β-Adrenergic blockade enhances coronary vasoconstrictor response to forehead cooling

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Submitted 10 October 2013; accepted in final form 16 January 2014

Muller MD, Gao Z, Patel HM, Heffernan MJ, Leuenberger UA, Sinoway LI. β-Adrenergic blockade enhances coronary vasoconstrictor response to forehead cooling. Am J Physiol Heart Circ Physiol 306: H910–H917, 2014. First published January 17, 2014; doi:10.1152/ajpheart.00787.2013.—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 that forehead cooling reduces CBV (i.e., coronary vasoconstriction) and that this vasoconstrictor effect would be enhanced under systemic β-adrenergic blockade. A total of 30 healthy subjects (age range, 23–79 years) underwent Doppler echocardiography evaluation of CBV in response to 60 s of forehead cooling (1°C ice bag on forehead). A subset of subjects (n = 10) also underwent the procedures after 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/s (P < 0.001), whereas mean arterial pressure 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 β-blockade. The results are consistent with sympathetic activation of β-receptor coronary vasodilation in humans, as has been demonstrated in animals.

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 years) and 13 older (5 women, 66 ± 2 years) subjects volunteered to participate and provided written informed consent. All subjects had supine resting blood pressures below 125/80 mmHg and were nonsmokers, and 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 heart rate, 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). Before 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 min of quiet rest. The average baseline brachial artery pressures [systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (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 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 (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 s 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. After baseline hemodynamic and coronary measurements were taken, local forehead cooling was conducted for 60 s, 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 s 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 to 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 effect of aging (young subjects versus older subjects) was determined once all data were collected.

Fig. 1. Representative recording of muscle sympathetic nerve activity (MSNA), arterial blood pressure (BP), heart rate (HR), and coronary blood flow velocity (CBV) obtained simultaneously in 1 young man during Experiment 1. Note that higher levels of MSNA and BP are associated with a reduction in CBV. MAP, mean arterial pressure.
Experiment 2: effect of β-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 (1 in a left antecubital vein and 1 in a right antecubital vein). After baseline measurements in the supine posture were taken, an intravenous infusion of isoproterenol, a nonselective β-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 1 min 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-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 (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 forehead cooling at 1°C raised SBP (8 mmHg, P = 0.001), while causing a modest reduction in HR (Δ = -3 ± 1 beats/min, P < 0.001). CBV was reduced from 19.5 ± 0.7 to 17.5 ± 0.8 cm/s (P < 0.001). As shown in Fig. 1, forehead cooling for 60 s 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 Fig. 2, and it is clear that CBV is reduced

RESULTS

Experiment 1: effect of forehead cooling on CBV. When the entire group of subjects (n = 30) was considered, 60 s of forehead cooling at 1°C raised SBP (Δ = 14 ± 3 mmHg, P < 0.001), DBP (Δ = 8 ± 1 mmHg, P < 0.001), and MAP (Δ = 11 ± 2 mmHg, P < 0.001), while causing a modest reduction in HR (Δ = -3 ± 1 beats/min, P < 0.001). CBV was reduced
Table 1. Effect of aging on hemodynamic and coronary responses to forehead cooling in Experiment 1

<table>
<thead>
<tr>
<th></th>
<th>Young (n = 16)</th>
<th>Older (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Peak</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>104 ± 2</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>60 ± 1</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>76 ± 2</td>
<td>84 ± 2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60 ± 3</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>RPP, beats/min × mmHg</td>
<td>6,309 ± 334</td>
<td>5,948 ± 332</td>
</tr>
<tr>
<td>CBV, cm/s</td>
<td>19.5 ± 0.9</td>
<td>16.8 ± 1.0</td>
</tr>
<tr>
<td>Forehead TS, au</td>
<td>–</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Forehead pain, au</td>
<td>–</td>
<td>4 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Subjects were exposed to 60 s of forehead cooling (1°C ice water bag on forehead) in the supine posture. No differences in coronary blood flow parameters between young (n = 16) and older (n = 13) subjects existed, but older adults had a larger change in mean arterial pressure (MAP). SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate pressure product; CBV, coronary blood flow velocity; TS, thermal sensation. *Difference from young subjects at same time point.

Consistently with forehead cooling, whereas RPP responses are quite variable (6,336 ± 245 beats/min × mmHg at baseline to 6,076 ± 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 ΔMAP response in the older subjects (P = 0.048) and a tendency for ΔDBP to also be greater in the older subjects (P = 0.072).

Experiment 2: effect of β-adrenergic receptor blockade on CBV response to forehead cooling. Systemic infusion of isoproterenol expectedly increased HR (from 60 ± 3 to 92 ± 3 beats/min) in the propranolol group while having no significant effect on MAP. After systemic infusion of propranolol, isoproterenol did not have an effect on HR (from 53 ± 3 to 53 ± 3 beats/min) or MAP (Fig. 3). Thus infusion of propranolol completely antagonized sinoatrial node β-adrenergic receptors.

After 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 β-blockade, forehead cooling caused a slight increase in myocardial oxygen demand albeit from a suppressed baseline level. Despite the increased RPP under propranolol, a reduction in CBV existed (i.e., augmented coronary vasoconstriction; Fig. 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 vs. 0.17 ± 1.1 au; P = 0.147).

Experiment 3: effect of α-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 6,376 ± 521 to 6,344 ± 384; P = 0.945). At this time point, CBV was reduced from 19.7 ± 1.1 to 13.9 ± 0.9 cm/s (P < 0.001). An example recording is shown in Fig. 4.

The lowest HR obtained after 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 5,183 ± 453 (all P < 0.001 vs. baseline). CBV remained at 13.9 ± 0.8 cm/s. 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 β-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 β-adrenergic receptor blockade enhances this vasoconstrictor response. These findings may also be clinically relevant in the context of cold exposure and angina pectoris.

Fig. 3. Tachycardia in response to systemic isoproterenol before (prepropranolol) and after (postpropranolol) systemic β-adrenergic receptor blockade (Experiment 2). Blood pressure was unchanged during these infusions.
forehead cooling and coronary vasoconstriction

Table 2. Effect of propranolol on hemodynamic and coronary responses to forehead cooling in Experiment 2

<table>
<thead>
<tr>
<th>SBP, mmHg</th>
<th>Propranolol Base</th>
<th>Propranolol Peak</th>
<th>Control Base</th>
<th>Control Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>114 ± 2</td>
<td>143 ± 5*</td>
<td>113 ± 2</td>
<td>125 ± 6*</td>
<td></td>
</tr>
<tr>
<td>72 ± 2</td>
<td>88 ± 3*</td>
<td>71 ± 3</td>
<td>78 ± 3*</td>
<td></td>
</tr>
<tr>
<td>86 ± 2</td>
<td>101 ± 3*</td>
<td>85 ± 3</td>
<td>96 ± 4*</td>
<td></td>
</tr>
<tr>
<td>53 ± 2†</td>
<td>50 ± 3</td>
<td>62 ± 3</td>
<td>59 ± 4</td>
<td></td>
</tr>
<tr>
<td>mmHg</td>
<td>6.007 ± 262†</td>
<td>6.708 ± 493†</td>
<td>6.731 ± 363</td>
<td>6.204 ± 534</td>
</tr>
<tr>
<td>CBV, cm/s</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>7 ± 1</td>
<td>–</td>
<td>8 ± 1</td>
<td></td>
</tr>
<tr>
<td>Forehead pain, au</td>
<td>4 ± 1</td>
<td>–</td>
<td>4 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10. Subjects were exposed to 60 s of forehead cooling (1°C ice water bag on forehead) in the supine posture. Studies were conducted after intravenous infusion of propranolol or control (no propranolol). *Significant difference from the respective baseline P < 0.05; †significant difference from control condition at the same time point.

Forehead cooling and coronary vasodilation in Experiment 3. Note that MAP increased, HR decreased, and CBV was reduced in response to systemic phenylephrine.
lol blockade in Experiment 2, this was clearly not an issue because RPP actually increased (Fig. 2, middle).

The ΔMAP response to forehead cooling was ~50% larger under propranolol, although this comparison was not statistically significant. There is a general consensus that blockade of β-adrenergic receptors enhances α-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 nonselective β-blockers are more effective for use in a cold environment (5, 35, 36, 56). Overall, we believe that β-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 α-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 Fig. 2 may stimulate a new area of research in coronary vasoconstriction, whereas most previous studies have focused on coronary vasodilation (41, 42). 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 ΔCBV-to-ARPP ratio complicated (i.e., the calculated slopes of the lines in Fig. 2). The complex interplay between α-adrenergic vasoconstriction, β-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 (14).

Clinical implications. The current study may partly explain why angina pectoris is often triggered by exposure to cold, windy conditions (38, 44). 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 β1-blockers (e.g., metoprolol, atenolol) would be more appropriate because they would leave the coronary vascular β2-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 effector effects of forehead cooling are a rise in sympathetic nerve activity (13, 26), limb vasoconstriction (51), renal vasoconstriction (52), and 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 β-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 β-receptor coronary vasodilation in humans, as has been demonstrated in animals. The concept that β-mediated vasodilation could provide cardioprotection during sympathetic stress warrants future study.

ACKNOWLEDGMENTS

We thank Cheryl Blaha, Jessica Mast, and Todd Nicklas for nursing support; Dr. Michael Herr for engineering support; Anne Muller for preparing the graphics for this study; and Kris Gray and Jen Stoner for administrative guidance.

GRANTS

This work was supported by National Institutes of Health Grants P01 HL-096570, R01 HL-070222, and UL1 TR-000127 (all to L.I. Sinoway) as well as Grant O6 RR016499 and a Wilderness Medical Society Research in Training Grant (to M. D. Muller).

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


