Depressive Symptoms Contribute to Increased Wave Reflection During Cold Pressor Test in Young Adult Men

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BACKGROUND
Major depressive disorder (MDD) is associated with increased cardiovascular risk. Although cardiovascular hyperactivity to stressors (e.g., cold pressor test (CPT)) is common in those with MDD, the aortic hemodynamic (AH) responses to sympatho-stimulation in healthy individuals with higher depressive scores (HDS) are not well understood. We hypothesized that individuals with HDS, compared with those with low depressive scores (LDS), would have greater changes in AH during the CPT.

METHODS
Thirty-five male participants (mean age, 22.3 ± 0.7 years) completed a self-report measure of depressive symptoms and were classified as having an HDS or LDS. Radial waveforms were then obtained by means of applanation tonometry. The testing protocol consisted of a 10-minute seated rest, 5 minutes of baseline measurements, a 3-minute CPT, and a 3-minute recovery period.

RESULTS
At baseline, no differences were found between the LDS (n=16) and HDS (n=19) groups on any variables studied. During CPT, there was a significant group-by-time interaction for aortic mean blood pressure (HDS vs. LDS = 107 ± 3 mm Hg vs. 96 ± 3 mm Hg; P = 0.008); augmentation index (HDS vs. LDS =19% ± 3% vs. 11% ± 2%; P = 0.02), a surrogate of wave reflection; and systolic time interval (HDS vs. LDS = 2295 ± 78 mm Hg/s.min−1 vs. 1919 ± 74 mm Hg/s.min−1; P = 0.001), a marker of myocardial work, such that the HDS group had significantly higher responses than the LDS group.

CONCLUSIONS
HDS may be associated with cardiac hyperactivity during sympatho-stimulation, contributing to increased central blood pressure, wave reflection, and myocardial work. Prospective studies to unveil mechanisms explaining increased AH in healthy individuals with high depressive symptomatology are warranted.

Keywords: aortic hemodynamics; augmentation index; blood pressure; cold pressor test; hypertension; major depressive disorder; pulse wave analysis.

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Major depressive disorder (MDD), a major cause of disability worldwide, is associated with the development of adverse cardiovascular outcomes, including hypertension, increased left ventricular mass, coronary artery disease, arrhythmias, stroke, and myocardial infarction.1–4 Although converging evidence demonstrates that patients with MDD are at increased cardiovascular risk,1,2 the specific underlying mechanisms that account for this association remain elusive. However, it has been suggested that increased wave reflection (augmentation index (AI)) and arterial stiffness, as well as dysautonomia, may play a pivotal role.5–7

Previous research has shown that increased cardiovascular reactivity, defined as an exaggerated blood pressure (BP) and heart rate response (HR) to laboratory stressors (e.g., mental stress, cold pressor test (CPT)), can predict the development of hypertension and coronary artery disease.8–10 However, studies that have examined the association between depressive symptoms and cardiovascular hyperactivity provide conflicting and, in some instances, hard-to-interpret results. A recent line of studies has demonstrated that cardiovascular reactivity is blunted in patients with major depression, which may be a reflection of dysautonomia.11–13 In contrast, depressive symptoms have been shown to be associated with cardiac hyperactivity.14–16 Taken together, these studies seem to suggest that cardiac hyperactivity may well be an early manifestation of impaired autonomic modulation and increased hemodynamics, which may ultimately lead to cardiovascular disease. This is clinically important because subclinical depression, defined as some depressive symptoms without meeting the criteria for MDD,17 may have a deleterious effect on cardiovascular autonomic modulation and hemodynamics even in the absence of hypertension. Although the CPT has been widely used as a laboratory stressor to evaluate vascular function, the aortic hemodynamic responses, including the AI, in healthy subjects with different depression scores are poorly understood. Casey et al.18 demonstrated
that the CPT increases peripheral (brachial) BP and central (aortic) BP, as well as the AI, in healthy young adults. The acute hypertensive effects of the CPT are linked to increases in sympathetic nervous system (SNS) activity, which in turn increases vascular tone and, ultimately, afterload.\textsuperscript{18–21} Interestingly, during the CPT the increase in aortic BP is higher than the increase in brachial BP, suggesting that aortic BP may be a more sensitive marker of cardiac responsiveness. In fact, markers of pulse wave analysis, including the AI and aortic systolic BP (ASBP), have been shown to be superior markers of cardiovascular disease in comparison to brachial BP.\textsuperscript{22,23} It is therefore reasonable to propose the use of pulse wave analysis as a viable clinical assessment tool to evaluate the hemodynamic responses to the CPT in healthy individuals varying in depressive scores.

Accordingly, the aim of this study was to examine the association between depressive symptoms and the aortic hemodynamic responses to SNS stimulation by means of the CPT in healthy, young adult men. We hypothesized that individuals with higher depressive scores (HDS), compared with those with low depressive scores (LDS), would have a greater increase in BP and AI during the CPT.

METHODS

Subjects

Thirty-five apparently healthy, young adult men (aged 20–36 years) were enrolled in this study. Participants were not smokers or regular exercisers (defined as >120 minutes per week) in the previous 6 months of the study. Participants were excluded from the study if they had hypertension (BP ≥140/90 mm Hg) or chronic diseases or were taking medications (e.g., beta blockers, antidepressants, and stimulants) that could affect the outcome variables. Participants were asked to abstain from caffeine, alcohol, and strenuous physical activity for at least 24 hours before testing. All participants were recruited from a university sample and gave their written consent prior to the experiments, as approved by the Florida State University Institutional Review Board.

Study design and experimental protocol

Participants were first introduced to the study procedures and familiarized with the laboratory setting. Anthropometrics and arm circumference (for BP cuff selection) were then measured, and participants filled out a health questionnaire indicating their physical and health history in addition to a test assessing depressive symptoms.

Data collection was conducted in the afternoon after at least a 4-hour postprandial period in a quiet, temperature-controlled (23 ± 1 °C) room with dimmed lighting and at the same time of the day (±2 hours) to minimize potential circadian variations in vascular reactivity. Before the CPT, participants completed a self-report measure of depressive symptoms. Participants were seated and then given a 10-minute rest before any baseline measurements were performed. Within 5 minutes after the rest period, baseline measurements for brachial BP and applanation tonometry were performed. Immediately following the baseline measurements, participants completed the CPT by submerging their hand in cold water (4 °C) for 3 minutes to evoke SNS stimulation and increased hemodynamics.\textsuperscript{18,21} During the CPT, a research assistant made sure the participant kept their hand in the water throughout the entire task. BP and applanation tonometry measurements were obtained between 2 and 3 minutes of the CPT.

After the CPT, participants were told to remove their hand from the cold water; a 3-minute recovery period followed. BP measurements followed directly by hemodynamics measurements were taken within 2–3 minutes from the start of the recovery period. All recovery period measurements ended after 3 minutes.

Anthropometrics

Height was measured using a stadiometer to the nearest 0.5 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 kilograms per square meter.

Depression scale

Depressive symptoms were measured the same day the participant came into the lab using the 10-item Center for Epidemiologic Studies Depression Scale.\textsuperscript{24,25} The Center for Epidemiologic Studies Depression Scale has been widely used as a stable nondiagnostic measure of chronic depressive symptoms. Responses were summed into 1 overall score, with a possible range of 0–30. Prior studies involving the longer 20-item version of this scale have used an estimate of the top quintile of scores to define participants as “depressed,” and a validation study found that a score of 16 or higher (approximately the upper quintile) had 99% sensitivity in identifying acute depression.\textsuperscript{26,27} Using the median split approach, we classified the participants with a score of ≥6 as having a HDS and those with <6 as having a LDS.

Cardiovascular measurements

Vascular function and aortic hemodynamics were obtained using brachial BP and applanation tonometry. Brachial BP and applanation tonometry were obtained in duplicates at each time point.

Pulse wave analysis

Brachial BP was recorded using an automated oscillometric device (HEM-705CP; Omron Healthcare, Vernon Hill, IL). Brachial systolic BP and diastolic BP were used to calibrate radial waveforms obtained from a 10-second epoch using a high-fidelity tonometer (SPT-301B; Millar Instruments, Houston, TX). Aortic BP waveforms were derived using a generalized transfer function (SphygmoCor; AtCor Medical, Sydney, Australia). The aortic BP wave comprises a forward wave (P1) caused by stroke volume ejection and a reflected wave (P2) that returns to the aorta from peripheral sites.\textsuperscript{28} The AI is defined as the augmented pressure (AP = P2 − P1) expressed as a percentage of the aortic pulse pressure. Transit
time of the reflected wave (Tr) indicates the roundtrip travel of the forward wave to the peripheral reflecting sites and back to the aorta. Because AI is influenced by HR, it was adjusted at 75 bpm (AI @ 75).\textsuperscript{29} HR was obtained from the time between pulse waveforms. Additional calculations derived from the synthesized aortic pressure wave were the systolic pressure time interval (STI) and the diastolic pressure time interval (DTI), which have been shown to be indicators of left ventricular work as well as myocardial oxygen consumption and coronary perfusion respectively.\textsuperscript{30} The subendocardial viability index (SVI) was obtained from the ratio of DTI to STI expressed as a percentage of subendocardial perfusion.\textsuperscript{30} Only high-quality measurements (>80% operator index) were considered for analysis.

Statistics

Differences in subject characteristics and cardiovascular variables at baseline between participants classified as having either an HDS or an LDS were analyzed with independent samples t tests. A 2 × 3 mixed design analysis of variance with repeated measures was used to determine differences across time and group ((HDS vs. LDS) × (baseline vs. CPT vs. recovery period)) on cardiovascular variables. When significant interactions were found, the Fisher Least Significant Difference (LSD) test was used for pairwise comparisons. The difference between the peripheral and central systolic BP response to the CPT within each group was analyzed using a Student t test. Statistical significance was accepted at P < 0.05. All statistical analyses were performed using SPSS version 19 (SPSS, Chicago, IL).

RESULTS

All data are presented as mean ± SEM. The subject characteristics were aged 22.3 ± 0.7 years, had a height of 1.78 ± 0.17 m, had a weight of 82.2 ± 2.6 kg, and had a body mass index of 22.7 ± 0.7 kg/m\textsuperscript{2}. All subjects completed the study: 19 were classified as having an HDS, whereas 16 were classified as having an LDS. We did not identify any individuals with scores indicative of MDD. There were no significant differences (P > 0.05) between the HDS and LDS groups in subject characteristics (Table 1) and cardiovascular parameters at baseline (Table 2). The analysis of variance revealed significant group-by-time interactions for brachial systolic BP (Figure 1a) (P = 0.02), brachial diastolic BP (Figure 1b) (P = 0.005), brachial mean arterial pressure (P = 0.008), ASBP (Figure 1c) (P = 0.003), aortic diastolic BP (Figure 1d) (P = 0.004), aortic mean arterial pressure (P = 0.008), AI (Figure 2a) (P = 0.02), AI @ 75, P1 (Figure 2b) (P = 0.007), P2 (Figure 2c) (P = 0.005), and STI (Figure 2d) (P = 0.001) values, but HR (P = 0.44), augmented pressure (P = 0.06), Tr (P = 0.19), ejection duration (P = 0.58), DTI (P = 0.09), and SVI (P = 0.233) differences were not significant. Follow-up univariable contrasts revealed significant differences (P < 0.05) at CPT such that brachial systolic BP, brachial diastolic BP, brachial mean arterial pressure, ASBP, aortic diastolic BP, aortic mean arterial pressure, AI, AI @ 75, P1, P2, and STI values were higher in the HDS group than the LDS group (Table 2). The change from baseline to CPT in central BP (ASBP = 31%) was higher (P = 0.04) compared with the change in peripheral BP (brachial systolic BP = 24%) in the HDS group. There were no significant interactions or significant differences (P > 0.05) at recovery between the groups in any of the cardiovascular parameters.

DISCUSSION

We sought to evaluate the acute BP and aortic hemodynamic responses to SNS stimulation in healthy, young adult men that varied in depressive symptoms. Accordingly, the novel findings of this study are that, during the CPT, individuals with more depressive symptoms (HDS) have higher BP (brachial and aortic), wave reflection, and STI than those with lower depressive symptoms (LDS). These findings suggest that higher depressive symptoms may be associated with hyperactive hemodynamic responses to stress by augmenting left ventricular afterload and, ultimately, myocardial oxygen consumption. Although both groups showed increased hemodynamics during the CPT, as hypothesized, we found significant differences in cardiovascular responses during the CPT between the HDS and LDS groups. In a group of 15 healthy, young adults, Casey et al.\textsuperscript{18} showed that a 3-minute CPT increased brachial BP, aortic BP, AI, and SVI. Similarly, Geleris et al.\textsuperscript{31} demonstrated that the CPT induced increases in brachial BP, AI, and arterial stiffness (pulse wave velocity). In accordance with the above-mentioned studies, our results demonstrate that the CPT evokes increases in peripheral BP and central BP, as well as wave reflection. Taken together, these results suggest that brachial BP may underestimate cardiovascular responses to SNS stimulation, and hence evaluation of pulse wave analysis in individuals with varying depression scores may be a more sensitive screening tool for identifying those that may be at increased cardiovascular risk.

Recent epidemiological evidence suggests that MDD is associated with increased cardiovascular adverse outcomes even in the absence of hypertension.\textsuperscript{1–4} However, the association between adverse cardiovascular functioning and depressiveness remains poorly understood. It has been proposed that altered autonomic modulation and increased hemodynamics may be early indicators of SNS hyperactivity in those individuals with high depression symptoms.\textsuperscript{14–16} For instance, Light et al.\textsuperscript{14} reported that healthy women with depressive symptomatology showed higher cardiac hyperactivity, increased brachial BP, and increased plasma norepinephrine to laboratory stressors compared with those with low depression symptomatology. Similarly, we observed

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>HDS (n = 19)</th>
<th>LDS (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.76 ± 0.13</td>
<td>1.73 ± 0.20</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.6 ± 4.0</td>
<td>82.6 ± 3.6</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>25.7 ± 0.1</td>
<td>25.9 ± 0.2</td>
</tr>
<tr>
<td>Age, years</td>
<td>22.0 ± 0.9</td>
<td>22.3 ± 0.6</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. Abbreviations: BMI, body mass index; HDS, high depression score; LDS, low depression score.
### Table 2. Hemodynamic responses to cold pressor test (4ºC) between HDS and LDS groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>HDS (n = 19)</th>
<th>LDS (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>CPT</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65 ± 3</td>
<td>69 ± 3****</td>
</tr>
<tr>
<td>BSBP, mm Hg</td>
<td>112 ± 2</td>
<td>139 ± 4***</td>
</tr>
<tr>
<td>BDBP, mm Hg</td>
<td>70 ± 2</td>
<td>91 ± 3***</td>
</tr>
<tr>
<td>BMAP, mm Hg</td>
<td>82 ± 1</td>
<td>107 ± 3***</td>
</tr>
<tr>
<td>ASBP, mm Hg</td>
<td>96 ± 2</td>
<td>126 ± 4***</td>
</tr>
<tr>
<td>ADBP, mm Hg</td>
<td>71 ± 2</td>
<td>93 ± 3***</td>
</tr>
<tr>
<td>AMAP, mm Hg</td>
<td>82 ± 2</td>
<td>107 ± 3***</td>
</tr>
<tr>
<td>AP, mm Hg</td>
<td>1 ± 1</td>
<td>7 ± 1***</td>
</tr>
<tr>
<td>AI, %</td>
<td>3 ± 2</td>
<td>19 ± 3***</td>
</tr>
<tr>
<td>AI @ 75, %</td>
<td>-2 ± 2</td>
<td>16 ± 2***</td>
</tr>
<tr>
<td>P1, mm Hg</td>
<td>95 ± 2</td>
<td>119 ± 3***</td>
</tr>
<tr>
<td>P2, mm Hg</td>
<td>95 ± 2</td>
<td>126 ± 4***</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>150 ± 3</td>
<td>139 ± 2***</td>
</tr>
<tr>
<td>ED, ms</td>
<td>271 ± 5</td>
<td>282 ± 4***</td>
</tr>
<tr>
<td>STI, mm Hg/(s.min⁻¹)</td>
<td>1592 ± 57</td>
<td>2295 ± 78*****</td>
</tr>
<tr>
<td>DTI, mm Hg/(s.min⁻¹)</td>
<td>3357 ± 70</td>
<td>4157 ± 152***</td>
</tr>
<tr>
<td>SVI, %</td>
<td>215 ± 9</td>
<td>185 ± 8***</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

Abbreviations: ADBP, aortic diastolic blood pressure; AI, augmentation index; AI @ 75, augmentation index adjusted at 75 bpm; AMAP, aortic mean arterial pressure; AP, augmented pressure; ASBP, aortic systolic blood pressure; BDBP, brachial diastolic blood pressure; BMAP, brachial mean arterial pressure; BSBP, brachial systolic blood pressure; CPT, cold pressor test; DTI, diastolic time interval; ED, systolic ejection duration; HDS, high depressive score; HR, heart rate; LDS, low depressive score; P1, first systolic peak pressure; P2, second systolic peak pressure; Tr, reflection time; STI, systolic time interval; SVI, subendocardial viability index.

*P < 0.05; **P < 0.01 different than LDS; ***P < 0.05; ****P < 0.01 different than baseline.

**Figure 1.** Peripheral and central blood pressure changes from baseline to cold pressor test (4 ºC) between high depressive score (HDS) and low depressive score (LDS) groups. (a) Brachial systolic blood pressure (BSBP). (b) Brachial diastolic blood pressure (BDBP). (c) Aortic systolic blood pressure (ASBP). (d) Aortic diastolic blood pressure (ADBP). Data are mean ± SEM. *P < 0.05 different than LDS.
Sanchez-Gonzalez et al. higher brachial and, more important, higher central BP responses during SNS stimulation in those classified as having an HDS than in those classified as having an LDS. The results of this study seem to point toward the conclusion that cardiac hyperactivity is an early manifestation of cardiovascular dysfunction in healthy individuals with an HDS.

A novel aspect of our study is the documentation of increased aortic hemodynamics during SNS stimulation among individuals with higher, rather than lower, depressive scores. We observed that, during the CPT, P1 (approximately 10 mm Hg), P2 (approximately 13 mm Hg), AI (10%), and STI (707 mm Hg/s/min⁻¹) were higher in the HDS group compared with the LDS group. It is worth noting that the response in P1 was lower than the response in P2. Because the aortic pressure waveform is a composite of P1 and P2, our results demonstrate that the amplitude of the reflected wave is a more influential factor associated with the augmented hemodynamics in individuals with relatively higher depressive scores. Similarly, the AI is a dynamic factor affected by both P1 and P2 in addition to time of reflection and HR. Furthermore, the AI has been proposed as a more sensitive marker of cardiovascular disease than brachial BP because it is a more reliable indicator of left ventricular afterload than BP per se. Our data indicate that the AI response during SNS stimulation among individuals with HDS is mostly driven by P2, suggesting increased vascular smooth muscle tone. Although we did not find statistically significant differences between the groups in HR or Tr during the CPT, we observed a decrease in Tr (approximately 7.1%) that was evident in the HDS group only. Because Tr and P1 are associated with aortic arterial stiffening, in addition to the current notion that increased pulse wave velocity is an early alteration associated with MDD, our results may have clinical implications for the evaluation of pulse wave velocity in nondepressed individuals with higher depressive scores.

Consistent with the increase in afterload during the CPT, as suggested by increased ASBP and AI, the HDS group had a higher STI (approximately 20%) than the LDS group. STI is an accepted indicator of left ventricular work and myocardial oxygen consumption. Moreover, under normal physiological conditions, increases in myocardial oxygen demand, such as the one evoked by SNS stimulation, is usually compensated for by a concurrent increase in coronary perfusion. In contrast, the increase in STI (approximately 44%) from baseline to CPT in the HDS group did not match the increase in DTI (24%). We speculate that the increase in myocardial oxygen demand (STI) during the CPT was intended to overcome the augmented reflected wave pressure. Because the HDS group was unable to properly match the increase in STI with a concurrent increase in DTI, our results suggest that depressive symptoms may have deleterious effects on coronary perfusion and ultimately in the development of coronary artery disease.

The potential mechanisms that may explain cardiac hyperactivity during SNS stimulation may be associated with impaired autonomic modulation. Previous studies have shown an association between depressive symptoms and increased SNS activity as well as plasma catecholamine concentration during laboratory stressors. The hyperactive cardiovascular responses to the CPT in the HDS group could be driven by increased adrenergic stimulation owing to altered plasma catecholamines concentration, which may ultimately increase smooth muscle vascular tone. Because P2 is influenced by peripheral vascular tone and was more affected than the other factors contributing to AI, our results suggest that the muscular arteries are hyper-responsive in individuals with relatively higher depressive symptomatology.

Potential limitations of this study include a small sample size and a lack of measurements of plasma catecholamines and autonomic activity. We are unable to provide a clear understanding of the physiological mechanisms underlying these findings.
mechanism to explain our results without plasma catecholamine and autonomic function measures. Although we found increases in P1 during the CPT in the HDS group, suggesting decreased aortic compliance, this study did not evaluate aortic pulse wave velocity, a gold standard measure for arterial stiffness. Finally, our sample was comprised of young adult men who were not clinically depressed, and hence we cannot generalize our results to other populations.

In conclusion, our results indicate that higher depressive symptoms in individuals without MDD may be associated with cardiac hyperactivity during SNS stimulation, contributing to increased aortic hemodynamics, increased left ventricular afterload, and increased myocardial oxygen consumption. These findings may have clinical implications for the evaluation of depressive symptoms in healthy, young adult men. Prospective studies intended to confirm whether an HDS may indicate a higher cardiovascular risk and/or early manifestations of cardiovascular disease are warranted.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES