 2) the lowest HR following infusion of phenylephrine (which always occurred after the highest MAP was obtained).
RESULTS

Experiment 1: Effect of Forehead Cooling on CBV

When considering the entire group of subjects (n = 30), 60 seconds of forehead cooling at 1°C raised SBP ($\Delta = 14 \pm 3$ mmHg, $P < 0.001$), diastolic blood pressure (DBP, $\Delta = 8 \pm 1$ mmHg, $P < 0.001$), and MAP ($\Delta = 11 \pm 2$ mmHg, $P < 0.001$), while causing a modest reduction in HR ($\Delta = -3 \pm 1$ beats/min, $P < 0.001$). CBV was reduced from $19.5 \pm 0.7$ to $17.5 \pm 0.8$ cm/sec ($P < 0.001$). As shown in Figure 1, forehead cooling for 60 seconds caused a significant rise in MSNA and a reduction in CBV, coincident with a rise in MAP. Thus the time course of the change in MSNA and MAP suggests that sympathetic activation occurs simultaneously with the reduction in CBV. Individual data from Experiment 1 are shown in Figure 2 and it is clear that CBV is reduced consistently with forehead cooling whereas RPP responses are quite variable (6336 ± 245 beats/min*mmHg at baseline to 6076 ± 310 beats/min*mmHg at the end of forehead cooling, $P = 0.176$).

As shown in Table 1, forehead cooling responses were comparable between young and older subjects. There was an augmented $\Delta$MAP response in the older subjects ($P = 0.048$) and a tendency for $\Delta$DBP to also be greater in the older subjects ($P = 0.072$).

Experiment 2: Effect of Beta-Adrenergic Receptor Blockade on CBV Response to Forehead Cooling

Systemic infusion of isoproterenol expectedly increased HR (from $60 \pm 3$ to $92 \pm 3$ beats/min) in the pre-propranolol state while having no significant effect on MAP. After systemic infusion of propranolol, isoproterenol did not have an effect on HR (from $53 \pm 3$
to 53 ± 3 beats/min) or MAP (Figure 3). Thus, infusion of propranolol completely antagonized sinoatrial node beta-adrenergic receptors.

Following propranolol, HR and RPP were lower at baseline (P < 0.001, Table 2). CBV was also lower at baseline in 8 of the 10 subjects with propranolol but this comparison did not reach statistical significance (P = 0.131). In response to forehead cooling, RPP increased significantly under propranolol (P = 0.029) but not under control conditions (P = 0.216). Thus, under beta-blockade, forehead cooling caused a slight increase in myocardial oxygen demand albeit from a suppressed baseline level. Despite the increased RPP under propranolol there was a reduction in CBV (i.e., augmented coronary vasoconstriction, Figure 2 middle). The ratio of changes in CBV to changes in RPP was larger under control conditions in 8 of the 10 subjects (i.e., more vasoconstriction under propranolol). However, because of large variability, this comparison was not statistically significant (-4.6 ± 4.5 versus 0.17 ± 1.1 au, P = 0.147).

**Experiment 3: Effect of Alpha-Adrenergic Stimulation on CBV**

Systemic bolus injection of phenylephrine raised MAP from 83 ± 2 to a peak level of 89 ± 2 mmHg in the four young men studied. At the highest level of MAP, HR had fallen from 48 ± 2 beats/min to 44 ± 2 beats/min and (RPP from 6376 ± 521 to 6344 ± 384, P = 0.945). At this time point, CBV was reduced from 19.7 ± 1.1 to 13.9 ± 0.9 cm/sec (P < 0.001). An example recording is shown in Figure 4.

The lowest HR obtained following phenylephrine always occurred after the peak MAP response (i.e., highest vagal activation and/or lowest sympathetic activation). At this time point, HR was 42 ± 2 beats/min, MAP was 87 ± 2 mmHg, and RPP was reduced to 5183 ± 453 (all P < 0.001 versus baseline). CBV remained at 13.9 ± 0.8 cm/sec. Taken
together, whether myocardial oxygen demand stayed constant (i.e. analyzing the peak MAP) or was reduced (i.e., analyzing the lowest HR), systemic bolus injection of phenylephrine caused a profound reduction in CBV along with the systemic pressor response (i.e., pharmacologically-induced coronary vasoconstriction).

DISCUSSION

The purpose of this study was to determine how forehead cooling influences CBV in healthy human subjects. The current data support our original hypotheses; forehead cooling reduced CBV across time (Experiment 1). Additionally, under intravenous beta-blockade forehead cooling lowered CBV despite a significant rise in RPP (Experiment 2). However, aging was not associated with a greater coronary vasoconstriction. We are the first to report that forehead cooling elicits a reduction in CBV in healthy humans; additionally, we provide evidence that beta-adrenergic receptor blockade enhances this vasoconstrictor response. These findings may also be clinically relevant in the context of cold exposure and angina pectoris.

Experiment 1: Effect of Forehead Cooling on CBV

The concept that sympathetic stress can evoke coronary vasoconstriction has been studied in patients with atherosclerotic coronary disease. For instance, handgrip exercise and the cold pressor test (hand in ice water for 90-120 seconds) elicit vasodilation in normal coronary arteries and vasoconstriction in stenotic arteries (23, 48). The increased coronary blood flow in normal arteries is predominantly due to the increase in cardiac metabolism and resultant shear-stress mediated release of nitric oxide, whereas endothelial dysfunction and overt atherosclerosis lead to impaired (or even reduced) flow and ischemia in these patients. Published studies from our laboratory (40)
and others (63, 67, 70) have found that sympathetic activation via lower body negative pressure and the Valsalva maneuver reduces CBV and/or raises coronary resistance in healthy subjects. The current data from Experiment 1 are consistent with these previous findings and also support a prior cardiac catheterization study (50). Specifically, Neill et al. (50) found that forehead cooling elicited angina in 5 of the 25 patients studied. Because our study measured CBV with Doppler ultrasound in healthy subjects whereas Neill et al. (50) measured coronary blood flow invasively in patients with coronary disease, future studies are needed to address this process in more detail.

Sub-analysis of the data in Experiment 1 found an augmented pressor response to forehead cooling in healthy older adults but no difference in CBV relative to young subjects (Table 1). The augmented pressor response is consistent with a recent study by Patel et al. (52) and may indicate a greater level of sympathetic activation in these older subjects to this laboratory stimulus; however higher MAP levels also induce a greater shear stimulus to the coronary vascular endothelium such that the net result is CBV being similar to that in young people. In other words, healthy older adults appear to have a preserved ability to offset higher MAP levels to forehead cooling with coronary vasodilation. Whether this ability is also observed in patients with atherosclerotic disease has not been determined but, based on previous literature (23, 48), we speculate this is not the case and augmented vasoconstriction may prevail.

Experiment 2: Effect of Beta-Adrenergic Receptor Blockade on CBV Response to Forehead Cooling
Beta-blockers are commonly used to treat cardiovascular disease (72) and can be safely infused in high doses to test physiological mechanisms in human subjects (49, 68). For these reasons, we sought to evaluate if beta-adrenergic receptor blockade would influence the CBV response to forehead cooling. When designing Experiment 2, we considered that the net effect of short-duration sympathetic activation on the coronary circulation is predominantly due to the combined effects of: 1) cardiac metabolism (i.e., RPP), 2) alpha-adrenergic vasoconstriction, and 3) beta-adrenergic vasodilation. The control data in Fig 2A and 2B where both CBV and RPP decreased may simply result from a decrease in local metabolic vasodilation. However, this does not preclude the possibility of concomitant beta vasodilation and alpha vasoconstriction. The addition of beta blockade with propranolol (Experiment 2) unmasked alpha vasoconstriction as indicated by a decrease in CBV accompanied by an increase in RPP. Coronary vasodilation mediated by beta-adrenergic receptors has been demonstrated during exercise in swine (9) and dogs (20). Intracoronary salbutamol (a beta-2 agonist) elicits coronary vasodilation in human patients with coronary artery disease (3, 55). The current data in healthy subjects are best explained by propranolol blocking beta-2 coronary vasodilation thereby unmaking alpha-adrenergic vasoconstriction (Figure 2B). Interestingly, alpha-adrenergic coronary vasoconstriction during exercise has been observed in dogs (20) but not in swine (9, 10).

It is worth noting that propranolol tended to reduce CBV at baseline which is consistent with previous human experiments (49). It is unclear if this baseline reduction in CBV was due to reduced RPP, impaired vascular tone, or a combination of both factors. In other words, a reduced RPP (due to drug effects or vagal activation) could lower CBV independent of alpha receptors. Indeed, in Experiment 1 and the control trial of
Experiment 2 some subjects had a reduction in RPP which complicates the interpretation of the coronary data. However, under propranolol blockade in Experiment 2, this was clearly not an issue because RPP actually increased (Figure 2 middle).

The ΔMAP in response to forehead cooling was ~50% larger under propranolol although this comparison was not statistically significant. There is a general consensus that blockade of beta-adrenergic receptors enhances alpha-adrenergic vasoconstrictor responses to stress and pharmacological stimulation (28, 29, 57). Our data obtained from the LAD artery support and extend upon these previous studies. There is debate over whether selective or non-selective beta-blockers are more effective for use in a cold environment (5, 35, 36, 56). Overall, we believe that beta-mediated vasodilation plays an important role in offsetting the coronary vasoconstrictor response to forehead cooling in vivo. Whether this is modified by age, sex, disease, or genetics is yet to be determined (21, 27, 73).

Experiment 3: Effect of Alpha-Adrenergic Stimulation on CBV

Based on our findings from Experiments 1 and 2 using physiological stress (i.e., forehead cooling), we next wanted to test whether a pharmacological stimulus would also elicit coronary vasoconstriction. At similar levels of ΔMAP to that observed with forehead cooling, phenylephrine caused profound reductions in CBV. These data acquired using Doppler echocardiography are consistent with prior invasive studies in animals (7, 53). Analyzing both the highest MAP and the lowest HR following bolus injection of phenylephrine allowed for us to determine how changes in RPP influence CBV.

To our knowledge, this is the first report of coronary vasoconstrictor responses to different stimuli in humans (i.e., a reduction in CBV along with a systemic pressor
response). Overall, the data from Figure 2 may stimulate a new area of research in coronary vasoconstriction whereas most previous studies have focused on coronary vasodilation (14, 19, 35, 36, 38, 41, 42, 44). As the field moves forward, it is important to note that baseline RPP and CBV can be quite variable between people which makes statistical comparisons of the $\Delta$CBV/$\Delta$RPP ratio complicated (i.e., the calculated slopes of the lines in Figure 2). The complex interplay between alpha-adrenergic vasoconstriction, beta-adrenergic vasodilation, and/or cholinergic vasodilation in response to forehead cooling and how these factors influence the predilection to atherosclerotic disease is currently unknown and remains to be prospectively tested.

Clinical Implications

The current study may partly explain why angina pectoris is often triggered by exposure to cold, windy conditions. Specifically, a reduction in CBV coincident with a rise (or no change) in RPP may indicate a myocardial oxygen supply-demand mismatch. When coupled with vigorous exertion (e.g., snow shoveling which further raises cardiac demand), this situation may be particularly problematic. The data from Experiment 2 also question whether high dose propranolol should be used for patients who undergo frequent forehead cooling in their daily lives. We speculate that cardioselective beta-1 blockers (e.g., metoprolol, atenolol) would be more appropriate because they would leave the coronary vascular beta-2 receptors unblocked. This speculation warrants future study.

CONCLUSIONS

Exposure of the forehead to cold ambient conditions is commonly experienced throughout the world and is sometimes linked with adverse cardiovascular events. Prior human studies have shown that the net efferent effects of forehead cooling are: 1) a rise
in sympathetic nerve activity (13, 26); 2) limb vasoconstriction (51); 3) renal vasoconstriction (52); and 4) a rise in arterial BP (8, 11). In the current study, we provide evidence that CBV also decreases in response to forehead cooling (Experiment 1). In Experiment 2, we then observed that forehead cooling under beta-adrenergic blockade also reduced CBV despite a significant rise in RPP (which should elicit metabolic vasodilation). Taken together, these results are consistent with sympathetic activation of beta-receptor coronary vasodilation in humans, as has been demonstrated in animals. The concept that beta-mediated vasodilation could provide cardioprotection during sympathetic stress warrants future study.

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GRANTS

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DISCLOSURES

There are no conflicts of interest.
REFERENCES


FIGURE LEGENDS

Figure 1. Representative recording of muscle sympathetic nerve activity (MSNA), arterial blood pressure (BP), heart rate (HR), and coronary blood flow velocity obtained simultaneously in one young man during Experiment 1. Note that higher levels of MSNA and BP are associated with a reduction in coronary blood flow velocity (CBV).

Figure 2. Individual coronary O\textsubscript{2} demand (RPP, x-axis) and coronary O\textsubscript{2} supply (CBV, y-axis) are displayed for Experiment 1 (top), Experiment 2 (middle), and Experiment 3 (bottom). The arrows point from baseline to the end of forehead cooling. The bold lines represent group averages. Note that a reduction in CBV along with a rise in RPP is strong evidence for coronary vasoconstriction.

Figure 3. Tachycardia in response to systemic isoproterenol before (pre-propranolol) and after (post-propranolol) systemic beta-adrenergic receptor blockade (Experiment 2). Blood pressure was unchanged during these infusions.

Figure 4. Representative recording of coronary blood flow velocity (in m/sec) following systemic infusion of phenylephrine (Experiment 3). Note that mean arterial pressure (MAP) increased, heart rate (HR) decreased, and coronary blood flow velocity was reduced in response to systemic phenylephrine.
Table 1. Effect of aging on hemodynamic and coronary responses to forehead cooling in Experiment 1

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Subjects were exposed to 60-seconds of forehead cooling (1°C ice water bag on forehead) in the supine posture. There were no differences in coronary blood flow parameters between young (n = 16) and older (n = 13) subjects but older adults had a larger ΔMAP. Data are M ± SEM. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, RPP = rate pressure product, CBV = coronary blood flow velocity, TS = thermal sensation. * denotes difference from young subjects at same time point.
Table 2. Effect of propranolol on hemodynamic and coronary responses to forehead cooling in Experiment 2

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<tr>
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<th>Propranolol Base</th>
<th>Propranolol Peak</th>
<th>Control Base</th>
<th>Control Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP mmHg</td>
<td>114 ± 2</td>
<td>134 ± 5 *</td>
<td>113 ± 2</td>
<td>125 ± 6 *</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>72 ± 2</td>
<td>84 ± 3 *</td>
<td>71 ± 3</td>
<td>78 ± 3 *</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>86 ± 2</td>
<td>101 ± 3 *</td>
<td>85 ± 3</td>
<td>96 ± 4 *</td>
</tr>
<tr>
<td>HR beats/min</td>
<td>53 ± 2 †</td>
<td>50 ± 3</td>
<td>62 ± 3</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>RPP beats/min * mmHg</td>
<td>6007 ± 262 †</td>
<td>6708 ± 493 * †</td>
<td>6731 ± 363</td>
<td>6204 ± 534</td>
</tr>
<tr>
<td>CBV cm/sec</td>
<td>17.2 ± 2.1</td>
<td>13.9 ± 1.5 * †</td>
<td>20.3 ± 1.6</td>
<td>16.9 ± 1.5 *</td>
</tr>
<tr>
<td>Forehead TS au</td>
<td>--</td>
<td>7 ± 1</td>
<td>--</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Forehead pain au</td>
<td>--</td>
<td>4 ± 1</td>
<td>--</td>
<td>4 ± 1</td>
</tr>
</tbody>
</table>

Subjects were exposed to 60-seconds of forehead cooling (1°C ice water bag on forehead) in the supine posture. Studies were conducted following intravenous of propranolol or control (no propranolol). Data are M ± SEM, n=10. * Denotes a significant difference from the respective baseline P < 0.05 and † denotes a significant difference from control condition at the same time point.
Heart Rate (beats/min)

Base Time Control
Systemic Isoproterenol
Pre-Propranolol

Base
Peak
Systemic Isoproterenol
Pre-Propranolol

Base
Time Control
Systemic Isoproterenol
Post-Propranolol
Base
MAP = 82 mmHg

Phenylephrine
MAP = 91 mmHg