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Bipolar disorder and related mood states are not associated with endothelial function of small arteries in adults without heart disease

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ABSTRACT

Background: Individuals with bipolar disorder are at increased risk for adverse cardiovascular disease (CVD) events. This study aimed to assess endothelial function and wave reflection, a risk factor for CVD, as measured by finger plethysmography in bipolar disorder to investigate whether CVD risk was higher in bipolar disorder and altered during acute mood episodes. We hypothesized that EndoPAT would detect a lower reactive hyperemia index (RHI) and higher augmentation index (AIX) in individuals with bipolar disorder compared with controls. Second, we predicted lower RHI and higher AIX during acute mood episodes.

Methods: Reactive hyperemia index and augmentation index, measures of microvascular endothelial function and arterial pressure wave reflection respectively, were assessed using the EndoPAT 2000 device in a sample of 56 participants with a DSM-IV diagnosis of bipolar I disorder with 82 measures spanning different mood states (mania, depression, euthymia) and cross-sectionally in 26 healthy controls.

Results: RHI and AIX were not different between adults with and without bipolar disorder (mean age 40.3 vs. 41.2 years; RHI: 2.04 ± 0.67 vs. 2.05 ± 0.51; AIX@75 (AIX adjusted for heart rate of 75): 1.4 ± 19.7 vs. 0.8 ± 22.4). When modeled in linear mixed models with a random intercept (to account for repeated observations of persons with bipolar disorder) and adjusting for age and sex, there were no significant differences between those with bipolar disorder and controls ($p = 0.89$ for RHI; $p = 0.85$ for AIX@75).

Conclusions: Microvascular endothelial function and wave reflection estimated by finger plethysmography were unable to detect differences between adults with and without bipolar disorder or changes with mood states. Future research is necessary to identify more proximal and sensitive, yet relevant, biomarkers of abnormal mood-related influences on CVD risk or must target higher risk samples.

1. Introduction

Cardiovascular mortality is known to be one of the leading cause of excess mortality in bipolar disorder [1]. Large, contemporary population-based studies suggest an elevated risk of cardiovascular disease mortality with estimated standardized mortality ratios ranging from 1.6 to 2.7 [2–4]. Traditional risk factors of cardiovascular disease such as smoking, obesity, inflammation, glucose homeostasis, and diabetes mellitus are more prevalent in the population of people with bipolar disorder [5–9]. Overall, adults with bipolar disorder in the US population have a 5-fold increased risk of CVD as well as 14 year earlier onset of CVD compared to adults without mood disorders [10]. In a nationally representative sample, the association between bipolar disorder and vascular disease, at least in women, was found to be independent of age, urbanicity, marital status, race, employment, family history of heart disease, obesity, high blood pressure and diabetes [11].

In its classic form, bipolar disorder is characterized by recurrent episodes of mania and depression [12]. The individual course of illness can vary considerably with regards to the propensity for and persistence of mood episodes [13]. The specific mechanisms by which the risk of

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cardiovascular disease in bipolar disorder have not been fully elucidated [14], although there is some evidence that those with a greater symptom burden or a more persistent course of illness are at greater relative risk, suggesting that mood symptom burden may contribute to risk in a dose-dependent fashion [15–18]. In a meta-analysis of 27 studies with 2161 patients with bipolar disorder and 81,932 controls, CRP levels were moderately elevated during episodes of depression and euthymia, and greatly elevated during manic episodes [6], suggesting mechanisms beyond traditional risk factors may be involved.

Through the process of deposition of lipids and smooth muscle cells, inflammatory infiltration, plaque formation, continued remodeling, and eventual destruction of vessel lumen, endothelial dysfunction is a useful marker for poor vascular health [19,20]. Furthermore, chronic endothelial dysfunction may have a shared inflammatory mechanism between insulin resistance, metabolic syndrome, and severe mental disorders that result in poor vascular health [7]. To investigate mechanisms by which mood states can influence cardiovascular disease events or mortality, intermediate physiological measures reactive hyperemia index (RHI) and augmentation index (AIX) were collected as surrogate outcomes for CVD. There have been no prospective studies of endothelial function across mood episodes in bipolar disorder. Two prospective studies in those with depressive episodes have demonstrated changes in endothelial function, as measured by finger plethysmography with EndoPAT, corresponding to onset of depressive symptoms. The first demonstrated worsening endothelial function in adolescent and young adult females who developed depressive symptoms, which did not persist when depression resolved [21]. Similarly in a study of medical interns, worsening depressive symptoms over follow-up were inversely associated with endothelial function [22]. EndoPAT, which measures volumetric changes in the fingertip, quantifies microvascular endothelial function with a reactive hyperemia index [23,24]. A cuff occludes blood flow through the brachial artery, and nitric oxide-mediated vascular dilation results when the cuff is deflated as a result of elevation in blood flow and shear stress [23,25]. Additionally, augmentation index, a value derived from the timing and amplitude of pressure wave reflection, is a strong independent risk marker for coronary vascular disease in some studies [26]. EndoPAT has several advantages over other methods, which include being non-invasive, correlated to multiple traditional risk factors for cardiac events, and predictive of cardiovascular events [27,28].

Previous studies utilizing EndoPAT have identified peripheral endothelial dysfunction in patients during depression episodes [21,22]. This current study is the first to utilize EndoPAT to evaluate endothelial function in clinically diagnosed sample with bipolar disorder and does so across different mood states. In a sample of individuals with diagnosed bipolar disorder and healthy controls, we tested the hypothesis that RHI would be lower and AIX adjusted for heart rate of 75 (AIX@75) would be higher in individuals with bipolar I disorder compared with controls. In addition, we predicted lower RHI and higher AIX@75 during acute mood episodes compared with normal mood state.

2. Methods

A total of 82 unique volunteers participated in this study, consisting of a group of 56 participants with a DSM-IV diagnosis of bipolar I disorder and a group of 26 healthy control participants, balanced by age and sex (Table 1). Community diagnosis was confirmed by a semi-structured, one-hour clinical interview by a study psychiatrist (JGF), using a template that ensured DSM-IV criteria for bipolar I disorder were met and also specifically screened for tobacco, alcohol and drug use/abuse/dependence as well as common comorbidities such as psychosis, obsessions, compulsions, and panic attacks. Participants with bipolar I disorder were in either a manic episode (Young Mania Rating Scale (YMRS) ≥ 20), a depressive episode (Montgomery–Åsberg Depression Rating Scale (MADRS) > 20), or a euthymic state (YMRS ≤ 12 and MADRS < 10) during the assessment. Some participants were evaluated repeatedly in different mood states. Healthy control participants had no history of psychiatric illness (DSM-IV Axis I or Axis II), confirmed using a telephone screener and the semi-structured clinical interview administered by a research assistant. Participants were recruited through advertisements, referrals from the University of Iowa Hospitals and Clinics (outpatient and inpatient), and a research registry. Controls were recruited through advertisements in the same media. The sample was primarily recruited for a neuroimaging study in bipolar disorder that prospectively imaged individuals across discrete mood episodes, identified by either participants themselves or intermittent compensated research assistant follow-up calls [29–32]. Exclusion criteria included history of brain damage, neurological problems such as seizure disorder, syncope, or migraine with aura, cardiac or respiratory diseases, alcohol or drug dependence, amphetamine use, or any contraindication to magnetic resonance imaging (MRI). Participants provided written informed consent for this study, which was approved by the University of Iowa Institutional Review Board.

Trained research nurses confirmed that participants fasted for at least 12 h and had not smoked for at least 2 h prior. They then measured vital signs, height (without shoes to nearest 0.1 cm), and weight (without shoes in light clothing to the nearest 0.25 kg). A member of the research team then obtained a health and psychiatric history, and administered psychiatric rating scales, MADRS and YMRS. Basic assessments of clinical and demographic data were acquired. Information regarding cardiovascular risk factors including family history, diabetes, dyslipidemia, and smoking history was collected by trained health professional.

RHI and AIX, which are measures of microvascular endothelial function and pressure wave reflection, respectively were gauged using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel) on

Table 1
Baseline participant sociodemographic characteristics of sample (N = 82).

	Controls	Bipolar disorder	
	(N = 26)	(N = 56)	*p*-Value
Sex, N (%)			
Female	9 (35%)	22 (39%)	0.81[a]
Male	17(65%)	34 (61%)	
Marital status			
Single	9 (35%)	22 (39%)	0.14[a]
Married	15 (58%)	21 (38%)	
Divorced	2 (8%)	13 (23%)	
Race			
American Indian/Alaskan Native	0	2 (4%)	0.59[a]
Asian	0	1 (2%)	
African American	0	2 (4%)	
White	26 (100%)	51 (91%)	
Ethnicity			
Hispanic	0	1 (2%)	0.69[a]
Not Hispanic	26 (100%)	52 (93%)	
Unknown	0	3 (5%)	
Employment			
Unemployed	2 (8%)	20 (36%)	< 0.001[a]

	Controls	Bipolar disorder	
	(N = 26)	(N = 56)	p-Value
	Mean (SD)		
Age (years)	41.2 (13.8)	40.3 (12.8)	0.81
Education years	16.6 (2.1)	14.7 (2.1)	< 0.001
Smoking (pack ∗ years)	1.4 (3.5)	7.3 (12.5)	0.002
Body mass index (kg/m^2)	26.2 (3.9)	29.7 (8.9)	0.08

[a] Exact tests used across categorical variables for consistency given low observed cell counts with most variables.