Aortic Hemodynamics and Arterial Stiffness Responses to Muscle Metaboreflex Activation With Concurrent Cold Pressor Test

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BACKGROUND

Overweight/obese young men have increased sympatho-excitation to cold and pain stress-induced by the cold pressor test (CPT) that may lead to abnormal hemodynamic responses. Concurrent CPT and exercise may augment the sympathetic-induced increases in aortic blood pressure (BP), pressure wave reflection (augmentation index, Alx), and arterial stiffness (pulse wave velocity, PWV). Since obesity is related with hypertension and sympathetic activity, we evaluated the aortic hemodynamic and PWV responses to muscle metaboreflex activation imposed by postexercise muscle ischemia (PEMI) concurrent with CPT in overweight/obese men.

RESULTS

During IHG, brachial BP, aortic BP, AP, Alx, Alx@75, P1, and P2 increased (P < 0.01) while Tr decreased (P < 0.05) compared with baseline. During PEMI, all hemodynamic parameters remained elevated (P < 0.05) and baPWV increased (P < 0.05) while Tr and HR returned to baseline. Compared with PEMI, the increases in HR, brachial BP, aortic BP, Alx@75, P1, P2, and baPWV were greater (P < 0.05) during PEMI + CPT. During PEMI + CPT, Tr remained lower (P < 0.05) than baseline.

CONCLUSIONS

Cold exposure with concurrent metaboreflex activation induces a significant increase in aortic hemodynamics and arterial stiffness, which may explain the high risk of adverse cardiovascular events during physiological stress.

CLINICAL TRIALS REGISTRATION

Trial Number NCT02104375

Keywords: aortic hemodynamics; arterial stiffness; blood pressure; cold exposure; hypertension; isometric exercise; wave reflection.

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Overweight and obesity are associated with early arterial dysfunction characterized by increased arterial stiffness (pulse wave velocity, PWV) and central blood pressure (BP) in young people.1,2 Increased PWV promotes a faster return of reflected waves from peripheral arterial sites to the aorta increasing aortic BP.3 Altered arterial function is associated with the development of pre-hypertension and greater cardiovascular risk in young healthy obese men.2 The cold pressor test (CPT) has been extensively used to evaluate sympathetic-mediated BP responses to limb (arm or foot) immersion in cold water.4-7 Previous work indicates that the BP response to CPT is determined by the intensity of cold and pain stress.5,8 Although sympathetic activity is greater during CPT in overweight individuals, peripheral BP reactivity is similar in young overweight and lean adults.1 This disparity may be due to the underestimation of the hypertensive effects of CPT by brachial BP measurements.5,6 In addition, acute cold exposure increases aortic PWV, aortic BP, and pressure wave reflection (augmentation index (Alx)), indices of left ventricular (LV) afterload.6,7,9,10 Interestingly, cold exposure with concurrent physical effort11 could be additive factors for cardiovascular events.12

Submaximal isometric-handgrip exercise (IHG) has been used to evaluate hemodynamic reactivity.13,14 Acute sympathetic stimulation increases aortic BP, Alx, and PWV during IHG.7,13,14 The simultaneous application of 2 stimuli of sympathetic activity such as cold exposure and IHG results in greater increases in aortic Alx and aortic PWV compared to each stimulus alone in young healthy men.10,14 However, an increase in heart rate (HR) during IHG may attenuate the increase in Alx due to an inverse relationship between HR and pressure wave reflection.15

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Alternatively, cardiovascular responses to metaboreflex activation can be isolated using postexercise muscle ischemia (PEMI) by trapping metabolites released from the previously exercised muscle through circulatory occlusion. PEMI maintains the vascular sympathetic stimulation observed during IHG with a simultaneous HR recovery. Therefore, HR recovery allows for a further increase in AIx during PEMI in young healthy men. Previous studies have shown increases in central BP, AIx, and leg PWV during PEMI in young healthy adults. Evidence suggests that despite a similar peripheral pressor response, obese young males have an altered hemodynamic response during PEMI. Since aortic BP and AIx are more sensitive to physiological stimuli and pathophysiologically relevant than peripheral BP, elucidation of cardiovascular responses to acute sympathetic stimulation induced by muscle metaboreflex activation with concurrent cold exposure in overweight/obese individuals is of clinical importance.

The aim of the present study was to evaluate acute aortic hemodynamic and PWV responses to PEMI with and without CPT in overweight/obese men. We hypothesized that PEMI with CPT would evoke greater increases in central BP, wave reflection, and PWV than during PEMI alone.

**METHODS**

**Participants**

Sixteen overweight or obese (body mass index >25 and <40 kg/m²) young men (18–35 years of age) volunteered to participate in this study. All participants were healthy (assessed by medical history), nonsmokers, and sedentary (defined as <120 min/week of moderate–intensity exercise) at least 6 months preceding the study. Participants were asked to maintain their normal diet and exercise habits during the study period. Candidates were excluded from the study if they had a brachial systolic BP (SBP) ≥140 mm Hg, overt chronic diseases, or were taking any supplement that could affect the outcome variables. The study was approved by the Human Subjects Committee of Florida State University and all participants gave their informed consent before data collection.

**Experimental protocol**

After completion of initial screening, participants were familiarized with the study procedures. Height, weight, and waist circumference were assessed and brachial BP was measured after a 5-minute rest in the supine position. Maximal voluntary contraction for the IHG exercise was determined using the highest of 3 attempts separated by 1 minute. Measurements were conducted in the morning after 8 hours of an overnight fast in order to avoid potential diurnal variations in BP and vascular reactivity. The participants refrained from caffeine and alcohol-containing beverages and from heavy or unusual physical activity during the previous 12 and 24 hours, respectively. All cardiovascular measurements were evaluated in a quiet temperature-controlled room (22–24 °C).

Experiments were conducted at least 24 hours following a familiarization session. The participants rested in the supine position for 15 minutes before resting data collection. Following 5 minutes of resting measurements, participants were asked to perform 2 trials in a randomized order. In 1 trial, IHG was followed by a 3-minute PEMI without CPT. Following a 20-minute recovery period and resting measurements, participants were asked to perform IHG exercise followed by a 3-minute PEMI concurrently with CPT (PEMI + CPT). Cardiovascular parameters were collected in duplicate at rest and during IHG and PEMI or PEMI + CPT, except that PWV was measured at rest and PEMI or PEMI + CPT.

**Isometric-handgrip exercise and postexercise muscle ischemia test**

Isometric-handgrip exercise was performed at 30% of maximal voluntary contraction for 2 minutes using a handgrip dynamometer (Lafayette Instrument, Lafayette, IN). Participants had visual feedback to maintain their target force during the test. Participants also received verbal encouragement throughout the test. Ten seconds before the cessation of IHG, a cuff positioned proximally on the exercising forearm was rapidly inflated to suprasystolic levels (200 mm Hg or at least 50 mm Hg above the systolic BP during IHG) for 3 minutes using an automated pneumatic device (Hokanson E20; Bellevue, CA). Brachial BP and pressure waves were recorded during the last minute of the IHG and PEMI.

**Cold pressor test**

The left foot of the participants was passively immersed in ice-water (4 °C) to a point just above the ankle for 3 minutes during the PEMI + CPT trial. Participants were instructed to maintain a constant rate and depth of breathing throughout the experiment.

**Pulse wave velocity**

PWV was measured using an automatic device (VP-2000; Omron Healthcare, Vernon Hills, IL). BP cuffs were placed around the right arm (brachial artery) and ankle (posterior tibial artery) to obtain BP and brachial-ankle PWV (baPWV). The baPWV is considered an accurate and reliable measurement of systemic arterial stiffness. PWV was measured as the time a pulse takes to travel from the arm sensor to the ankle sensor, divided by the distance between the sensors (expressed in meters per second (m/s)). The brachial and ankle arterial waveforms were measured concurrently by cuff sensors and the transient time was calculated automatically by relating the foot of the forward wave to the R-wave of the electrocardiogram. The distance between sampling points was calculated automatically according to the height of the participants. BaPWV was not measured during IHG due to difficulty to collect pulse waveforms in the exercising arm. HR was measured from the electrocardiogram.

**Pulse wave analysis**

Brachial SBP and diastolic BP (DBP) were recorded using an automatic device (VP-2000; Omron Healthcare, Vernon Hills, IL).
Hills, IL). Brachial SBP and DBP were used to calibrate radial waveforms obtained from a 10-second epoch using a high-fidelity tonometer (SPT-301B; Millar Instruments, Houston, TX). Aortic waveforms were derived using a generalized transfer function (SphygmoCor; AtCor Medical, Sydney, Australia). The aortic wave is composed of a forward wave (P1), caused by the stroke volume, and a reflected wave (P2) that returns to the aorta from peripheral arteries.23 The AIx is defined as the augmented pressure (AP = P2 − P1) and expressed as a percentage of the aortic PP. AIx was normalized to a HR of 75 beats per minute (AIx@75) since it is negatively influenced by HR.24 Transit time of the reflected wave (Tr) indicates the round-trip travel of the forward wave to the peripheral arteries and back to the aorta. AIx and Tr have been used as markers of wave reflection and aortic stiffness, respectively.25 Two high-quality measurements (operator index ≥ 80%) were collected and the average was used in the analysis. In our laboratory, the intraclass correlation coefficient for aortic hemodynamics calculated on 2 separate days is ≥ 0.94.

**Anthropometrics**

Height was measured using a stadiometer to the nearest 1 cm, and body weight was measured using a Seca Scale (Sunbeam Products, Boca Raton, FL) to the nearest 0.1 kg. Body mass index was calculated as kg/m². Waist circumference was measured at the superior border of the iliac crest using a nonelastic tape measure to the nearest 1 cm.

**Statistical analysis**

Normal distribution of the data was examined with the Shapiro–Wilk test. Possible differences at rest between trials were analyzed by independent samples t-test. Analysis of variance with repeated measures was used to test the effect of conditions (rest, IHG, PEMI) and trials (PEMI with and without CPT) on cardiovascular parameters. When analysis of variance produced a significant condition-by-trial interaction, paired t-tests and Tukey’s test were used for post hoc comparisons. A statistical significance was defined as P < 0.05. All statistical analyses were performed using SPSS, version 21 (SPSS, Chicago, IL).

**RESULTS**

**Subject characteristics**

All data are presented as mean ± SE. Age, height, weight, body mass index, and waist circumference of the participants are shown in Table 1. Cardiovascular parameters at rest, IHG, and PEMI in both trials are shown in Table 2. There were no significant differences in all the variables at rest between the trials.

| Table 1. Study participant characteristics (n = 16) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Age, years      | Height, m       | Weight, kg      | Body mass index, kg/m² | Waist circumference, cm |
|                 | 23.7 ± 1.7      | 1.72 ± 0.01     | 86.8 ± 3.7      | 29.3 ± 1.1         | 98 ± 3          |
| Data are mean ± SE. |

| Table 2. Cardiovascular parameters at rest and during the experimental trials (n = 16) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Rest            | IHG            | PEMI            | Rest            | IHG            | PEMI + CPT     |
|                 | HR (beats/min)  | 63 ± 2         | 74 ± 2¹         | 62 ± 2          | 61 ± 2         | 72 ± 3¹        | 70 ± 1,a       |
|                 | bSBP (mm Hg)    | 123 ± 3        | 143 ± 4¹        | 135 ± 2²        | 122 ± 2        | 140 ± 3¹       | 145 ± 2,b       |
|                 | bDBP (mm Hg)    | 68 ± 2         | 76 ± 3¹         | 72 ± 2²         | 67 ± 1         | 76 ± 2¹        | 81 ± 2,b       |
|                 | bMAP (mm Hg)    | 89 ± 2         | 102 ± 4¹        | 98 ± 2²         | 88 ± 2         | 106 ± 3¹       | 109 ± 2,b       |
|                 | bPP (mm Hg)     | 55 ± 2         | 67 ± 4¹         | 63 ± 2²         | 55 ± 2         | 64 ± 3¹        | 64 ± 2¹        |
|                 | aDBP (mm Hg)    | 68 ± 2         | 78 ± 3¹         | 77 ± 2²         | 69 ± 1         | 77 ± 2¹        | 84 ± 2,a       |
|                 | aMAP (mm Hg)    | 84 ± 2         | 100 ± 3¹        | 96 ± 2²         | 84 ± 1         | 98 ± 3¹        | 105 ± 3,a       |
|                 | aPP (mm Hg)     | 36 ± 1         | 46 ± 3¹         | 43 ± 2²         | 36 ± 1         | 45 ± 2²        | 48 ± 3¹        |
|                 | AP (mm Hg)      | 2.5 ± 0.8      | 9.1 ± 1.2¹      | 9.4 ± 2.1²      | 2.1 ± 0.9      | 8.1 ± 1.1¹     | 11.1 ± 1.9¹    |
|                 | AIx (%)         | 7.9 ± 1.7      | 18.9 ± 2.7¹     | 18.4 ± 3.5²     | 6.7 ± 2.2      | 16.1 ± 2.2²    | 20.7 ± 3.3¹    |
|                 | Tr (ms)         | 168 ± 5        | 155 ± 6²        | 159 ± 6         | 166 ± 5        | 155 ± 5⁴       | 148 ± 5⁴       |

Data are mean ± SE. Abbreviations: aDBP, aortic diastolic blood pressure; aMAP, aortic mean arterial pressure; AP, augmentation pressure; aPP, aortic pulse pressure; AIx, augmentation index; bDBP, brachial diastolic blood pressure; bMAP, brachial mean arterial pressure; bPP, brachial pulse pressure; bSBP, brachial systolic blood pressure; CPT, cold pressor test; HR, heart rate; IHG, isometric-handgrip exercise; PEMI, postexercise muscle ischemia; Tr, reflection time.

P* < 0.05, P† < 0.01 different than rest; P0 < 0.05, P‡ < 0.01 different than PEMI.
Cold Exposure, Hemodynamics, and Arterial Stiffness

In accordance with previous studies in young healthy non-obese adults, we showed that an acute bout of IHG increases brachial SBP (~19 mm Hg), aortic SBP (~18 mm Hg), AIx (~10%), and HR (~11 bpm). During IHG, increased sympathetic activity causes vasoconstriction and a faster return of the reflected wave back to the aorta. The earlier arrival of the reflected wave during late systole

Acute Hemodynamics

During IHG, brachial BP, aortic BP, AP, AIx, AIx@75 (Figure 1B), P1 (Figure 1C), and P2 (Figure 1D) increased (P < 0.01) while Tr decreased (P < 0.05) similarly in both trials compared to resting values. During PEMI, all hemodynamic parameters remained elevated (P < 0.05) compared with resting values while the HR and Tr returned to their resting values. BaPWV increased during PEMI (P < 0.05, Figure 2) compared to its resting value.

During PEMI + CPT, HR increased (P < 0.01) and Tr decreased (P < 0.05) compared with the resting value and PEMI. The increases in brachial SBP, DBP, and mean arterial pressure (P < 0.01); aortic SBP (Figure 1A), DBP, and mean arterial pressure (P < 0.01); AIx@75 (P < 0.01, Figure 1B), P1 (P < 0.01, Figure 1C), P2 (P < 0.01, Figure 1D), and baPWV (P < 0.05, Figure 2B) were greater during PEMI + CPT compared with PEMI. The increases in AP and AIx during PEMI were similar in both trials.

DISCUSSION

In the present study, local cold exposure using CPT concurrently with muscle metaboreflex activation (PEMI + CPT) amplified the increases in BP (peripheral and central), pressure wave amplitude (forward and reflected), and baPWV, while preventing HR recovery when compared to PEMI without CPT.

In accordance with previous studies in young healthy non-obese adults, we showed that an acute bout of IHG increases brachial SBP (~19 mm Hg), aortic SBP (~18 mm Hg), AIx (~10%), and HR (~11 bpm). During IHG, increased sympathetic activity causes vasoconstriction and a faster return of the reflected wave back to the aorta.
leads to increased LV afterload indicated by augmented aortic SBP and AIx resulting in increased myocardial oxygen demand.\textsuperscript{3,21}

Muscle metaboreflex activation was achieved by means of PEMI to maintain sympathetic-mediated vasoconstriction above resting levels but similar to that observed during IHG.\textsuperscript{15,17,24} We demonstrated that during PEMI, brachial BP, aortic BP, and pressure wave parameters were kept elevated, whereas HR returned to resting levels owing to a baroreflex-mediated cardiovagal reactivation and absence of central command.\textsuperscript{15} It has been previously shown that sympathetic stimulation induced by PEMI evokes further increases in aortic SBP and AIx compared to IHG.\textsuperscript{13,16} In this regard, we found that aortic SBP and AIx remained significantly elevated when compared with baseline but there were no additional increases during PEMI, which is in contrast to previous reports in non-obese individuals.\textsuperscript{13,16} These attenuated aortic hemodynamic responses may be attributed to a diminished muscle sympathetic nerve activity during PEMI reported in young overweight women.\textsuperscript{25} It is possible that increased intramuscular fat reduces metaboreceptor sensitivity during PEMI,\textsuperscript{25} which can be restored after weight loss in obese adults.\textsuperscript{24}

In the present study, CPT was applied concurrently with PEMI in order to evaluate the cardiovascular responses to the additive sympathetic stimuli. In previous studies, CPT increased aortic SBP, AIx, and aortic PWV in young normotensive adults.\textsuperscript{5,6,14} Furthermore, Geleris et al.\textsuperscript{14} showed greater increases in aortic AIx and aortic PWV during simultaneous CPT and IHG than either condition alone. Unlike Geleris et al.,\textsuperscript{14} we used CPT during PEMI as this maneuver maintains the exercise pressor response active without the stimulatory influence of the “central command” on HR.\textsuperscript{15} Accordingly, we found that aortic BP and wave reflection magnitude (P2) were significantly higher during PEMI + CPT than PEMI alone, suggesting an additional sympathetic-mediated vasoconstriction. However, AP and AIx responses were not significantly affected by the addition of CPT to PEMI. In contrast, Geleris et al.\textsuperscript{14} showed that the combined effect of IHG and CPT imposed a greater increase in AIx compared to either condition alone. Possible factors that may explain this discrepancy are changes in HR, P1, and P2. The inverse relationship between HR and AIx is well known.\textsuperscript{22} An unresponsive HR during CPT at 4 °C\textsuperscript{5,6,14} and an increased HR during IHG\textsuperscript{13} are common findings in young non-obese adults.\textsuperscript{6,13} Thus, unchaged HR during the concurrent performance of CPT and IHG\textsuperscript{14} may explain a greater increase in AIx. We found an elevated HR during PEMI + CPT whereas HR returned to baseline during PEMI without CPT, as it has been reported in healthy men.\textsuperscript{13} We speculate that the increased HR induced by the additive sympathetic stimulus (CPT) prevented a further increase in AIx during PEMI + CPT. Moreover, we observed that both P1 (influenced by stroke volume and aortic stiffness)\textsuperscript{26} and P2 (influenced by peripheral vasoconstriction) were higher during PEMI + CPT compared to PEMI, suggesting increased LV contractility and vascular tone.\textsuperscript{5,21} Interestingly, adjusting AIx for HR reveals an increased Alx@75 with the addition of CPT to PEMI. Our findings suggest that CPT induces an exaggerated LV afterload (aortic SBP) due to augmented wave reflection during PEMI.

Obesity is associated with increased sympathetic activity\textsuperscript{27} and elevated central\textsuperscript{4} and peripheral\textsuperscript{12} PWV in young adults. We examined baPWV because it is strongly associated with aortic PWV,\textsuperscript{20} peripheral (arms and legs) PWV,\textsuperscript{21} and abdominal adiposity.\textsuperscript{28} In the present study, baPWV was significantly increased by 1.1 m/s during PEMI and the addition of CPT further increased baPWV to 1.8 m/s. In healthy young adults, Davies et al.\textsuperscript{17} observed that leg PWV increased by 0.9 m/s during PEMI. Moreover, a similar increase in aortic PWV has been reported during CPT,\textsuperscript{7,14} which corresponds to the difference in baPWV between PEMI and PEMI + CPT. Although we did not measure the main arterial segments in baPWV (aortic and leg),\textsuperscript{20} the time for wave reflection (Tr) and P1 are related with aortic stiffness.\textsuperscript{26,29} In the present study, Tr was reduced only during PEMI + CPT, which supports the increase in aortic PWV previously observed in young men during CPT and CPT + IHG.\textsuperscript{7,14} Thus, the greater increase in P1 during PEMI + CPT could be attributed to the ejection of stroke volume into a stiffer aorta.\textsuperscript{21,26} This excessive increase in systemic arterial stiffness imposed by PEMI and CPT\textsuperscript{7,17} causes an increase in reflected wave amplitude (P2) and aortic SBP.\textsuperscript{29} Previous findings have suggested that increased sympathetic reactivity to CPT in young overweight normotensive adults may precede the development of hypertension,\textsuperscript{4} which can be predicted by baPWV.\textsuperscript{30} Although early arterial alterations occur in young overweight men, increased resting peripheral and central BP at the pre-hypertensive level is evident only in the obese.\textsuperscript{2}

Continuous cold-induced hypertensive response may lead to hypertension and myocardial hypertrophy in rats.\textsuperscript{31} In humans, exercise-induced hypertension has been implicated in stress-induced takotsubo cardiomyopathy.\textsuperscript{32} Sympathetic hyperactivity has been proposed as a mechanism responsible for acute stress cardiomyopathy. Increased catecholamine secretion induced by CPT has been shown to reproduce typical features (abnormal LV wall motion and coronary blood flow) of takotsubo cardiomyopathy in patients who recovered from a previous episode.\textsuperscript{29} During CPT at 4 °C, pain can be perceived as painful or very painful.\textsuperscript{7,33} Intense pain and skin cooling increase BP during CPT due to enhanced sympathetic activity.\textsuperscript{8} However, the vascular reactivity to CPT is not uniform and greater pain sensation contributes to an exaggerated BP response in hyper-reactors (increase in SBP or DBP >15 mm Hg).\textsuperscript{7} Previous studies have shown that simultaneous exposure to exercise-related metabolites and pain-cold stimuli impose an additional increase in LV afterload and myocardial work in healthy adults,\textsuperscript{10,14} which is consistent with our findings. In cardiac patients, acute physiological stress induced by exercise, pain, and cold stimuli can increase LV afterload and decrease coronary blood flow leading to adverse cardiac responses.\textsuperscript{11,32,33} The magnitude of the increases in aortic SBP, AIx, and baPWV observed during PEMI + CPT, if maintained chronically, may increase the risk for cardiovascular events by 9%, 32%, and 12%, respectively.\textsuperscript{34,35} Therefore, our findings suggest that cold exposure after isometric exercise may confer a greater risk.
for cardiac events by increasing LV afterload in overweight/obese adults.2,3,6

The present study has some limitations. First, the sample size was relatively small; however, it was appropriate to detect differences in hemodynamic responses to Pemi with and without CPT. Second, our study evaluated hemodynamic parameters in healthy overweight/obese men free of overt cardiovascular diseases and therefore we cannot generalize our results to other populations. Inclusion of young lean men for comparisons would have strengthened our study. Third, hemodynamic responses to CPT may differ from environmental conditions that predispose cardiovascular events during and following exercise. Fourth, we did not measure aortic PWV, the gold standard marker of aortic stiffness. However, baPWV and aortic PWV are highly associated, and thus, baPWV has been recognized as a marker of central arterial stiffness. Moreover, baPWV also includes peripheral arteries which are more affected by obesity in young men.2 Last, we did not perform wave separation analysis that provides the amplitudes of the forward and backward waves.

In conclusion, metaboreflex activation concurrent with CPT induces a significant increase in cardiac afterload and systemic arterial stiffness which may be of clinical importance in healthy young overweight and obese individuals. Further studies are needed to understand these vascular responses in obese adults with hypertension.

DISCLOSURE

The authors declare no conflict of interest.

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