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Title: **Sympathetic Vasomotor Tone is Associated with Depressive Symptoms in Young Females: A Potential Link Between Depression and Cardiovascular Disease**

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Short title: Depression and Sympathetic Vasomotor Tone

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Key words: *major depressive disorder; sympathetic activity; heart rate variability; blood pressure variability; ambulatory blood pressure.*

Abbreviations:

MDD = major depressive disorder

PNS = parasympathetic nervous system

SNS = sympathetic nervous system

CPT = cold pressor test

AASI = ambulatory arterial stiffness index

HRV = heart rate variability

LFSBP = systolic blood pressure variability in the low frequency domain

CES-D = Center for Epidemiologic Studies Depression Scale

pNN50 = adjacent R-R intervals that differ by 50 ms

RMSSD = root mean square of successive R-R differences

TP = total power

ASBP = ambulatory systolic blood pressure

ADBP = ambulatory diastolic blood pressure

AHR = ambulatory heart rate

Abstract

Background: Although increased sympathetic nervous system (SNS) activity is commonly associated with major depressive disorder (MDD) and cardiovascular disease (CVD), a biomarker linking these two entities remains elusive. We therefore evaluated the relationship between depressive symptoms and cardiovascular modulation via heart rate variability (HRV), brachial blood pressure (BP), ambulatory BP (ABP), and low frequency component of systolic blood pressure variability (LFSBP), a surrogate of sympathetic vasomotor tone. We hypothesized that LFSBP would be the strongest predictor of depressive symptoms compared to HRV and BP measurements.

Methods: Eighty young healthy females (20.51±2.82years) were evaluated for depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D). Data collection was conducted after a 10-min resting period. Beat-to-beat blood pressures were recorded for 5-min at baseline (BASE) followed by a 3-min cold pressor test (CPT). ABP was obtained for 24 h. **Results:** Hierarchical multiple regression analyses indicated that LFSBP at BASE was a stronger predictor of CES-D variance than BP and HRV indices, with LFSBP uniquely accounting for 8.1% of variance in CES-D scores during laboratory beat-to-beat BP assessments and 44.7% in ABP assessments. Individuals with acute depression scores ($n=12$;CES-D ≥ 16) had significantly higher ($p<.001$) mean LFSBP values ($6.66\pm2.54 mmHg^2$) than the remaining sample ($3.32\pm2.2 mmHg^2$) whereas no other significant differences were detected in any of the other cardiovascular variables. Cardiovascular responses to CPT did not predict CES-D scores. **Conclusion:** These findings suggest that LFSBP could be a biomarker of neurovascular functioning with potential clinical implications for understanding the interaction between MDD and CVD.

INTRODUCTION

Major depressive disorder (MDD) is associated with increased cardiovascular morbidity and mortality. [1,2] However, the mechanisms that underlie how the interaction between MDD and vascular functioning impacts cardiovascular disease (CVD) progression remain unknown. Although dysautonomia, including increased sympathetic nervous system (SNS) activity and/or decreased vagal tone, may be a common pivotal factor between MDD and CVD, a clinical test or biomarker linking MDD and CVD remains elusive. [3-6]

The influence of depressive symptoms on vascular function and cardiovascular responsiveness to stress, both in laboratory and home settings, have been well established. [7-10] In laboratory measurements, Seldenrijk et al. [11] reported that MDD severity is associated with lower carotid compliance. Recently, we demonstrated that higher depressive symptoms, in individuals without MDD, are associated with cardiac hyperactivity during SNS stimulation (cold pressor test, CPT) contributing to increased aortic hemodynamics. [12] Light et al. [13] showed that catecholamine concentrations were associated with exaggerated BP responses to laboratory stressors, including CPT, in females with high depressive symptoms. Similarly home based measurements, by means of ambulatory blood pressure (ABP), have shown that morning systolic blood pressure (SBP) surge and nocturnal SBP dipping are positively correlated and negatively correlated with depressive symptoms, respectively. [14,15] Furthermore, the ambulatory arterial stiffness index (AASI) may be increased in patients with MDD owing to increased arterial stiffness and potentially increased SNS activity. [16,17] Together these studies suggest that MDD has a profound impact on the vasculature most likely to be mediated via increased SNS tone, and hence markers of neurovascular modulation may better demonstrate the association between MDD and CVD.

Power spectral analysis of heart rate variability (HRV), measured in time and/or frequency domains, has been used for evaluating cardiac autonomic regulation in patients with mood disorders and CVD. [18-21] Patients with MDD have been shown to have lower HRV suggesting reduced cardiovagal modulation and increased SNS activity. [22-25] Since increased sympatho-vagal tone increases cardiac risk, the association between decreased HRV and MDD seems to predispose psychiatric patients to adverse cardiac events such as myocardial infarction, arrhythmias as well as sudden cardiac arrest. [4,23,26] Together these studies suggest that MDD decreases cardiac parasympathetic nervous system (PNS) activity rather than affecting SNS tone, especially at the subclinical level. This may be expected due to the greater influence of vagal tone over SNS flow on heart rate modulation. [21,27] However, vascular autonomic modulation is known to have a predominant SNS tone, [28-30] and hence the evaluation of the rhythmical oscillations in systolic blood pressure in the low frequency domain (LFSBP), a surrogate of sympathetic vasomotor tone, [31] may be more appropriate for understanding the influence of SNS hyperactivity on vascular function in MDD. Although several studies have shown a robust association between vascular dysfunction and MDD, the association between LFSBP and depressive symptoms has not been explored.

As MDD is known to result in SNS hyperactivity and impaired vascular functioning, it is reasonable to explore LFSBP as a potential biomarker of cardiovascular functioning in healthy individuals that vary in depressive symptoms. Since females have higher prevalence rates of MDD than males [2], the present study evaluated sympathetic vasomotor tone at rest and during SNS stimulation in healthy young females. We tested the hypothesis that LFSBP would be a stronger predictor of depressive symptoms than laboratory brachial BP, time and frequency domain measures of HRV, and ABP.

METHODS

STUDY SUBJECTS

Eighty apparently healthy young adult female undergraduates (19-31 years of age) participated in this study. Participants were excluded from the study if they had hypertension (BP ≥140/90 mmHg), chronic diseases and/or were taking medications (e.g., beta blockers, antidepressants, and stimulants) that could affect the cardiovascular variables. Participants were asked to abstain from caffeine, alcohol, and strenuous physical activity for at least 24 hours prior to testing. Participants were tested in the early follicular phase of the menstrual cycle in order to avoid potential variations in pressure wave morphology and cardiac reactivity. 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. Height, weight, waist, arm circumference, as well as finger circumference were then measured and participants filled out a health questionnaire indicating their physical health history and depressive symptomatology.

Data collection was conducted in the morning after at least a 10 hour postprandial period at the same time of the day (± 2 hours) in order to minimize potential diurnal variations in vascular reactivity. In order to test cardiac reactivity, we used the cold pressor test (CPT) as a stressor since it evokes SNS stimulation, increases hemodynamics, and increases LFSBP. [32-34] Participants were seated, and then given a 10 minute rest period in a quiet, dimmed light, and temperature controlled room (23 ± 1° C). Within 5 minutes after the rest period, brachial BP was

measured and used to calibrate beat-by-beat finger BP waveforms in order to obtain hemodynamic variables during a 5 minute baseline (BASE) period. Immediately following the BASE measurements, participants completed the CPT by submerging their hand in cold water (4ºC) for 3 minutes. During the CPT a researcher made sure the participant kept their hand in the water, to wrist level, throughout the entire task. Beat-by- beat BP was continuously obtained for 8 minutes (5minutes BASE and 3 minutes CPT). We did not control breathing frequency (12-14 rsp/min) throughout the test since it has been shown to be similar to spontaneous breathing in healthy volunteers [35] for HRV and LFSBP determinations. In addition, controlling breathing frequency may impose an additional stress to the participants. [36]

Participants were then fitted with an ABP monitoring device. The unit was calibrated to take 4 measurements per hour for 24 hours (resulting in 96 assessments) of SBP, diastolic BP (DBP), and HR. The ABP setup and monitoring began between 09:00-11:00 h and concluded with the ABP monitor being returned to the laboratory the following day. Participants were instructed to keep the ABP cuff on throughout the entire 24 hours.

DEPRESSION SCALE

Depression was measured the same day the participant came into the lab using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D). [37,38] The CES-D has been widely used as a stable measure of chronic depressive symptoms. [39,40] Responses were summed into one overall score, with a possible range of 0 to 30. Prior studies involving the longer 20-item version of this scale have used a rough estimate of the top quintile of scores to define participants as "depressed," and a validation study found that a score of 16 or higher has 99% sensitivity to identifying acute depression. [39,40]

CARDIOVASCULAR MEASUREMENTS

Beat-by-beat blood pressure

Brachial SBP was used to calibrate beat-by-beat blood pressure which was recorded for an 8-minute epoch via finger plethysmography (NIBP-100 Biopac Inc., Goleta, CA, USA). This method is validated and has been shown to provide accurate measurement of BP changes when compared with intra-arterial blood pressure. [41]

Heart rate variability

The BP peaks were used to calculate the time duration of intervals between heartbeats (RRI) and were automatically detected using commercially available software (WinCPRS, Turku, Finland). The RRI were inspected for artifacts, premature beats and ectopic episodes in order to calculate HRV parameters. The HRV was calculated through the time domain statistics percentage of adjacent R-R intervals that differ by 50 ms (pNN50), root mean square of successive R-R differences (RMSSD), and total power (TP) or variance in RRI. These are considered markers of cardiac vagal modulation [19] and the TP of HRV is an estimation of the global activity of the autonomic nervous system. [29] The main spectral components of the HRV that we calculated, by means of Fast Fourier transformation, were the low frequency (LF; 0.04-.15Hz) and the high frequency (HF; 0.15-0.4Hz). HF is a marker of cardiac PNS activity. [29] The LF component of HRV is mediated by both SNS and PNS activities [19] and may also represents baroreflex function. [42] Alternatively, the use of absolute units (ms^2) for HF and LF may be obtained in proportion to the TP which is expressed in normalized units (nu). Normalization is used to exclude the

influence of other fractal components and to control for the changes in TP hence it is more appropriate to report LF and HF responses to stress in nu. [19]

Blood pressure variability

The SBP time series was resampled at 5 Hz and the continuous data stream passed through a low pass impulse response filter with a cutoff frequency of 0.5 Hz. The data were then subjected to Fast Fourier transform algorithms using a Hanning spectral window and subsequently smoothed using a triangular averaging function to produce a spectrum. The power was calculated by measuring the area under the peak of the power spectra density curve. Power spectra within the 0.04–0.15 Hz range were defined as LFSBP and taken as an estimate of sympathetic vasomotor modulation. [31] In our laboratory, the intraclass correlation coefficients for resting SBP, DBP, LFSBP, nLF and nHF taken on two separate days are 0.97, 0.97, 0.95 0.94, and 0.94 respectively.

Ambulatory blood pressure

The ABP measurements were obtained for 24 hours using a validated oscillometric 90217A SpaceLabs (Spacelabs, Wokingham,Berkshire, UK) BP monitors. To calculate the ambulatory arterial stiffness index (AASI), the regression slope of ambulatory diastolic BP (ADBP) on ambulatory SBP (ASBP) from unedited 24 hour recordings, taken at a rate of 4 per hour, were computed for each participant. The ASBP dipping (ASBP-D) and ADBP dipping (ADBP-D) were obtained using the SpaceLabs analysis software. AASI was defined as one minus the regression slope. The stiffer the arterial tree, the closer the regression slope and AASI are to zero and one, respectively. [43]

STATISTICS

Shapiro-Wilk normality tests were used for absolute values for all HRV variables. Results indicated TP, pNN50, and RMSSD to be non-normally distributed therefore a logarithmic transformation (Ln) was performed for these variables. Hierarchical multiple regression (HMR) analyses were conducted to test the association between CES-D scores and cardiovascular parameters and to demonstrate the incremental contribution of sets of predictors in accounting of CES-D variance. Two laboratory and one ambulatory HMR analysis was conducted. The first laboratory HMR analysis contained three sets of predictors: Model 1 contained the hemodynamic indices (SBP, DBP), Model 2 the HRV indices (HR, LnTP, LnpNN50, LnRMSSD, nLF, nHF) and Model 3 the LFSBP. To evaluate cardiovascular changes from BASE to CPT, paired sample *t*-tests were conducted. Student's *t*-tests were used to evaluate the differences in cardiovascular parameters at rest between acutely depressed (CES-D $\geq$ 16) and healthy controls. Additionally, difference scores were created (BASE - CPT values) for SBP, DBP, HR, nLF, nHF, and LFSBP. The difference scores were then used as CES-D predictors in a second laboratory HRM analysis. Difference scores for LnTP, LnpNN50, and LnRMSSD were not calculated due to potential confounding results of the non-steady state condition of the CPT. For this HRM analysis, Model 1 contained the hemodynamic indices (ΔSBP, ΔDBP), Model 2 the HRV indices (ΔHR, ΔnLF, ΔnHF) and Model 3 the ΔLFSBP. The ambulatory HRM analysis contained three sets of predictors: Model 1 contained the averaged 24 hour SBP, DBP, and HR values plus the AASI index, Model 2 the average SBP and DBP dipping values and Model 3 the laboratory assessed LFSBP values.

RESULTS

Demographics. No correlations were significant between CES-D scores and any physical characteristic (M ± SD): height 1.61 ± 0.62 m, weight 63.54 ± 13.70 kg, and body mass index 24.23 ± 3.50 kg/m^2. Ethnic composition of the sample was 73% Caucasian, 11% African American, 10% Asian, and 6% endorsed either biracial or non-disclosed ethnicity. Multinomial logistic regression analyses indicated that CES-D scores were not associated with ethnicity, $\chi^2(4) = 3.17$, $p = .53$. These analyses warrant the exclusion of demographics in further CES-D analyses. CES-D scores indicated that 12 individuals met qualification for acute depression.

Laboratory Analyses. HMR analysis indicated that Model 1 predictors accounted for 13.8% of the variance in reported CES-D scores $F(2, 77) = 6.18$, $p = .003$. The addition of Model 2 predictors accounted for a nonsignificant additional 13.2% of the variance in CES-D scores, $\Delta F(6, 71) = 2.15$, $p = .06$. The addition of LFSBP in Model 3 accounted for an additional 8.1% of variance, $\Delta F(1, 70) = 8.80$, $p = .004$. LFSBP had a positive relationship with CES-D scores and was the only significant predictor in the full model (see Table 2). Figure 1 displays the regression of CES-D scores on laboratory LFSBP values. In comparing BASE cardiovascular indices, Student's *t*-tests indicated that individuals qualifying with acute depression scores (CES-D score >16) had significantly higher mean LFSBP scores than the remaining sample, $t(78) = 4.75$, $p = < .001$, Cohen's $d = 1.40$ (see Table 4).

CPT Difference Score Analyses. Paired sample *t*-tests comparing CPT to BASE changes indicated all cardiovascular variables, except LFSBP, significantly changed in the expected directions with increases in SBP, DBP, HR, LnTP, LnpNN50, LnRMSSD, nLF and a decrease in nHF (see Table 3). HMR results of difference scores showed none of the models accounted for a significant amount of variance in reported CES-D scores: Model 1 [Model $R^2 = .017$, $F(2, 77) =$

0.60, p = .550], Model 2 [ΔR^2 = .022, $\Delta F(3, 74) = 2.15$, p = .679], Model 3 [ΔR^2 = .023, $\Delta F(1, 73) = 8.80$, p = .211]. No full model predictors of CES-D scores were significant (see Table 2).

Ambulatory Blood Pressure Analyses. Fifty eight females completed the ABP measurements. Those who did not complete this measurement had similar baseline characteristics than those with the complete high quality measurements as compared by means of Student's *t*-tests (Table 4). HMR results indicated Model 1 predictors accounted for a nonsignificant 15% of the variance in CES-D scores, $F(4, 53) = 1.41$, p = .243. The addition of the Model 2 predictors accounted for an additional, nonsignificant 2.6% of the variance in CES-D scores, ΔF (2, 51) = 0.48, p = .621. The addition of LFSBP in Model 3 significantly accounted for an additional 44.7% of variance, $\Delta F(1, 50) = 34.34$, $p < .001$. As shown in Table 2, although both average 24 hour HR and LFSBP in the full model were significant CES-D predictors, calculation of 95% CI of final model semi-partial correlations indicate LFSBP [.490, .795] to be a significantly greater CES-D predictor than HR [.063, .488]. The ABP measurements of ASBP, ADBP, ASBP-D, ADBP-D, and ASSI were not significant full model HMR predictors of CES-D (Table1) and were not different between participants with CES-D ≥16 and CES-D <16 (Table 3).

DISCUSSION

The aim of the present study was to evaluate sympathetic vasomotor tone as a potential biomarker of cardiovascular functioning in apparently healthy females that varied in depressive symptoms. The novel findings of the present study are the following: 1) LFSBP was a stronger predictor of depressive symptoms than conventional measures of cardiovascular functioning such as laboratory measurement of BP and HRV, as well as home based ABP monitoring, 2) depressive symptoms are associated with a blunted LFSBP response to CPT, and 3) participants with acute depression had higher LFSBP than those with normal depressive scores without any clinically significant alterations in brachial BP, HRV (time and frequency domains), ABP, and AASI. Our data suggest that in females apparently free of CVD, high depressive symptoms are associated with increased sympathetic vasomotor tone, and to some extent, an early manifestation of dysautonomia. Therefore, LFSBP could be a reasonable biomarker with potential clinical applications for the diagnosis of MDD and its associated CVD risk.

Recently, the use of biomarkers for diagnosing and evaluating therapeutic effectiveness in patients with MDD has been explored. Some studies have suggested novel serum biomarkers for detecting individuals at increased risk of MDD in addition to noninvasive measures for evaluating psychological status. [44-47] Nevertheless, an easily obtained noninvasive biomarker which may be indicative of cardiovascular alterations in healthy and MDD patients remains elusive. Previous research, using laboratory and/or home based cardiovascular measurements, has shown that depressive symptoms contribute to cardiovascular functioning impairments in addition to increased CVD risk in both healthy and clinical populations. [1,6,12,25,48] In home based ABP measurements, prior studies have shown associations between depressive symptoms and nocturnal SBP [14]. Here we did not find associations between ABP, AASI and depressive

symptoms suggesting a potential limitation of ABP for detecting CVD risk in healthy young females with higher depressive symptoms. In laboratory measurements, during SNS stimulation, we and others have shown an association between depressive symptoms and increased brachial BP, aortic BP, as well as blood catecholamine concentration. [12,13,49,50] In addition, Gordon et al. [51] and Solomon et al. [52] documented that after SNS stimulation depressive symptoms were associated with attenuated heart rate recovery or impaired cardiovagal reactivation. In the present study we observed that LFSBP was the strongest predictor of depressive symptoms at rest in comparison to time and frequency domains of HRV, brachial SBP, brachial DBP, and ABP. We identified 12 participants with acute depression (CES-D $\geq$ 16) that displayed a twofold increase in LFSBP at rest compared to those with normal depressive scores. Furthermore, a blunted LFSBP response during CPT was associated with higher depressive symptoms which may be indicative of dysautomia in view of the fact that blunted cardiac and LFSBP responses to stress have been documented in MDD and autonomic failure patients, respectively. [4,52-54] Our data demonstrate that depressive symptoms are associated with dysautonomia and increased sympathetic vasomotor tone, even in the absence of clinically meaningful cardiovascular alterations, suggesting that LFSBP could be an early indicator of increased cardiovascular risk in females with high depressive scores.

Although it is unclear how depressive symptoms evoke SNS hyperactivity and attenuated PNS activity, dysautonomia seems to be a common pathway, and it may represent a common manifestation in the development of MDD and CVD. [18,55-57] Moreover, MDD is commonly associated with dysautonomia, reflected as increased sympathovagal tone, which may be a pivotal process in the development of cardiovascular complications such as arrhythmias, hypertension, arterial stiffening, and atherosclerosis. [4,11] Currently, the impact of depressive

symptoms and LFSBP on vascular function is not well understood. However, increased vasomotor tone may lead to vascular dysfunction and endothelial damage which are pivotal factors in the development of CVD. [58-60] Chen et al. [61] demonstrated that, in healthy subjects without significant CVD, high depressive scores were associated with impaired brachial flow, medicated vasodilation and depletion of circulating endothelial progenitor cells suggesting endothelial dysfunction and remodeling. It could be that the associated depressive state with SNS hyperactivity may promote an atherosclerotic environment and inflammation affecting the endothelial cells. Since we observed that high depressive symptoms are associated with increased LFSBP, our main finding adds to the notion that MDD may evoke endothelial dysfunction and damage as a result of the complex interaction between SNS activity and nitric oxide production. [61,62] Together the results of previous studies and our data suggest that increased sympathetic vasomotor tone may be a pivotal physiological alteration associated with depressive symptoms and may ultimately promote cardiovascular damaging and subclinical CVD.

Potential limitations of this study include a limited sample size; only female participants were included, lack of autonomic function serum markers including catecholamines and cortisol, as well as 24 hour HRV. In addition, cardiovascular responses during the recovery period after SNS stimulation were not evaluated. In this study we did not evaluate aortic PWV, a gold standard measure for arterial stiffness and a strong cardiovascular risk factor, or direct measures of SNS such as muscle SNS activity. We did not measure sleep quality in this study, which may influence autonomic function. However, the selected scale of CES-D has questions regarding sleep quality. Our statistical model did not control for anxiety and/or physical activity. Finally, our sample comprised young adult females who were not clinically diagnosed as suffering from

MDD and hence we may not generalize our results to other populations. However, the study was designed to evaluate potential markers of cardiovascular functioning in a population susceptible to MDD.

These results indicate that LFSBP is a strong predictor of depressive symptoms, in healthy females without clinically diagnosed MDD, in the absence of clinically significant alterations in BP, ABP, and HRV. Although MDD may be associated with cardiac hyperactivity during SNS stimulation, we found an association of blunted LFSBP response with depressive scores suggesting dysautonomia. The findings of the present study point towards the conclusion that LFSBP may be a feasible biomarker of neurovascular functioning with potential clinical implications for understanding the interaction between MDD and CVD. Prospective studies intended to confirm whether LFSBP may indicate a higher cardiovascular risk and/or early manifestations of cardiovascular disease in individuals with high depressive scores are warranted.

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The authors declare no conflicts of interest

REFERENCES

1. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99(16)**:** 2192-2217.

2. Niranjan A, Corujo A, Ziegelstein RC, Nwulia E. Depression and heart disease in US adults. *Gen Hosp Psychiatry* 2012; 34(3)**:** 254-261.

3. Hamer M, Malan L. Sympathetic nervous activity, depressive symptoms, and metabolic syndrome in black Africans: the sympathetic activity and ambulatory blood pressure in Africans study. *Stress* 2012; 15(5)**:** 562-568.

4. Koschke M, Boettger MK, Schulz S, Berger S, Terhaar J, Voss A, Yeragani VK, Bar KJ. Autonomy of autonomic dysfunction in major depression. *Psychosom Med* 2009; 71(8)**:** 852-860.

5. Shinba T, Kariya N, Matsui Y, Ozawa N, Matsuda Y, Yamamoto K. Decrease in heart rate variability response to task is related to anxiety and depressiveness in normal subjects. *Psychiatry Clin Neurosci* 2008; 62(5)**:** 603-609.

6. Hughes JW, York KM, Li Q, Freedland KE, Carney RM, Sheps DS. Depressive symptoms predict heart rate recovery after exercise treadmill testing in patients with coronary artery disease: results from the Psychophysiological Investigation of Myocardial Ischemia study. *Psychosom Med* 2008; 70(4)**:** 456-460.

7. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *J Adolesc Health* 2011; 48(6)**:** 579-584.

8. Hamer M, Frasure-Smith N, Lesperance F, Harvey BH, Malan NT, Malan L. Depressive Symptoms and 24-Hour Ambulatory Blood Pressure in Africans: The SABPA Study. *Int J Hypertens* 2012; 2012**:** 426803.

9. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak-the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012; 26 9(9)**:** 526-539.

10. Scuteri A, Castello L, Coluccia R, Modestino A, Nevola E, Volpe M. Depression is associated with increased occurrence of left ventricle concentric geometry in older subjects independently of blood pressure levels. *Nutr Metab Cardiovasc Dis* 2011; 21(12)**:** 915-921.

11. Seldenrijk A, van Hout HP, van Marwijk HW, de Groot E, Gort J, Rustemeijer C, Diamant M, Penninx BW. Depression, anxiety, and arterial stiffness. *Biol Psychiatry* 2011; 69(8)**:** 795-803.

12. Sanchez-Gonzalez MA, May RW, Brown PC, Koutnik AP, Fincham FD. Depressive Symptoms Contribute to Increased Wave Reflection During Cold Pressor Test in Young Adult Men. *American Journal of Hypertension* 2013; (In press).

13. Light KC, Kothandapani RV, Allen MT. Enhanced cardiovascular and catecholamine responses in women with depressive symptoms. *Int J Psychophysiol* 1998; 28(2)**:** 157-166.

14. Scuteri A, Spalletta G, Cangelosi M, Gianni W, Assisi A, Brancati AM, Modestino A, Caltagirone C, Volpe M. Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging Clin Exp Res* 2009; 21(4-5)**:** 292-297.

15. FitzGerald L, Ottaviani C, Goldstein IB, Shapiro D. Effects of dipping and psychological traits on morning surge in blood pressure in healthy people. *J Hum Hypertens* 2012; 26(4)**:** 228-235.

16. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, Stanton AV, Zhu DL, O'Brien E, Staessen JA. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension* 2006; 47(3)**:** 359-364.

17. Wang MY, Huang CJ, Wu YL, Liu JC, Tsai PS. The influence of baroreflex sensitivity on ambulatory arterial stiffness index in individuals with cardiovascular risk. *Blood Press Monit* 2010; 15(5)**:** 262-267.

18. Malliani A, Pagani M, Lombardi F. Neurovegetative regulation and cardiovascular diseases. *Ann Ital Med Int* 1991; 6(4 Pt 2)**:** 460-469.

19. Anon. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93(5)**:** 1043-1065.

20. Berntson GG, Bigger JT, Jr., Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997; 34(6)**:** 623-648.

21. Montano N, Porta A, Cogliati C, Costantino G, Tobaldini E, Casali KR, Iellamo F. Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. *Neurosci Biobehav Rev* 2009; 33(2)**:** 71-80.

22. Fuller BF. The effects of stress-anxiety and coping styles on heart rate variability. *Int J Psychophysiol* 1992; 12(1)**:** 81-86.

23. Einvik G, Dammen T, Namtvedt SK, Hrubos-Strom H, Randby A, Kristiansen HA, Nordhus IH, Somers VK, Omland T. Type D personality is associated with increased prevalence of ventricular arrhythmias in community-residing persons without coronary heart disease. *Eur J Prev Cardiol* 2012.

24. Yeragani VK, Pohl R, Balon R, Ramesh C, Glitz D, Jung I, Sherwood P. Heart rate variability in patients with major depression. *Psychiatry Res* 1991; 37(1)**:** 35-46.

25. Bajko Z, Szekeres CC, Kovacs KR, Csapo K, Molnar S, Soltesz P, Nyitrai E, Magyar MT, Olah L, Bereczki D, Csiba L. Anxiety, depression and autonomic nervous system dysfunction in hypertension. *J Neurol Sci* 2012; 317(1-2)**:** 112-116.

26. Tsuji H, Larson MG, Venditti FJ, Jr., Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996; 94(11)**:** 2850-2855.

27. Iellamo F, Pizzinelli P, Massaro M, Raimondi G, Peruzzi G, Legramante JM. Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability. *Circulation* 1999; 100(1)**:** 27-32.

28. Floras JS, Hara K. Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. *J Hypertens* 1993; 11(6)**:** 647-655.

29. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; 59(2)**:** 178-193.

30. Julien C, Malpas SC, Stauss HM. Sympathetic modulation of blood pressure variability. *J Hypertens* 2001; 19(10)**:** 1707-1712.

31. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; 84(2)**:** 482-492.

32. Koch DW, Leuenberger UA, Proctor DN. Augmented leg vasoconstriction in dynamically exercising older men during acute sympathetic stimulation. *J Physiol* 2003; 551(Pt 1)**:** 337-344.

33. Casey DP, Braith RW, Pierce GL. Changes in central artery blood pressure and wave reflection during a cold pressor test in young adults. *Eur J Appl Physiol* 2008; 103(5)**:** 539-543.

34. Wecht JM, Weir JP, DeMeersman RE, Schilero GJ, Handrakis JP, LaFountaine MF, Cirnigliaro CM, Kirshblum SC, Bauman WA. Cold face test in persons with spinal cord injury: age versus inactivity. *Clin Auton Res* 2009; 19(4)**:** 221-229.

35. Song HS, Lehrer PM. The effects of specific respiratory rates on heart rate and heart rate variability. *Appl Psychophysiol Biofeedback* 2003; 28(1)**:** 13-23.

36. Madden K, Savard GK. Effects of mental state on heart rate and blood pressure variability in men and women. *Clin Physiol* 1995; 15(6)**:** 557-569.

37. Radloff LS. The CES-D Scale. *Applied Psychological Measurement* 1977; 1(3)**:** 385-401.

38. Santor DA, Coyne JC. Shortening the CES–D to improve its ability to detect cases of depression. *Psychological Assessment* 1977; 9(3)**:** 233-243.

39. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977; 106(3)**:** 203-214.

40. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. *JAMA* 1990; 264(12)**:** 1541-1545.

41. Imholz BP, Wieling W, Langewouters GJ, van Montfrans GA. Continuous finger arterial pressure: utility in the cardiovascular laboratory. *Clin Auton Res* 1991; 1(1)**:** 43-53.

42. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clin Auton Res* 2011; 21(3)**:** 133-141.

43. Adiyaman A, Dechering DG, Boggia J, Li Y, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Thijs L, Torp-Pedersen C, Ohkubo T, Dolan E, Imai Y, Sandoya E, Ibsen H, Wang J, Lind L, O'Brien E, Thien T, Staessen JA. Determinants of the ambulatory arterial stiffness index in 7604 subjects from 6 populations. *Hypertension* 2008; 52(6)**:** 1038-1044.

44. Zarate CA, Jr., Mathews DC, Furey ML. Human Biomarkers of Rapid Antidepressant Effects. *Biol Psychiatry* 2013.

45. Schneider B, Prvulovic D. Novel biomarkers in major depression. *Curr Opin Psychiatry* 2012; 26(1)**:** 47-53.

46. Hepgul N, Cattaneo A, Zunszain PA, Pariante CM. Depression pathogenesis and treatment: what can we learn from blood mRNA expression? *BMC Med* 2013; 11(1)**:** 28.

47. Milanesi E, Minelli A, Cattane N, Cattaneo A, Mora C, Barbon A, Mallei A, Popoli M, Florio V, Conca A, Bignotti S, Gennarelli M. ErbB3 mRNA leukocyte levels as a biomarker for major depressive disorder. *BMC Psychiatry* 2012; 12**:** 145.

48. Baune BT, Stuart M, Gilmour A, Wersching H, Heindel W, Arolt V, Berger K. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. *Transl Psychiatry* 2012; 2**:** e92.

49. Betensky JD, Contrada RJ. Depressive symptoms, trait aggression, and cardiovascular reactivity to a laboratory stressor. *Ann Behav Med* 2010; 39(2)**:** 184-191.

50. Guinjoan SM, Bernabo JL, Cardinali DP. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. *J Neurol Neurosurg Psychiatry* 1995; 59(3)**:** 299-302.

51. Gordon JL, Ditto B, D'Antono B. Cognitive depressive symptoms associated with delayed heart rate recovery following interpersonal stress in healthy men and women. *Psychophysiology* 2012; 49(8)**:** 1082-1089.

52. Salomon K, Clift A, Karlsdottir M, Rottenberg J. Major depressive disorder is associated with attenuated cardiovascular reactivity and impaired recovery among those free of cardiovascular disease. *Health Psychol* 2009; 28(2)**:** 157-165.

53. Pichon A, Nuissier F, Chapelot D. Heart rate variability and depressed mood in physical education students: a longitudinal study. *Auton Neurosci* 2010; 156(1-2)**:** 117-123.

54. Okamoto LE, Raj SR, Peltier A, Gamboa A, Shibao C, Diedrich A, Black BK, Robertson D, Biaggioni I. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clin Sci (Lond)* 2012; 122(4)**:** 183-192.

55. Floras JS. Sympathetic activation in human heart failure: diverse mechanisms, therapeutic opportunities. *Acta Physiol Scand* 2003; 177(3)**:** 391-398.

56. Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. *Hypertension* 1983; 5(1)**:** 86-99.

57. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombardi F, Pagani M, Malliani A. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation* 1990; 81(2)**:** 537-547.

58. Mallamaci F, Tripepi G, Cutrupi S, Malatino LS, Zoccali C. Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardiopathy in patients with ESRD. *Kidney Int* 2005; 67(6)**:** 2330-2337.

59. Seals DR, Moreau KL, Gates PE, Eskurza I. Modulatory influences on ageing of the vasculature in healthy humans. *Exp Gerontol* 2006; 41(5)**:** 501-507.

60. Tang EH, Vanhoutte PM. Endothelial dysfunction: a strategic target in the treatment of hypertension? *Pflugers Arch* 2010; 459(6)**:** 995-1004.

61. Chen H, Yiu KH, Tse HF. Relationships between vascular dysfunction, circulating endothelial progenitor cells, and psychological status in healthy subjects. *Depress Anxiety* 2011; 28(8)**:** 719-727.

62. Gamboa A, Okamoto LE, Diedrich A, Choi L, Robertson D, Farley G, Paranjape S, Biaggioni I. Sympathetic activation and nitric oxide function in early hypertension. *Am J Physiol Heart Circ Physiol* 2012; 302(7)**:** H1438-1443.

Table 1. Parameter Estimates of Cardiovascular Predictors of CES-D for Baseline, Cold Pressor Test, and Ambulatory Assessment.

Models parameter estimates. *sr*, semi-partial correlation; BASE, baseline; CPT, cold pressor test; ABP, ambulatory blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR ,heart rate; LnTP , Ln Total Power; LnpNN50 , Ln percentage of adjacent R-R intervals that differ by 50 ms; LnRMSSD, Ln root mean square of successive R-R differences; nLF, normalized low frequency; nHF, normalized high frequency; LFSBP, low frequency systolic blood pressure; ASBP, ambulatory SBP; ADBP, ambulatory DBP; AHR, ambulatory HR; ASSI, ambulatory arterial stiffness index; ASBP-D, ambulatory systolic blood pressure dipping; ADBP-D, ambulatory diastolic blood pressure dipping.

Table 2. Paired Sample T-Tests comparing Cardiovascular changes from BASE to CPT (n=80).

BASE, baseline; CPT, cold pressor test; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LnTP, Ln Total Power; LnPNN50, Ln time domain statistics percentage of adjacent R-R intervals that differ by 50 ms; LnRMSSD, Ln root mean square of successive R-R differences; nLF, normalized low frequency of heart rate varibility; nHF, normalized high frequency of heart rate varibility; LFSBP, low frequency component of systolic blood pressure variability.

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Table 3. Student's T-Test comparing Cardiovascular Parameters between Acutely Depressed and Healthy Controls.

CES-D, Center for Epidemiologic Studies Depression Scale; BASE, baseline; CPT, cold pressor test; SBP,systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LnTP, Ln Total Power; LnpNN50, Ln percentage of adjacent R-R intervals that differ by 50 ms; LnRMSSD, Ln root mean square of successive R-R differences; nLF, normalized low frequency component of heart rate variability; nHF, normalized high frequency of heart rate varibility; LFSBP, low frequency component of systolic blood pressure variability. ASBP, ambulatory SBP; ADBP, ambulatory DBP; AHR, ambulatory HR; ASSI, ambulatory arterial stiffness index; ASBP-D, ambulatory systolic blood pressure dipping; ADBP-D, ambulatory diastolic blood pressure dipping.

Table 4. Student's T-Test comparing Cardiovascular Parameters between participants with and without ambulatory blood pressure measurements.

ABP, ambulatory blood pressure; SBP,systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LnTP, Ln Total Power; LnpNN50, Ln percentage of adjacent R-R intervals that differ by 50 ms; LnRMSSD, Ln root mean square of successive R-R differences; nLF, normalized low frequency component of heart rate variability; nHF, normalized high frequency of heart rate varibility; LFSBP, low frequency component of systolic blood pressure variability.

Figure 1. Regression of Depressive Scores on Sympathetic Vasomotor Tone.

CES-D, Center for Epidemiologic Studies Depression Scale; LFSBP, low frequency component of systolic blood pressure variability.

Table 1

	BASE (n=80)			CPT (n=80)				ABP (n=58)			
	Predictor	β	*sr*	*p*	Predictor	β	*sr*	*p*	Predictor	β	*sr*	*p*
Model 1	SBP (mmHg)	.32	.29	.008	ΔSBP (mmHg)	-.09	-.07	.638	ASBP (mmHg)	.45	.25	.125
	DBP (mmHg)	.11	.10	.359	ΔDBP (mmHg)	.12	.09	.563	ADBP (mmHg)	-.18	-.10	.541
Model 2	SBP (mmHg)	.33	.29	.005	ΔSBP (mmHg)	-.19	-.14	.384	ASBP (mmHg)	.50	.29	.089
	DBP (mmHg)	.05	.04	.691	ΔDBP (mmHg)	.10	.07	.646	ADBP (mmHg)	-.14	-.07	.660
	HR (bpm)	.31	.18	.078	ΔHR (bpm)	.01	.01	.972	AHR (bpm)	-.13	-.11	.525
	LnTP (ms^2)	-.23	-.14	.173	ΔnLF	.37	.26	.111	ASSI	.06	.05	.754
	LnpNN50 (ms^2)	.09	.06	.558	ΔnHF	.35	.26	.110	ASBP-D (%)	.21	.13	.422
	LnRMSSD (ms^2)	.44	.25	.016					ADBP-D (%)	.00	.00	.999
	nLF	-.44	-.09	.368								
	nHF	-.50	-.10	.323								
Model 3	SBP (mmHg)	.12	.09	.364	ΔSBP (mmHg)	.38	.07	.551	ASBP (mmHg)	-.36	-.16	.180
	DBP (mmHg)	.09	.07	.470	ΔDBP (mmHg)	-.61	-.14	.240	ADBP (mmHg)	.14	.07	.525
	HR (bpm)	.24	.14	.157	ΔHR (bpm)	-.21	-.06	.640	AHR (bpm)	.36	.29	.014
	LnTP (ms^2)	-.20	-.11	.268	ΔnLF	.16	.04	.774	ASSI	-.09	-.08	.487
	LnpNN50 (ms^2)	.15	.09	.333	ΔnHF	.51	.09	.453	ASBP-D (%)	.31	.20	.081
	LnRMSSD (ms^2)	.34	.18	.062					ADBP-D (%)	-.35	-.20	.093
	nLF	-.55	-.11	.242								
	nHF	-.50	-.10	.298								
	LFSBP ($mmHg^2$)	.37	.29	.004	ΔLFSBP ($mmHg^2$)	-.41	-.15	.211	LFSBP($mmHg^2$)	.95	.67	<.001

Table 2

	BASE	CPT		
VARIABLE	**M ± SD**	**M ± SD**	***t***	***p***
SBP (mmHg)	120 ± 11	125 ± 15	-3.78	< .001
DBP (mmHg)	79 ± 7	87 ± 10	-7.93	< .001
HR (bpm)	74 ± 10	82 ± 12	-5.42	< .001
LnTP (ms^2)	8.50 ± 1.23	9.64 ± 2.48	-3.86	< .001
LnRMSSD (ms^2)	4.34 ± 0.65	5.42 ± 1.62	-6.53	< .001
LnpNN50 (ms^2)	3.39 ± 0.42	3.60 ± 0.42	-4.46	< .001
nLF	0.56 ± 0.15	0.63 ± 0.19	-3.64	< .001
nHF	0.40 ± 0.13	0.32 ± 0.18	4.78	< .001
LFSBP ($mmHg^2$)	3.89 ± 3.15	3.80 ± 4.09	0.21	.837

Table 3

	n	CES-D < 16	n	CES-D ≥16		
VARIABLE		**M ± SD**		**M ± SD**	***t***	***p***
SBP (mmHg)	68	118 ± 11	12	124 ± 13	-1.71	.091
DBP (mmHg)	68	79 ± 8	12	81 ± 4	-0.91	.366
HR (bpm)	68	78 ± 9	12	82 ± 11	-1.27	.208
LnTP (ms^2)	68	8.52 ± 1.21	12	8.46 ± 1.48	0.15	.881
LnRMSSD (ms^2)	68	4.32 ± 0.61	12	4.59 ± 1.13	-1.24	.219
LnpNN50 (ms^2)	68	3.40 ± 0.42	12	3.27 ± 0.38	1.06	.293
nLF	68	0.57 ± 0.12	12	0.52 ± 0.24	1.20	.233
nHF	68	0.39 ± 0.11	12	0.43 ± 0.21	-0.89	.376
LFSBP ($mmHg^2$)	68	3.32 ± 2.21	12	6.66 ± 2.54	-4.75	< .001
ASBP (mmHg)	46	114 ± 8	12	117 ± 10	-1.36	.180
ADBP (mmHg)	46	71 ± 6	12	71 ± 5	0.05	.960
AHR (bpm)	46	79 ± 8	12	79 ± 9	-0.11	.834
ASSI	46	0.28 ± 0.16	12	0.35 ± 0.21	-1.11	.272
ASBP-D (%)	46	4.49 ± 6.11	12	3.10 ± 6.62	0.61	.544
ADBP-D (%)	46	7.14 ± 9.34	12	6.35 ± 11.82	0.99	.326

Table 4

	n	With ABP	n	Without ABP		
VARIABLE		**M ± SD**		**M ± SD**	***t***	***p***
SBP (mmHg)	58	121 ± 13	22	117 ± 10	-1.69	.095
DBP (mmHg)	58	79 ± 8	22	79 ± 4	0.11	.916
HR (bpm)	58	80 ± 9	22	77 ± 10	-1.45	.152
LnTP (ms^2)	58	8.46 ± 1.32	22	8.54 ± 1.19	0.32	.754
LnRMSSD (ms^2)	58	4.32 ± 0.65	22	4.40 ± 0.75	0.58	.565
LnpNN50 (ms^2)	58	3.35 ± 0.42	22	3.42 ± 0.41	1.08	.283
nLF	58	0.58 ± 0.14	22	0.54 ± 0.15	-1.57	.121
nHF	58	0.37 ± 0.12	22	0.42 ± 0.13	1.67	.100
LFSBP ($mmHg^2$)	58	3.92 ± 3.21	22	3.75 ± 2.43	-.268	.789

BW Figure 1
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