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Adverse Impact of Mood on Flow-Mediated Dilation

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Abstract

Objective—To examine the impact of mood states on endothelial function, as measured noninvasively by brachial artery flow-mediated dilation (FMD). Substantial literature indicates that negative mood is linked to cardiovascular disease (CVD). However, the mechanisms underlying this relationship are not well defined. CVD is often preceded by dysfunction of the endothelium.

Methods—Healthy adults ($n = 70$; mean age, 36 years) completed the Profile of Mood States (POMS), which contains six subscales (depression/dejection; tension/anxiety; anger/hostility; confusion/bewilderment; fatigue/inertia; vigor/activity) that are used to compute a total mood disturbance score for overall psychological distress. FMD was calculated (maximum percentage change in brachial artery diameter) from ultrasound assessment of arterial diameter at baseline and for 10 minutes after occlusion.

Results—Regressions showed that increases in POMS total mood disturbance scores were associated with decreases in endothelial function. Mood disturbance explained 10% of the variance in FMD ($p < .01$), after controlling for age, sex, mean arterial pressure, body mass index, and socially desirable response bias. An exploratory set of separate regressions conducted to decompose the link between FMD and total mood disturbance revealed that the following POMS subscales were inversely correlated with FMD: depression/dejection, tension/anxiety, anger/hostility, fatigue/inertia (p 's $< .05$), and confusion/bewilderment ($p < .01$).

Conclusions—Mood disturbance could contribute to CVD via impaired vasodilation. These preliminary results show that even mild levels of adverse psychological states, particularly depressed, anxious, angry, confused, and fatigued states, might be linked to increased cardiovascular risk.

Keywords

endothelial function; vasodilation; mood; depression; anxiety; fatigue

INTRODUCTION

Substantial literature points to the adverse effects of negative mood states on cardiovascular disease (CVD). Whereas some biopsychosocial studies have focused on clinical end points (e.g., myocardial infarction), others have investigated ostensible intermediary physiological events (e.g., sympathetic nervous system activation, cardiovascular reactivity, wall motion

abnormalities) (1,2). However, relatively few studies have examined mood in relation to indicators of vascular impairment, such as endothelial dysfunction.

Impairment of the endothelium is observed in early atherosclerosis and is associated with increased plaque rupture in myocardial infarction and other adverse outcomes (3-5). The endothelium functions to control vascular homeostasis by secreting a variety of substances (3), such as nitric oxide. Brachial artery flow-mediated dilation (FMD) provides a bioassay for in vivo endothelial function of the coronary arteries (6). In response to increased shear stress induced by reactive hyperemia, the endothelium is stimulated to produce and release nitric oxide, which relaxes vascular smooth muscle and increases artery diameter (7,8). FMD noninvasively measures endothelium-dependent vasodilation in response to reactive hyperemia (7).

FMD is highly correlated with invasive quantification of the vasomotor responses by epicardial arteries to acetylcholine, which can be considered the gold standard (9,10). In addition to these associations with invasive measures of endothelial function, FMD also exhibits inverse relations with cardiovascular risk, though methodological differences have contributed to some inconsistent findings (11-15). Prospective studies supported the prognostic value of FMD in predicting cardiovascular events in older adults after 5 years (16) and in patients with peripheral artery disease after roughly 2 years (17), as well as in-stent restenosis in patients with coronary artery disease (18) and postoperative outcomes of vascular surgery (19-21).

A small literature has developed that supports links between endothelial function and psychosocial factors. Several laboratory investigations revealed relationships between exposure to mental stress and decreased FMD (22-24), with one such investigation suggesting this association may be particularly strong among hostile individuals (25). Other examinations of FMD have found impaired vasodilation in healthy adults with negative psychological traits (26-31) and in patients diagnosed with major depression (32-34), but results have been mixed regarding depression-related differences among adults at elevated risk for CVD (35,36).

Growing evidence indicates that subclinical negative mood symptoms are relatively prevalent and may be linked to cardiovascular outcomes (1,2). However, research is scarce with respect to whether these more mild levels of mood disturbance also relate to endothelial functioning. Although two small studies in Japan found no associations with mood states in men (28) or older adults (29), a report from the Healthy Women Study revealed that FMD was inversely associated with depressive symptoms among postmenopausal women only if they were not using hormone replacement therapy (27). The purpose of the current study is to expand the literature on mood and endothelial dysfunction by examining how mild mood disturbance relates to FMD in a sample of young to middle-aged adults.

METHODS

Participants

The sample included 70 employed (30+ hours/week), young to middle-aged adults (mean age, 36.2 years; 52% white; 48% black), who were recruited through community advertisements or referrals to participate in a larger cardiovascular study conducted between 2005 and 2008. Although 13% of participants were mildly hypertensive, the sample was otherwise healthy and medication free, as determined by a physician's evaluation of medical histories and physical status. Two of the volunteers were on antihypertensive medication regimens and underwent a 3-week closely monitored drug tapering before participating in the study. All study participants were free of major medical diseases and psychiatric

disorders, with no use of psychiatric drugs or other medications. Excluded were persons with diagnoses of secondary hypertension, diabetes (or a fasting glucose of >120 mg/dL), morbid obesity (body mass index [BMI] ≥ 40 kg/m²), known sleep disorders (e.g., narcolepsy), current drug or alcohol abuse, creatinine levels of >1.4 mg/dL, proteinuria, hematuria, or renal bruit on examination. Women were ineligible if they were pregnant, postmenopausal, taking oral contraceptives, or diagnosed with premenstrual syndrome. Informed consent was obtained from all participants in accordance with the Institutional Review Board of the University of California, San Diego.

Procedures

After a physical examination and medical history to confirm eligibility, demographic and psychosocial questionnaires (including the Profile of Mood States or POMS) were collected, along with measures of resting mean arterial pressure (MAP) and BMI. Participants underwent FMD testing the morning after an overnight stay at the General Clinical Research Center of the University of California, San Diego. Before testing, participants avoided smoking and consumption of caffeine, alcohol, and foods containing high fat or nitrates for at least 12 hours before the examination.

Measures

Flow-Mediated Dilation—A single examiner blinded to the hypotheses conducted noninvasive assessments of endothelial functioning in all participants, using the methods described by Celermajer and colleagues (37). This examiner (M.S.M.) has extensive experience in brachial artery imaging and providing reliable measurements (e.g., intraobserver reliability based on two blinded evaluations of 20 randomly selected recordings: intraclass correlation, 0.96; 95% confidence interval, 0.89–0.98). Participants relaxed in the supine position for >30 minutes in a quiet room with room temperature maintained at 22°C to 25°C to avoid mental stress that can affect vasodilator responses (24). The right brachial artery was visualized in longitudinal section 2 cm to 8 cm proximal to the antecubital fossa with a high-resolution 5 MHz to 12 MHz broadband linear array transducer (ATL HDI5000 SonoCT System, Philips; Oceanside, California). After optimal transducer positioning and adjusting the ultrasound depth and gain for the best images of the intimal layers, diameter was measured from the anterior to the posterior intima line at end diastole, synchronous with ECG R wave. Baseline brachial artery diameter was determined by averaging three diameter measurements taken immediately before cuff inflation. Then, the cuff was inflated to a pressure 50 mm Hg greater than the systolic blood pressure. After 5 minutes, the cuff was deflated and ultrasound scans were acquired for postocclusion diameter measurements at 15-second intervals for 1 minute and then at 30-second intervals for an additional 9 minutes. FMD was calculated as the maximum percentage change in brachial artery diameter from the baseline value to the maximum value measured after cuff deflation (6,37) with the following formula: $\text{max FMD\%} = \frac{(\text{maximum diameter cm}) - (\text{baseline diameter cm})}{(\text{baseline diameter cm})} \times 100$.

Profile of Mood States—The POMS questionnaire is a factor analytically derived measure of psychological distress that has been widely used in biomedical research with both healthy and patient samples (38,39). The 37-item POMS short form is highly correlated ($r = .95-.99$) with the original version and shows adequate psychometric properties (40,41). It contains six subscales: depression/dejection; tension/anxiety; anger/hostility; confusion/bewilderment; fatigue/inertia; and vigor/activity. Respondents are asked to indicate on a 0 to 4 scale (0 = not at all to 4 = extremely) how much they have experienced a particular feeling during the past week, including today. Research has utilized the POMS subscales as well as the POMS total mood disturbance (TMD) score. The TMD is an index of overall distress that is obtained by summing all subscale scores except for the score on the vigor/activity

subscale; the latter subscale score is subtracted from the sum of the other subscales. The current study assesses both the TMD and decomposes the POMS by subscale to assess the contribution of specific mood states.

Covariate Measures—Covariates were age and sex, along with the potential confounders of resting MAP, BMI, and socially desirable response bias.

Resting MAP: After 5 minutes of seated rest, three measures of MAP were obtained with a Dinamap 1846X monitor (Critikon, Tampa, Florida) and averaged to compute resting MAP.

BMI: Weight and height measured on a calibrated scale were used to derive BMI to the nearest 0.1 kg and 0.1 cm, respectively.

Social Desirability: The Marlowe Crowne Social Desirability Scale contains 33 true/false items representing socially desirable behaviors that are rather unlikely to occur in the general population (42). Higher scores on this measure suggest a tendency for respondents to underreport information they believe may reflect negatively on them and to overreport positively viewed behaviors. We have previously reported (43) variations in the willingness to report psychosocial distress; thus, Marlowe Crowne Social Desirability Scale scores are included as a covariate to control for this type of response bias.

Data Analysis

The primary analysis was a hierarchical multiple regression, which was conducted with POMS TMD as the predictor and FMD as the criterion variable. This was followed by a secondary set of regressions to decompose the mood and endothelial function relationship, with separate exploratory regressions of each of the following POMS subscale scores on FMD: depression/dejection; tension/anxiety; anger/hostility; confusion/bewilderment; fatigue/inertia; and vigor/activity. The values for FMD and the POMS were analyzed as continuous scores. FMD and Marlowe-Crowne Social Desirability scores were square root transformed to reduce skew.

With consideration of the power allowed by the sample size, each model contained the following standard set of covariates that were selected based on prior literature (44) and/or their correlations with the primary variables of interest: age, sex, BMI, resting MAP, and socially desirable response bias. (Neither FMD nor POMS scores differed according to hypertension status, smoking status, or racial group; thus, these variables were not included in the regressions.) All regression models included the following covariates in the first step: age, sex (male = 0, female = 1), BMI, resting MAP, and socially desirable response bias. POMS TMD was included in the final step in the primary regression model, while the POMS subscale of interest was entered in the last step in the exploratory regressions of subscales on FMD.

RESULTS

Sample Characteristics

Table 1 shows the characteristics of the sample. The sample ranged in age from 19 to 53 years, with a mean of 36 years of age. The mean for the POMS TMD was 6.6. On average, participants exhibited a 14.2% change in brachial artery FMD, with a range of 1.9% to 31.0%.

Simple Correlations

As indicated in Table 2, higher POMS TMD scores showed simple correlations with marginally lower FMD ($p = .065$) and a significantly higher tendency to give socially desirable responses (i.e., Marlowe-Crowne scores) ($p < .001$). Among this sample of young to middle-aged adults, age was positively related to FMD ($p < .05$), BMI ($p < .01$), and resting MAP ($p < .05$).

Primary Analyses of Mood Disturbance and FMD

Table 3 details the results for the regression model of POMS TMD on FMD, after controlling for age, sex, resting MAP, BMI, and socially desirable response bias. Increased overall psychological distress, as measured by the POMS TMD, was significantly correlated with reduced endothelial function (Fig. 1). Mood disturbance explained 10% ($p < .01$) of the variance in the full model of POMS TMD on FMD [$F(6,63) = 3.39$; $p < .01$, $R^2 = .24$]. Although the aforementioned regression utilized a single value of maximal percentage change in diameter as the measure for FMD, the pattern of endothelial response relative to level of mood disturbance is better illustrated over the course of the FMD testing period. Figure 2 illustrates that participants with high mood disturbance (dichotomized by median split) exhibited less vasodilation than those with low mood disturbance throughout the FMD testing period (after adjustment for original covariates and baseline diameter; analyses not shown).

Exploratory Analyses of Mood Subscales

Separate exploratory regressions of each individual POMS subscale on FMD were conducted to reveal the underpinnings of the observed relationship between POMS TMD and FMD. With all exploratory models adjusted for covariates (i.e., age, sex, BMI, resting MAP, social desirability), regression results suggested that no single mood dimension was driving this relationship. Rather, increasing scores on each POMS subscale were significantly correlated with decreased FMD, with the exception of vigor/activity, which showed no significance.

Specifically, the regression model of POMS-depression/dejection on FMD showed the depressed/dejected mood scores accounted for 7% ($p < .05$) of the variance in FMD ($F[6,64] = 2.91$; $p < .05$, $R^2 = .21$). Likewise, the separate models for the POMS-tension/anxiety ($F[6,64] = 2.88$; $p < .05$, $R^2 = .21$) and the POMS-anger/hostility ($F[6,63] = 2.92$; p 's $< .05$, $R^2 = .22$) subscales indicated that each of these mood dimensions explained 7% ($p < .05$) of the variance in FMD. The regression of POMS-confusion/bewilderment on FMD revealed that this subscale contributed 9% ($p < .01$) of the variance explained by the model ($F[6,64] = 3.32$; $p < .01$, $R^2 = .24$). POMS-fatigue/inertia contributed 6% ($p < .05$) of the total variance in FMD ($F[6,64] = 2.71$; $p < .05$, $R^2 = .20$).

Exploratory Analyses of Potential Confounders

Although cholesterol showed no simple correlation with FMD in this healthy sample ($p > .05$), prior studies (44) suggested that it might influence FMD. We explored this possibility by modifying the primary regression model to add cholesterol as a covariate (data not shown). Results indicated that controlling for cholesterol had virtually no impact on the relationship between POMS TMD and FMD. Other exploratory regressions (data not shown) to test possible interactions between POMS TMD scores and demographic characteristics (i.e., sex, race, age) found no significant effects for FMD.

DISCUSSION

A variety of traditional, novel, and genetic risk factors for atherosclerosis may share endothelial dysfunction as a “final common pathway” in promoting CVD (3). Endothelial function can be considered a “barometer” for one’s susceptibility to cardiovascular risk (3,4). Accordingly, it is one of the potential pathways linking negative mood to CVD.

Prior studies have found that impaired vasodilation is associated negative psychological trait measures (26-31) and mood disorders (32-34), but little is known about how endothelial function relates to state measures of mild forms of mood disturbance.

The present study found that increasing scores on the POMS TMD were accompanied by poorer endothelial function, as indicated by decreased FMD. Regression results indicated that overall psychological distress (i.e., POMS TMD scores) explained 10% of the variance in FMD, after adjustment for age, sex, BMI, resting MAP, and socially desirable response bias. These findings were decomposed with exploratory analyses of the individual mood dimensions measured by the POMS subscales to explore whether a particular mood state was dominant in driving the relationship between FMD and POMS TMD. Results for the POMS subscales showed that vasodilation decreased as levels of depressed, anxious, angry, confused, and fatigued states increased. Thus, a variety of mood states may be associated with increased endothelial dysfunction. Future research should examine how endothelial function relates to different types of mood disturbance, using more in-depth measures of each mood.

Due to a lack of comparable studies on vasodilation and general psychological distress (e.g., POMS TMD), it is difficult to synthesize our primary findings with the rest of the FMD literature. Although some mixed results have been reported (28,29,31), several investigations have found inverse associations between FMD and trait measures of negative affect (25,27,30,31,35). Similarly, our exploratory analyses of the POMS subscales showed that FMD was inversely related to depressed, anxious, and angry mood states. Although the mechanisms linking disturbed mood to endothelial functioning remain uncertain, Harris and Matthews posited (26) that negative affective states are linked to endothelial dysfunction via a predisposition for autonomic hyperactivity. This could disrupt the balanced functional antagonism between the endothelium and the autonomic nervous system, leading to adverse changes in vascular tone (26). It would be helpful for future research to assess mood in relation to both endothelial and autonomic functioning.

Our findings regarding states of fatigue and confusion add a new and interesting dimension to the literature on FMD. To our knowledge, this is the first report of a link between diminished FMD and increased fatigue. More research on this association is needed, given the prior literature that suggests fatigue and related symptoms (e.g., vital exhaustion) may be associated with poorer outcomes in cardiovascular patients (1,2). Behavioral cardiology has rarely focused on reports of confusion and unclear thinking as a CVD risk factor, but our findings suggest that struggling with one’s thoughts could be associated with diminished vasodilation. In light of prior work showing neuropsychological decrements among clinically depressed patients with lower FMD (5), it may be productive to consider self-reported confusion and standardized neuropsychological tests in future research on endothelial function.

Most of the existing literature that links mood to endothelial function (26-29,31-36) is focused on associations found among samples with characteristics that may have increased their vulnerability to poorer cardiovascular function (e.g., older age, postmenopausal status, major mood disorders, elevated levels of cardiovascular risk factors). The current study offers evidence that endothelial dysfunction may be associated with mild mood disturbance

in healthy young to middle-aged adults as well. Our results are strengthened by the study's relatively strict exclusion criteria and physician confirmation of health status, which reduced the confounding effects of health factors (e.g., diabetes mellitus) on FMD. The findings also were bolstered by adjustments to the analyses that suggest the observed links between increased mood disturbance and reduced FMD were not due to varying levels of cardiovascular risk factors (e.g., blood pressure, BMI, cholesterol). Another strength is the study's consideration of socially desirable response bias as a covariate, given the variations in individuals' willingness to disclose potentially negative information on self-report measures, such as the POMS. It may be informative for future research on endothelial function to further examine social desirability, in light of its unexpected correlation with FMD (Table 3).

Several limitations must be noted. Replication of this study with a larger sample size is needed. The current results are based a relatively healthy sample and might have limited generalizability to less healthy populations. Generalizability of our findings to older men and postmenopausal women also is uncertain, because these groups were excluded from the sample. Although prior reports found aging-related reductions in vasodilation among older adults (6,44), our sample of healthy, young to middle-aged adults showed a correlation between increasing age and increasing vasodilation. This inconsistency might be partly due to aging of the vasculature being less influential on our sample than age-associated differences in other potential contributors to reduced vasodilation, such as depressed mood, which tended to decline as age increased ($p = .06$). The present study also may be limited by our reliance on self-reported psychiatric history for screening of exclusions and by our utilization of the POMS for a continuous measure of mood disturbance rather than using a formal diagnostic tool. However, support is growing for the use of nondiagnostic instruments like the POMS, as increasing evidence is found for associations between subclinical mood symptoms and physical illness. It would be informative for future studies of mood states and FMD to evaluate how much of this relationship might be explained by clinical history of mood disorder or negative psychological traits, which could have more enduring influences on endothelial function. Finally, the current study is limited by its cross-sectional design, which cannot establish that mood disturbance caused the variations in FMD.

Overall, the results suggest that mood states are associated with impaired endothelial-dependent vasodilation, even in young healthy adults. In particular, depressed, anxious, angry, confused, and fatigue states were inversely associated with FMD. These findings suggest that endothelial dysfunction could be a pathway through which mood states are linked to CVD.

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Glossary

FMD	flow-mediated dilation
POMS	Profile of Mood States
TMD	total mood disturbance
MAP	mean arterial pressure
BMI	body mass index

CVD cardiovascular disease

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Figure 1. Scatterplot of endothelial function and mood disturbance in healthy adults. Increases in overall psychological distress (i.e., total mood disturbance) were accompanied by decreases in maximum endothelium-dependent dilation of the brachial artery (i.e., flow-mediated dilation).

Figure 2.

Mean vasodilation across the 10-minute assessment period for flow-mediated dilation in adults with low versus high total mood disturbance scores. Adults with high mood disturbance exhibited less vasodilation (i.e., more endothelial dysfunction) than those with low mood disturbance throughout the testing period.

TABLE 1**Sample Characteristics**

Variable	Mean (SD) or %	Range
Flow-mediated dilation (% change from baseline)	14.2% (6%)	1.9%–31.0%
Baseline artery diameter (cm)	0.4 (0.1)	0.2–0.5
POMS: total mood disturbance	6.6 (20.8)	–20–69
Depression/dejection	3.7 (4.9)	0–21
Tension/anxiety	4.4 (4.3)	0–17
Anger/hostility	3.7 (4.5)	0–15
Confusion/bewilderment	3.0 (3.4)	0–15
Fatigue/inertia	4.3 (4.3)	0–16
Vigor/activity	12.4 (5.4)	0–24
Age (years)	36.2 (9.4)	19–53
BMI (kg/m ²)	26.5 (3.9)	19.1–35.1
Resting MAP (mm Hg)	89.1 (10.9)	68.7–119.4
Marlowe-Crowne Social Desirability Scale	19.7 (5.9)	3–32
Total serum cholesterol (mg/dL)	172.0 (39.1)	98.0–366.0

SD = standard deviation; POMS = Profile of Mood States; BMI = body mass index; MAP = mean arterial pressure.

Data shown as mean (SD), unless otherwise noted.

TABLE 2

Simple Correlations (r) Among Variables

Variable	1	2	3	4	5	6	7
1. FMD	—	0.25*	0.14	-0.08	0.01	0.04	-0.22 [‡]
2. Age		—	-0.04	0.23*	0.37**	0.20 [‡]	-0.15
3. Sex			—	-0.12	-0.05	-0.02	0.05
4. Resting MAP				—	0.51**	-0.02	0.17
5. BMI					—	0.02	0.13
6. Social desirability						—	-0.62**
7. Total Mood Disturbance							—

FMD = flow-mediated dilation; MAP = mean arterial pressure; BMI = body mass index.

* $p < .05$
** $p < .01$
[‡] $p = .06-.07$ (two-tailed).

TABLE 3
Regression of Profile of Mood States—Total Mood Disturbance on Flow-Mediated Dilation

Dependent Variable	Steps	ΔR^2	ΔF	B (SE)	β	p
Flow-mediated dilation	1) Covariates	.14	2.16			
	a) Age			0.02 (0.01)	0.29	.03*
	b) Sex			0.28 (0.18)	0.18	.13
	c) Resting MAP			-0.01 (0.01)	-0.18	.19
	d) BMI			0.02 (0.03)	0.11	.43
	e) Social desirability			-0.31 (0.13)	-0.33	.02*
	2) Total mood disturbance	.10	8.29	-0.02 (0.01)	-0.41	.005**

SE = standard error; MAP = mean arterial pressure; BMI = body mass index.

* $p < .05$

** $p < .01$.