Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

Shama Dinmohamed Panjwani _____

Date

Vascular Mechanisms of Depression in Patients with Coronary Artery Disease

By

Shama Dinmohamed Panjwani

Masters of Public Health

Epidemiology

Amit Shah, MD, MSCR

Thesis Advisor

Vascular Mechanisms of Depression in Patients with Coronary Artery Disease

By

Shama Dinmohamed Panjwani

MD, Angeles University Foundation, School Of Medicine, Philippines, 2009

Faculty Thesis Advisor: Amit Shah MD, MSCR

An abstract of

A thesis submitted to the Faculty of the Rollins School of Public Health at Emory University

in partial fulfillment of the requirements for the degree of Master of Public Health in

Epidemiology

2016

Vascular Mechanisms of Depression in Patients with Coronary Artery Disease

Background: Depression is associated with adverse outcomes in patients with coronary artery disease (CAD), yet the mechanism underlying endothelial dysfunction post mental stress is unclear. We hypothesized that depression is associated with impaired endothelial function at baseline, and larger declines in endothelial function after laboratory-induced mental stress challenge.

Methods: This was a cross sectional study of 277 subjects with a documented history of myocardial infarction in the previous 8 months at the time of screening. Depression was assessed using Beck Depression Inventory score (BDI). Vascular function was measured by Reactive Hyperemic Index (RHI) using PAT and Flow mediated vasodilation (FMD) at baseline and post mental stress.

Results: Microvascular endothelial dysfunction (RHI) was associated with higher BDI score at baseline (P=0.03), but the change from baseline RHI to post mental stress (P=0.31) was not associated with BDI. Brachial artery endothelial function (FMD) at baseline (P=0.29) and its change after mental stress (P=0.23) were not associated with BDI score.

Conclusion: Depressive symptoms are significantly associated with microvascular endothelial dysfunction at baseline. Our study did not show a significant relationship of depressive symptoms with changes in endothelial function after mental stress challenge.

By

Shama Dinmohamed Panjwani

MD, Angeles University Foundation, School Of Medicine, Philippines, 2009

Faculty Thesis Advisor: Amit Shah MD, MSCR

A thesis submitted to the Faculty of the

Rollins School of Public Health at Emory University

in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology

2016

ACKNOWLEDGMENTS

I would like to thank my mentor, Dr. Shah, for creating this great opportunity for me and guiding me through this process.

Also, I would like to thank my family for supporting me through this process.

TABLE OF CONTENTS

INTRODUCTION

Cardiovascular diseases (CVD) are the leading causes of death and disability in developed countries. The total number of CVD deaths in 2005 has increased globally to 17.5 million from 14.4 million in 1990. Of these, 7.6 million were due to coronary heart disease.[1] Some of the unmodifiable risk factors for coronary heart disease are age and family history; in contrast, others such as diabetes, body mass index (BMI), depression, hypertension, and cigarette smoking are easily identifiable and clinically treatable risk factors.[2,3] Psychological factors are increasingly recognized as major contributors to the development of CVD and secondary adverse events in CVD patients. Among all psychological factors, the association between depression and CAD is studied extensively and is considered a major risk factor for adverse outcomes in CAD, and associated with a nearly 2-fold increased risk of adverse CVD events and death.[4] These psychological factors may mediate adverse CVD effects through pathological influences on blood pressure and vascular function, although the full physiologic sequelae is not clear.[2,3]

Impaired vascular function in the peripheral arteries can be assessed in the larger, proximal arteries as well as the more distal, microvascular arterioles. Large artery endothelial function can be measured by flow-mediated dilation (FMD), which, when impaired, is associated with worse prognosis in both low risk patients and those with established CAD.[4,5,7] In contrast with FMD, peripheral arterial tonometry (PAT) likely reflects microvascular endothelial function in the arterioles.[6] The reactive hyperemic index measured by PAT (RHI-PAT) is a non-invasive technique that combines traditional flow-mediated dilatation with pneumatic fingertip probes to measure arterial pulse wave

amplitude. Acute mental stress can transiently have a negative influence on an endothelial function which may accelerate pathways underlying CVD.[8] Further understanding the change in endothelial function with RHI-PAT after a mental stress can help to identify those who are sensitive and at higher physiologic risk of developing CAD in the future.

Studies have been conducted to investigate the relationship of depression, stress and endothelial function measured by FMD in stable angina patients.[7] However, these studies have not directly studied the relationship between endothelial dysfunction measured by RHI-PAT and depression in post-myocardial infarction (MI) patients, which may also include individuals with silent ischemia. Factors like age, race, gender, BMI, smoking, alcohol, use of medications like antidepressants, co-morbidities like hypertension, diabetes, and high cholesterol may influence both depression and vascular function.[7,9] Therefore, studies in which such confounders may be controlled are necessary to further explore this possible association.

In order to study the association between depression and endothelial function while controlling for potential confounders, we conducted a cross-sectional study of 277 men and women 18 to 61 years of age who were hospitalized for myocardial infarction in the previous 8 months as part of the Myocardial Infarction and Mental Stress (MIMS) study.

We hypothesized that depression is associated with impaired endothelial function at baseline, and also associated with larger declines in endothelial function after laboratory-induced mental stress challenge.

METHODS

Participants

The purpose of the MIMS study was to evaluate sex differences in the prevalence, mechanisms and consequences of mental stress ischemia in young survivors of MI. Study participants were recruited from the pool of patients admitted with a confirmed diagnosis of MI at Emory-affiliated hospitals. Eligible patients were 18 to 61 years of age at the time of screening and had a documented history of MI within the past 8 months. The diagnosis of MI was verified by medical record review based on standard criteria of troponin level increase and electrocardiogram changes.[10] Participants were excluded if they had unstable angina or acute MI within the past week, or a severe comorbid medical or psychiatric disorder that could interfere with study results, such as cancer, renal failure, current alcohol or substance abuse, or schizophrenia. Participants were also excluded if they weighed more than 450 pounds (due to limits on the weight bearing of the nuclear stress test equipment), if they were pregnant or breast-feeding, or if they were currently using postmenopausal hormone therapy or psychotropic medications other than antidepressants. Finally, patients were excluded if they were unable to exercise to target and not eligible for a pharmacological stress test.

Study Design

Study participants underwent FMD and PAT measurements at rest and within 60 minutes after mental stress during their first visit. Baseline sociodemographic and psychosocial data were collected. Information on sociodemographic factors was collected using standard questionnaires from population studies. A detailed medical history including medication use was obtained by a research nurse. Weight and height were used to calculate body mass index as weight in kilograms divided by height in meters squared. Behavioral, social, and mental health information was obtained using psychometric instruments with established reliability and validity. The study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all participants.

Depression Assessment

Beck Depression Inventory was used to assess clinical depression during the initial visit. It is a self-administered 21-item scale which has acceptable sensitivity and specificity with regards to a clinical diagnosis of depression, and also provides a continuous measure of depressive symptoms. It has been used extensively in studies of CVD.[11,12]

Mental Stress Protocol

Initially, patients rested for 30 minutes in a quiet, dimly lit, temperature-controlled room. At the end of the resting period, mental stress was induced by a standardized public speaking task as previously described.[13] Patients were asked to imagine a real-life stressful situation, such as a close relative been mistreated in a nursing home, and asked to make up

a realistic story around this scenario. They were given 2 minutes to prepare a statement and then 3 minutes to present it in front of a video camera and an audience wearing white coats. Participants were told that their speech would be evaluated by the laboratory staff for content, quality, and duration. Blood pressure and heart rate were recorded at 5-minute intervals during the resting phase and at 1-minute intervals during and after the mental stress task. At the end of the test, patients were debriefed.

Endothelial Function Measures

Endothelium-dependent flow-mediated vasodilation (FMD)

Brachial artery FMD was used for determining endothelial function before and within 60 minutes after mental stress testing which has, in previous studies, associated with reduced endothelial function.[5,7] Endothelium-dependent FMD of the brachial arteries was measured from two-dimensional ultrasound images according to established and validated methodologies[7, 14] using an Acuson 10 mHz linear array transducer and an Acuson Aspen ultrasound system. Imaging was performed with the subject resting supine for at least 10 minutes on a hospital bed in a quiet setting. For each subject, optimal brachial artery images were obtained between 2 and 10 cm above the antecubital crease. After baseline measurements, a blood pressure cuff was inflated to 60 mm Hg above systolic pressure over the proximal portion of the right arm for 5 minutes. Endothelium-dependent function was determined during the first two minutes of release of the cuff as previous studies have shown that maximal dilatation occurs 1 minute after cuff deflation. The end point of measurement was the percent change in diameter in response to reactive hyperemia (FMD %). Since women have smaller vessels than men, we have adjusted for baseline brachial

artery diameter in the analysis. In addition, we also calculated the percentage change in mental stress FMD by subtracting FMD post mental stress from the baseline pre-mental stress FMD.

Peripheral Arterial Tonometry (PAT)

The EndoPAT^{TM} 2000 device (Itamar-Medical, Israel) was used to measure finger pulse wave amplitudes with a probe using a robust modified form of volume plethysmography as a means of estimating pulsatile arterial volume changes independently of venous pulsations/pooling.[15] An illustrative diagram of the device is shown in Figure 1. This device include a proximal probe component and application of a constant counter pressure of 7 mm of mercury within the whole probe to keep venous transmural pressure deliberately negative. The probe components are connected via thin flexible tubing to isolated volume reservoirs to buffer pressure changes within the probe. An additional volume reservoir not connected to the probe serves as a pressure reference. Pressure changes accompanying peripheral volume changes are fed to a personal computer by which the signal is bandpass filtered (0.3 to 30 Hz), amplified, displayed and stored.

To measure RHI using PAT, we performed a baseline recording of 5 minutes, followed by 5 minutes of occlusion, and then 5 minutes post-occlusion PAT signal (hyperemic period). Occlusion of the brachial artery was performed with an occlusion pressure least 60 mmHg above the systolic blood pressure (minimally 200 mmHg, and maximally 300 mmHg). RHI was then calculated as the ratio of the pulse wave amplitudes during the hyperemic periods compared to the rest period, while also adjusting for normal

variation due to respiration and other factors by controlling for the ratio in the opposite, non-occlusion arm.

RHI was measured both before mental stress challenge, and approximately 60 minutes after. We calculated the change in mental stress RHI by subtracting RHI post mental stress and baseline pre-mental stress to assess the sensitivity to mental stress and its influence on microvascular endothelial function.

DATA ANALYSIS

Our 2 primary outcomes (dependent variable) were RHI-PAT and FMD. Beck Depression Inventory score (BDI) as a measure of depressive symptoms was the main predictor. Covariates were selected based on literature review and substantive knowledge regarding the potential association between endothelial dysfunction and depression. Potential confounders we included in our study were age, gender, race, BMI, antidepressant, cardiovascular risk factors like smoking, alcohol use, diabetes, hypertension, dyslipidemia

To evaluate the distribution of baseline characteristics based on depressive symptoms, the BDI score was divided into two categories (minimal vs mild, moderate and severe) with a cutoff value of BDI < 14 and BDI ≥ 14. Baseline demographics, smoking, BMI, medication use and clinical characteristics were reported as means with standard deviation (SD) for continuous variables or proportions for categorical variables as appropriate. Student's t test was used to compare the distribution of continuous variables and Chi-square test was used for comparison of categorical variables between groups categorized by BDI score. For models evaluating the relationship between BDI and

endothelial function, BDI was used as a continuous measure to assess the dose-response relationship between the exposure and outcome. Univariate and multivariate models were used to examine the effects of covariates for prediction of continuous outcome. Covariates in multivariate model for prediction of RHI and FMD were age, race, gender, hypertension, dyslipidemia, diabetes mellitus, BMI and antidepressant. Multivariate adjusted analyses were done by creating three models to study the mediating effects by various factors. Statistical significance was based on 2-tailed tests, and P values ≤ 0.05 were considered significant. Statistical analyses was performed using the SAS statistical software (Version 9.4; SAS, Cary, NC)

RESULTS

Total of 277 subjects were studied. Table 1 summarizes demographics, clinical characteristics, and medication use in two categories of BDI patients. The prevalence of hypertension and diabetes mellitus was higher, and there were more females and smokers among minimal depression group (BDI<14) vs. the BDI ≥14 group. Antidepressant use was higher among those with BDI>14 compared to BDI < 14 group. There were no significant differences in age, race, alcohol use, BMI, dyslipidemia between subjects with BDI < 14 and BD I ≥ 14.

Table 2 summarizes the relationship between depression categories and endothelial function. FMD at baseline, post mental stress, and the change from baseline to stress were not significantly different in two BDI categories. Change in baseline to stress hyperemic index was not significantly different in two BDI categories but RHI at baseline and post mental stress was significantly lower in the mild to severe depression category (BDI ≥ 14) compared to the BDI < 14 group.

Table 3 shows the results of the linear regression models between BDI score and endothelial function. Unadjusted analysis in our study showed that there was a significant association significant between RHI at baseline and BDI score. Each unit increase in BDI score associated with 0.01 unit decrease in RHI (p=0.03). However, our study did not find any significant association between BDI score and change in RHI between the resting baseline and mental stress recovery period. Unadjusted analysis with FMD was not significant for any of the measures.

Table 3 shows the results of the multivariable-adjusted models. When we adjusted for demographic variables including age, race and gender, there was no significant association between BDI score and change in RHI from baseline to post mental stress or FMD baseline to post mental stress. We added cardiovascular risk factors like smoking, alcohol, hypertension, diabetes, and dyslipidemia to the model and then added antidepressant use and BMI to the model, results were still insignificant. Adjusted analysis for baseline RHI controlling for age, gender, race, antidepressant use, BMI, alcohol, smoking, hypertension, diabetes, and dyslipidemia showed a significant negative association between BDI score and baseline pre mental stress RHI. Each unit increase in BDI score associated with 0.01 unit decrease in RHI controlling for age, gender, race, antidepressant use, alcohol, smoking, hypertension, diabetes, dyslipidemia, antidepressant use and BMI (p=0.03). Association between the BDI score and FMD at baseline was not significant after controlling for the potential confounders in our study. There was no significant interaction with age, race, gender, and antidepressant user (Table 4).

DISCUSSION

The major findings of the study was that the subjects with higher Beck Depression Inventory scores demonstrated significantly impaired endothelial function at baseline measured by PAT. Our study did not demonstrate significant change from baseline to post mental stress in RHI by PAT or FMD. This implies that depression is associated with microvascular endothelial dysfunction at baseline, a precursor to cardiovascular outcomes in post MI patients. This relationship may help to explain the increased risk of adverse CVD outcomes in depressed patients.

Several studies have shown association between endothelial dysfunction and depression.[18,19,20] The case control study conducted by H. Shi *et al.* not only observed an association between depression and endothelial dysfunction measured by RHI but also showed improvement in depressive symptoms was synchronous with improvement in endothelial function.[19] The study conducted to investigate adverse impact of mood as an exposure that was assesses by Profile of Mood States (POMS) on endothelial function measured by FMD concluded that mood disturbance can contribute to impairment in endothelial function and can contribute to development of CVD.[18] In another study of healthy adolescent girls, depressive symptoms were associated with both baseline endothelial function and worsening over time.[21] Findings of our study is consistent with the literature.

The basis for the association between depressive symptoms and endothelial function is likely multifold. Depression may decrease the synthesis of nitric oxide synthase

and create imbalance between dilation and contraction of blood vessels, which then causes endothelial dysfunction.[22] Depression is associated with hyper-activation of hypothalamohypophysoadrenal (HPA) axis which in turn leads increase in cortisol levels; [23, 24] this impairs endothelial function as well. Behavioral mechanisms suggests that that there is an association between depression and obesity.[25] There is also disturbed metabolism of glucose and lipids in depression, which indirectly results in endothelial dysfunction.

The significant inverse association between baseline RHI and BDI score in this study suggests a possible clinical role for PAT as a screening tool to assess endothelial function in depressed patients. Screening patients with depression and appropriate referral for treatment may overall aid in decreasing cardiovascular disease burden by addressing depression as a risk factor.

This study was subject to several limitations. Since this was a cross-section study, it failed to show causative association. Causative relationship can be confirmed by prospectively following subjects over time, studying depression score and endothelial function. Further studies are needed to confirm these findings by comparing clinical characteristics in healthy individual since this study considered only post MI patients. Finally, future studies are required to establish whether improvement in RHI after treatment of depression.

CONCLUSION

In our cohort of post MI patients, depression is significantly associated with microvascular, but not brachial (large vessel), endothelial impairment. This signifies increased risk for cardiovascular events in those with depressive symptoms. Further research is required to validate this association in controls, and also by measuring endothelium function over time in post MI patients and healthy adults.

Table 1. Baseline characteristics of study subjects by BDI score category

	BDI < 14	**BDI ≥ 14**	***p* value**
sample size (n)	170	107	
Age, mean years ± SD	50±6	50±5	0.96
Female gender	44%	63%	<0.01
African American	59%	73%	0.07
Hypertension	68%	83%	0.01
Dyslipidemia	68%	76%	0.14
Diabetes	25%	36%	0.05
Current Smoker	46%	69%	<0.01
Alcohol use	54%	44%	0.09
Body mass index, mean kg/m² ± SD	31±7	32±8	0.07
Antidepressant use	9%	25%	<0.01

Table 2. Vascular measures by BDI score category

	BDI < 14	**BDI ≥ 14**	***p* value**
Flow Mediated Dilation			
Mean Baseline ± SD	4.00±2.98	3.93±2.01	0.84
Mean Post Mental Stress± SD	2.31±2.45	2.19±2.41	0.71
Mean change from baseline to stress± SD	-1.72±2.30	-1.74±2.01	0.94
Reactive Hyperemia Index			
Mean Baseline± SD	1.87 ±0.53	1.65±0.56	<0.01
Mean Post Mental Stress± SD	1.84±0.64	1.58±0.54	<0.01
Mean change from baseline to stress± SD	-0.03 ±0.53	-0.08 ±0.50	0.50

Table 3. Unadjusted and Adjusted association between total BDI score with FMD and RHI

	Unadjusted		**Adjusted**					
			Model 1		**Model 2**		**Model 3**	
	B	p	B	p	B	p	B	p
Flow Mediated Dilation								
Baseline	0.009	0.604	0.011	0.504	0.016	0.354	0.019	0.294
Change from baseline to stress	-0.017	0.211	-0.014	0.202	-0.010	0.394	-0.014	0.233
Reactive Hyperemia Index								
Baseline	-0.008	0.027	-0.006	0.071	-0.005	0.136	-0.007	0.033
Change from baseline to stress	-0.003	0.337	-0.005	0.087	-0.004	0.171	-0.003	0.308

Adjusted:
Baseline FMD:
Model 1**:** total BDI score, baseline brachial artery diameter, age, gender, race
Model 2: Model 1 + alcohol, smoke, hypertension, dyslipidemia, diabetes mellitus
Model 3: Model 2+ BMI, antidepressant
FMD change from baseline to stress:
Model 1: total BDI score, FMD at rest, baseline brachial artery diameter, age, gender, race
Model 2: Model 1 + alcohol, smoke, hypertension, dyslipidemia, diabetes mellitus
Model 3: Model 2+ BMI, antidepressant
Baseline RHI:
Model 1**:** total BDI score, age, gender, race
Model 2: Model 1 + alcohol, smoke, hypertension, dyslipidemia, diabetes mellitus
Model 3: Model 2+ BMI, antidepressant
Reactive Hyperemia Index change from baseline to stress:
Model 1**:** total BDI score, RHI at rest, age, gender, race
Model 2: Model 1 + alcohol, smoke, hypertension, dyslipidemia, diabetes mellitus
Model 3: Model 2 + BMI, antidepressant

Parameter estimates (B):
At baseline resting, every unit increase in BDI score 0.019 increase in FMD and 0.007 decrease in RHI is predicted holding all other variables constant

At resting baseline to post mental stress change, every unit increase in BDI score 0.014 decrease in FMD and 0.003 decrease in RHI stress is predicted holding all other variables constant

FMD: Flow Mediated Vasodilation; RHI: Reactive Hyperemic Index

Table 4. Sensitivity Analysis to evaluate for demographic effect modifiers in the relationship between depressive symptoms and reactive hyperemia index

	B	p	B	p	
	Unadjusted		Adjusted*		*P* value , interaction (Adjusted)
	B	p	B	p	
Women	-0.007	0.225	-0.006	0.301	0.82
Men	-0.013	0.021	-0.011	0.076	
Age ≤ 50 years	-0.009	0.076	-0.007	0.197	0.95
Age > 50 years	-0.012	0.034	-0.013	0.388	
AA Race	-0.005	0.175	-0.006	0.166	0.43
Non-AA Race	-0.012	0.156	-0.015	0.148	
AD User	-0.003	0.756	-0.001	0.939	0.30
Non-AD User	-0.013	0.002	-0.011	0.014	

Adjusted:
Reactive Hyperemia Index post mental stress:
age, gender, race, alcohol, smoke, hypertension, dyslipidemia, diabetes mellitus, BMI, antidepressant

RHI: Reactive Hyperemic Index

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, et al. Heart disease and stroke statistics 2015 update: a report from the American Heart Association. Circulation 2015; 131: e29-e322 doi: 10.1161/CIR.0000000000000152.
2. Ginsberg, J. P., Pietrabissa, G., Manzoni, G. M., & Castelnuovo, G. Treating the mind to improve the heart: the summon to cardiac psychology. Frontiers in Psychology.2015; 6, 1101. http://doi.org/10.3389/fpsyg.2015.01101.
3. Menezes AR, Lavie CJ, Milani RV, O'Keefe J, Lavie TJ. Psychological risk factors and cardiovascular disease: is it all in your head? Postgrad Med 2011; 123: 165–76.
4. Takase B, Matsushima Y, Uehata A, Ishihara M, Kurita A. Endothelial dysfunction, carotid artery plaque burden, and conventional exercise-induced myocardial ischemia as predictors of coronary artery disease prognosis. Cardiovascular Ultrasound 2008;6:61
5. Yoshida T, Kawano H, Miyamoto S, Motoyama T, Fukushima H, Hirai N, *et al*. Prognostic value of flow-mediated dilation of the brachial artery in patients with cardiovascular disease. Intern Med 2006; 45:575-9
6. Matsuzawa, Yasushi, Li, Jing, Aoki, Tatsuo; Guddeti, Raviteja R., *et al*. Predictive value of endothelial function by noninvasive peripheral arterial tonometry for coronary artery disease. Coronary Artery Disease, 2015; Vol. 26, No. 3, 22.04. p. 231-238.

7. Hua Chen, Lijie Zhang, Min Zhang, Xiantao Song, Hua Zhang, Yue Liu, Shuzheng Lv Relationship of depression, stress and endothelial function in stable angina patients. Physiology & Behavior. 2013; Volume 118, Pages 152–158 doi:10.1016/j.physbeh.2013.05.024.
8. Poitras, V. J., & Pyke, K. E. The impact of acute mental stress on vascular endothelial function: evidence, mechanisms and importance. Int J Psychophysiol, (2013); 88(2), 124-135. doi: 10.1016/j.ijpsycho.2013.03.019.
9. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation. 1995;91:999-1005
10. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiology 2007; 50: 2173Y95.
11. Beck AT, Steer RA, Brown GK. BDI-II. Beck Depression Inventory: Second Edition. San Antonio, TX: The Psychological Corporation; 1996
12. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation. 1995; 91:999-1005
13. Goldberg AD, Becker LC, Bonsall R, Cohen JD, Ketterer MW, Kaufman PG, et al Ischemic, hemodynamic, and neurohormonal responses to mental and exercise stress. Experience from the Psychophysiological Investigations of Myocardial Ischemia Study (PIMI). Circulation 1996;94:2402Y9
14. Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J. Am. Coll. Cardiology. 1995;26:1235-1241

15. Goor DA, Sheffy J, Schnall RP, Arditti A, Caspi A, Bragdon EE, et al. Peripheral arterial tonometry: A diagnostic method for detection of myocardial ischemia induced during mental stress tests: A pilot study. Clin. Cardiol. 2004;27:137-141
16. Schnall RP, Shlitner A, Sheffy J, Kedar R, Lavie P. Periodic, profound peripheral vasoconstriction--a new marker of obstructive sleep apnea. Sleep. 1999; 22:939-946.
17. Lavie P, Schnall RP, Sheffy J, Shlitner A. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nat. Med. 2000; 6:606.
18. Cooper DC, Milic MS, Tafur JR et al: Adverse impact of mood on flow-mediated dilation. Psychosom Med, 2010; 72: 122–27
19. Shi, H., Feng, G., Wang, Z., Zhou, C., Zhong, G., Hu, Y., & Wang, G. Relationships between Depressive Symptoms and Endothelial Function Among Outpatients of a General Hospital in China. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2015 21, 1812–1819. http://doi.org/10.12659/MSM.893531
20. Elizabeth A. Martin, Shen-Li Tan, Leslie R. MacBride, Shahar Lavi, Lilach O. . Sex differences in vascular and endothelial responses to acute mental stress, Clinical Autonomic Research, December 2008; 18:339.
21. Tomfohr, L. M., Murphy, M. L. M., Miller, G. E., & Puterman, E. Multiwave Associations Between Depressive Symptoms and Endothelial Function in Adolescent and Young Adult Females. Psychosomatic Medicine. 2011; 73(6), 456–461. doi.org/10.1097/PSY.0b013e3182228644

22. Chrapko WE, Jurasz P, Radomski MW et al: Decreased platelet nitric oxide synthase activity and plasma nitric oxide metabolites in major depressive disorder. Biol Psychiatry, 2004; 56: 129–34 35

23. Osika W, Montgomery SM, Dangardt F et al: Anger, depression and anxiety associated with endothelial function in childhood and adolescence. Arch Dis Child, 2011; 96: 38–43 36

24. Broadley AJ, Korszun A, Abdelaal E et al: Metyrapone improves endothelial dysfunction in patients with treated depression. J Am Coll Cardiol, 2006; 48: 170–75

25. C. F de Winter, C. F., et al. Associations of symptoms of anxiety and depression with diabetes and cardiovascular risk factors in older people with intellectual disability. 2015; Journal of Intellectual Disability Research 59(2): 176-185