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Impaired coronary microvascular reactivity in youth with bipolar disorder

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Original Article

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Abstract

Background. Cardiovascular disease (CVD) is excessively prevalent and premature in bipolar disorder (BD), even after controlling for traditional cardiovascular risk factors. The increased risk of CVD in BD may be subserved by microvascular dysfunction. We examined coronary microvascular function in relation to youth BD.

Methods. Participants were 86 youth, ages 13–20 years ($n = 39$ BD, $n = 47$ controls). Coronary microvascular reactivity (CMVR) was assessed using quantitative T_2 magnetic resonance imaging during a validated breathing-paradigm. Quantitative T_2 maps were acquired at baseline, following 60-s of hyperventilation, and every 10-s thereafter during a 40-s breath-hold. Left ventricular structure and function were evaluated based on 12–15 short- and long-axis cardiac-gated cine images. A linear mixed-effects model that controlled for age, sex, and body mass index assessed for between-group differences in CMVR (time-by-group interaction).

Results. The breathing-paradigm induced a significant time-related increase in T_2 relaxation time for all participants (i.e. CMVR; $\beta = 0.36$, $p < 0.001$). CMVR was significantly lower in BD *v.* controls ($\beta = -0.11$, $p = 0.002$). Post-hoc analyses found lower T_2 relaxation time in BD youth after 20-, 30-, and 40 s of breath-holding ($d = 0.48$, $d = 0.72$, $d = 0.91$, respectively; all $p_{FDR} < 0.01$). Gross left ventricular structure and function (e.g. mass, ejection fraction) were within normal ranges and did not differ between groups.

Conclusion. Youth with BD showed evidence of subclinically impaired coronary microvascular function, despite normal gross cardiac structure and function. These results converge with prior findings in adults with major depressive disorder and post-traumatic stress disorder. Future studies integrating larger samples, prospective follow-up, and blood-based biomarkers are warranted.

Introduction

Bipolar disorder (BD) is a severe, recurrent mood disorder characterized by a substantial burden of depression and mania symptoms, alongside comorbid psychiatric conditions (Vieta et al., 2018). Additionally, cardiovascular disease (CVD) is excessively prevalent in BD and occurs over a decade prematurely (Goldstein, Schaffer, Wang, & Blanco, 2015b; Nielsen, Banner, & Jensen, 2021; Westman et al., 2013). An American Heart Association scientific statement positioned BD as a condition that predisposes youth to accelerated atherosclerosis and early CVD (Goldstein et al., 2015a). Importantly, the excessive rates and premature onset of CVD exceeds what can be explained by traditional cardiovascular risk factors (e.g. hypertension, obesity, smoking), psychiatric medications, and substance use (Goldstein et al., 2015b).

This prompts the question of what other factors may contribute to the excess and prematurity of CVD, beyond traditional cardiovascular risk factors. While ischemic heart disease, a condition excessively prevalent in BD, is most commonly caused by atherosclerosis (Hsu, Chien, & Lin, 2021), other processes may explain and contribute to the BD-heart connection. For example, depression (Pimple et al., 2019; Wei et al., 2014), stress (Pimple et al., 2019), discrimination (McKinnon et al., 2021), and anger (Pimple et al., 2015) are associated with mental stress-induced myocardial ischemia, independent of demographic factors (e.g. sex, race, socioeconomic status) (McKinnon et al., 2021; Pimple et al., 2015; Wei et al., 2014),

medications (e.g. antidepressants, statins, beta-blockers) (Pimple et al., 2019; Wei et al., 2014), cardiovascular risk (e.g. smoking, hypertension, diabetes) (McKinnon et al., 2021; Pimple et al., 2015; Wei et al., 2014), and CVD severity (McKinnon et al., 2021; Pimple et al., 2015; Wei et al., 2014). Takotsubo cardiomyopathy, also known as broken heart syndrome, is characterized by left ventricular dysfunction after experiencing major emotional or psychological stressors (Pelliccia, Kaski, Crea, & Camici, 2017). Both stress-induced myocardial ischemia and takotsubo cardiomyopathy are thought to be related to microvascular dysfunction, even in the absence of coronary atherosclerosis (Pelliccia et al., 2017; Vaccarino et al., 2021a; Vitale, Rosano, & Kaski, 2016). We posit that BD, in part, is subserved by microvascular dysfunction (Goldstein, 2017; Goldstein et al., 2020), and that this may contribute to the increased risk of CVD, beyond traditional cardiovascular risk factors.

Myocardial flow reserve (MFR), a measure of myocardial microvascular function, refers to the vasodilatory capacity of the myocardial microvessels to increase myocardial perfusion in response to vasoactive substances such as adenosine (Kaufmann & Camici, 2005). MFR is impaired in adults with type 2 diabetes (Atar, Altuner, Bozbas, & Korkmaz, 2012; Nahser, Brown, Oskarsson, Winniford, & Rossen, 1995), hypertension (Galderisi et al., 2007; Kozàkovà et al., 1997; Rimoldi, Rosen, & Camici, 2014), and hypercholesterolemia (Galderisi et al., 2007; Yokoyama et al., 1996). Additionally, psychological stressors, such as mental stress (Arrighi et al., 2000; Hasegawa et al., 2005), post-traumatic stress disorder (Vaccarino et al., 2013; Vaccarino et al., 2021b), and depression (Vaccarino et al., 2009) have also been associated with impaired MFR. Furthermore, impaired MFR has also been observed in youth with Kawasaki disease (an illness characterized in part by inflammation and swelling of the coronary vessels) (Furuyama et al., 2003; Hamaoka, Onouchi, & Ohmochi, 1992; Muzik et al., 1996; Noto et al., 2002), and in children and neonates with congenital heart disease (Aburawi & Pesonen, 2011; Bengel et al., 1998). The gold standard measure of MFR is based on positron emission tomography with the injection of adenosine, which exposes individuals to radiation and arrhythmogenic risk (Li et al., 2016; Singh & McKintosh, 2021). Therefore, non-invasive approaches optimize the risk-benefit balance in certain populations, such as youth and individuals without clinical cardiovascular pathology.

Coronary microvascular reactivity (CMVR), defined as increased myocardial oxygenation in response to vasoactive stimuli (Fischer et al., 2018; Fischer, Guensch, & Friedrich, 2015), is a non-invasive measure of coronary microvascular function. CMVR can be measured via oxygen-sensitive cardiovascular magnetic resonance imaging (OS-CMR) using a combined breathing-paradigm of hyperventilation to elicit hypocapnia, followed by breath-holding to elicit hypercapnia (Fischer et al., 2015; Guensch et al., 2014; Teixeira, Nadeshalingam, Fischer, Marcotte, & Friedrich, 2016). In addition to the advantages of non-invasiveness and a strong safety and tolerability profile, CMVR exhibits sensitivity across the full physiological spectrum of myocardial microvascular function (Fischer et al., 2015). This sensitivity is attributed to the fact that breathing-paradigms assess the physiological mechanism of preserving myocardial oxygenation, which is regulated by the arterial partial pressure of oxygen and carbon dioxide (Broten & Feigl, 1992; Broten, Romson, Fullerton, Van Winkle, & Feigl, 1991).

We set out to examine CMVR in youth with BD *v.* controls. Our primary hypothesis was that youth with BD would have a lower CMVR compared to controls. Additionally, we evaluated gross cardiac structure (e.g. left ventricular mass) and/or function (e.g. ejection fraction), using MRI, although we did not expect between-group differences.

Methods

Participant recruitment for this study began in January 2017 and concluded in February 2020 due to the onset of the pandemic, followed by our research group's relocation to a different institution with a different MRI scanner and sequence. Consent was obtained from all participants and their parent and/or guardian prior to participating. Ethical approval was granted by the Research Ethics Boards at Sunnybrook Research Institute (REB 435-2015) and at the Centre for Addiction and Mental Health (REB 163/2020).

Participants

This study included youth between the ages of 13–20 years with BD (type I, II or not otherwise specified [NOS]) and controls. BD participants were primarily recruited from a tertiary subspecialty youth BD clinic. Control participants were recruited through public advertisements.

Psychiatric diagnoses of all participants were determined via the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (KSADS-PL) (Kaufman et al., 1997). The Diagnostic and Statistical Manual of Mental Disorders IV was used to define BD type I and II. BD-NOS diagnosis was defined using the same operationalized criteria as the Course and Outcome of Bipolar Youth Study (Birmaher et al., 2009). This study was recruited from an ongoing larger study from our clinic that began in 2012. Given that DSM V was released in 2013, and it took until 2016 for the updated KSADS to be released, we continued using the DSM IV criteria for consistency across the studies. The depression and mania rating scales from K-SADS-PL were used to assess current and lifetime symptom severity (Axelson et al., 2003). The K-SADS-PL post-traumatic stress disorder screener was used to obtain lifetime physical and sexual abuse history. The Children's Global Assessment Scale (CGAS) was used as a global assessment of psycho-social functioning and current and lifetime psychiatric symptoms (Shaffer et al., 1983). The socioeconomic status of parents was assessed using the Hollingshead Four-Factor Index (Hollingshed, 1975). The ethnicity and sex of participants were recorded based on participant self-reports. All interviewers had a bachelor's or master's degrees and completed training under the supervision of the senior author (B.I.G.). Diagnoses and symptom ratings were reviewed with a licensed child-adolescent psychiatrist (B.I.G.). The mood of participants with BD were classified as euthymic, depressed, and/or hypomanic/manic based on a score of: <13 on both the K-SADS-PL depression and mania scales, ⩾13 on the K-SADS-PL depression rating scale and ⩾13 on the K-SADS-PL mania rating scale respectively.

Control participants were excluded if they had a lifetime history of MDD, BD, or psychosis, or a first or second-degree family history of BD or psychosis. Participants in both groups were excluded if they were unable to provide informed consent; had substance dependence in the past three months; were taking any anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycemic agents; or had a cardiac condition, MRI contraindications such as claustrophobia, or an infectious illness in the past 14 days.

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Anthropometric measures

Height and weight measurements were obtained using standardized procedures (Krebs et al., 2007) and repeated twice for accuracy. To adjust for clothing differences weight was adjusted as follows: −1.3 kg if the participant was wearing long-pants and a long-sleeved shirt, −1.1 kg for short-pants or short-sleeves, and −0.9 kg for short-sleeves and short-pants.

Image acquisition

MRI data was collected with a 3 T Siemens Prisma scanner (Siemens Healthineers, Erlangen, Germany) using a 32-channel cardiac phased array coil placed on the chest, at the level of the heart. Cardiac imaging consisted of stacks of 12–15 slices of long-axis and short-axis cardiac-gated, true fast imaging with steady-state free precession (TRUFI) sequences showing dynamic heart function (also known as cine steady-state free precession (SSFP) sequences). Two, three, and four chamber views and a short axis stack were used to evaluate left ventricular (LV) structure and function (i.e. end-diastolic volume [EDV], end-systolic volume [ESV], systolic volume [SV], mass during diastole, and ejection fraction [EF]). Typical imaging parameters were: repetition time (TR) 3.51 ms, echo time (TE) 1.54 ms, spatial resolution 1.3 × 1.3 × 8.0 mm, field of view 270 × 320 mm, matrix 216 × 256, flip angle 49°. T1 mapping was performed using a modified Look-Locker (MOLLI) inversion recovery TRUFI sequence (Messroghli et al., 2004) with a 5-3-3 pattern at a mid-ventricular slice with the following parameters: TR 3.89 ms, TE 1.12 ms, TI 180 ms, spatial resolution 1.4 × 1.4 × 8.0 mm, field of view 306 × 360 mm, matrix 254 × 218, flip angle 35°. T2 mapping at a mid-ventricular slice was performed using a T_2-prepared fast low angle shot (FLASH) sequence (Wright, Hu, & Macovski, 1991) with the following parameters: TR 3.81 ms, TE (0, 30, 55 ms), spatial resolution 1.6 × 1.6 × 8.0 mm, field of view 289 × 359 mm, matrix 224 × 180, flip angle 12°. Motion-corrected pixel-wise T_2 maps were automatically generated by the scanner.

Breathing-paradigm

Figure 1 depicts the CMVR imaging protocol, which utilized an established and validated breathing-paradigm (Fischer et al., 2015; Guensch et al., 2014; Teixeira et al., 2016). First a baseline quantitative T_2 scan was acquired. Then participants were asked to hyperventilate for 60-s at 32 breaths per minute, inhaling between metronome beats and exhaling during metronome beats. Afterwards, participants were told to exhale fully, and subsequently perform a 40-s breath-hold, during which four additional quantitative T_2 scans were acquired at 10-, 20-, 30-, and 40-s post hyperventilation. Prior to entering the MRI, the protocol was explained to all participants, and they were asked to practice the breathing-paradigm with a trained staff member until they were able to adhere to the task. Adherence to the task during the MRI scan was monitored via respiratory bellows by a trained staff member.

Image processing and analysis

The two study cardiologists were masked to participant diagnosis by excluding any identifiable participant information within the MRI system. Non-imaging clinical and psychiatric data were kept in password-protected datasets that were not accessible by the cardiologists. Finally, the overall statistical analyses were conducted using a masked dummy group variable. All cardiac images were analyzed by a Society for Cardiovascular Magnetic Resonance Level 3 expert cardiologist using cvi42 (Circle Cardiovascular Imaging Inc., Calgary, AB, Canada). The 12-15 short- and long-axis cardiac-gated cine images of the LV were analyzed slice by slice by manually contouring the endocardial and epicardial borders, yielding the following structural and functional measures of the LV for: EDV, ESV, SV, mass during diastole and EF. Similarly, the endocardial and epicardial borders were manually contoured in the T_2 scans across each time point to yield CMVR.

Statistical analysis

Clinical study data were collected and managed using REDCap (Research Electronic Data Capture) (Harris et al., 2009). The normality of all continuous variables was assessed using the Shapiro–Wilks test. Between-group differences were examined using independent-samples *t* tests or Mann–Whitney *U* tests for continuous variables and χ^2 tests for categorical variables. Effect sizes were reported as a Cohen's *d* for continuous variables and Cramer's *V* for categorical variables. Statistical testing of clinical and demographics were performed using SPSS software version 26 (IBM Inc.). p values < 0.05 were considered statistically significant.

Statistical testing of clinical measures of cardiac structure and function, and CMVR was conducted in Matlab R2021b. General linear models investigated whether clinical measures of cardiac structure or function differed between youth with BD *v.* controls. In these models, clinical measures of cardiac structure or function (e.g. LV-EDV) were the dependent variables; diagnosis and sex

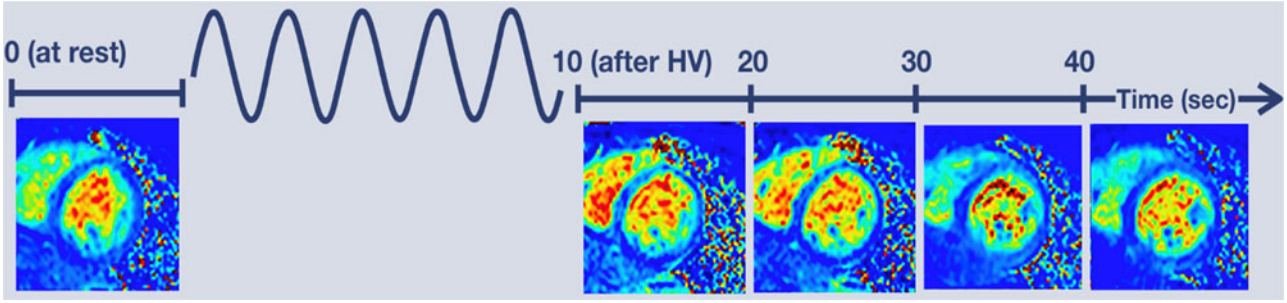

Figure 1. CMVR breathing paradigm and imaging protocol. A baseline quantitative *T2* scan was acquired then participants performed a 60-s hyperventilation task with a respiration rate of 32 breaths per minute. Afterwards participants fully exhaled and then performed a 40 s breath-hold during which four additional quantitative *T2* scans were acquired at 10-, 20-, 30-, and 40-s post hyperventilation.

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were categorical fixed variables, and age was a continuous fixed variable. Linear mixed effects models examined CMVR (i.e. change in T_2 relaxation time during the breathing-paradigm) in youth and whether CMVR differed between youth with BD *v.* controls. In these models, T_2 relaxation time was the dependent variable; diagnosis and sex were categorical fixed effects and age, time, body-mass-index (BMI), and time × diagnosis were continuous fixed effects; time and participant were random effects which allowed for the intercept to vary by time and subject, and for a correlated random slope of time. Post-hoc analyses at each time point were conducted to determine where CMVR in youth with BD diverged from control youth. To correct for multiple post-hoc analyses the Benjamini, Krieger, and Yekutieli two-stage step-up method of controlling for false discovery rate (FDR) was applied (Benjamini, Krieger, & Yekutieli, 2006). Additionally, linear mixed-effects models examined CMVR within each group separately using the aforementioned models without the fixed effects of diagnosis and time × diagnosis. Post-hoc pair-wise comparisons examined for when a significant change in CMVR relative to baseline occurred. Lastly, sensitivity analyses controlled for the potential confounding effects of medication usage, race, and duration of illness by running separate linear mixed effects models with the addition of either current use of second-generation antipsychotics, lithium, stimulants, any medication use, or race as categorical fixed effects or duration of illness and as a continuous fixed effect.

Results

This study enrolled 92 participants, of which 6 (3 controls, 3 BD) were withdrawn from the study either because a substance use disorder was identified after enrollment (1 control, 1 BD) or the participant did not complete cardiac MRI (2 controls, 2 BD). This study included 86 youth, 39 with BD (19 BD-I, 8 BD-II, 12 BD-NOS) and 47 controls. Within the BD group, 17 (44%) participants were euthymic, 18 (46%) had depression, and 9 (23%) had hypomania. Analyses for LV parameters included a total of 84 participants, as data for two BD-I participants were not obtained for technical reasons. Analyses for CMVR included a total of 83 participants, as one BD-I participant and two control participants had excessive motion during the scan. The BD group compared to the control group, had a significantly higher proportion of Caucasian participants (72% *v.* 50%; $p = 0.04$; $V = 0.22$), female participants (69% *v.* 45%; $p = 0.02$; $V = 0.25$), and higher BMI (23.28 ± 3.42 *v.* 21.29 ± 2.84; $p = 0.004$; $d = 0.64$). Psychiatric clinical characteristics are summarized in Table 1.

Left ventricular parameters in youth

The between-group differences (i.e. BD *v.* controls) in clinical measures of left ventricular structure and function are presented in Table 2. Overall, cardiac structure and function metrics were in the normal range in both groups, and there were no significant between-group differences in these metrics (all $p > 0.05$). Similarly, T_1 relaxation and baseline T_2 relaxation times were not significantly different between groups (both $p > 0.05$). For descriptive purposes, the clinical measures of LV structure and function were compared between males and females. Females had significantly smaller LV end-diastolic volume, end-systolic volume, systolic volume, and mass during diastole even after indexing for body surface area (all $p < 0.001$). Additionally, females had significantly higher T_1 relaxation ($p = 0.007$) and baseline T_2 relaxation times ($p < 0.001$) than males.

Coronary microvascular reactivity

Across all participants, the breathing-paradigm induced a significant change in T_2 relaxation time across all timepoints (i.e. CMVR; $\beta = 0.36$, $p < 0.001$). Post-hoc tests compared to baseline found that T_2 relaxation time was significantly lower 10 s post-hyperventilation ($d = 2.3$, $p_{FDR} < 0.001$), and higher 20-, 30-, and 40-s post-hyperventilation ($d = 1.7$, $d = 2.02$, $d = 1.93$ respectively; all $p_{FDR} < 0.001$). There was also a significant diagnosis-by-time interaction effect ($\beta = -0.11$, $p = 0.002$) on T_2 relaxation time, whereby youth with BD had lower CMVR than the control group, as shown in Fig. 2. Post-hoc tests revealed that at 20 s ($d = 0.48$, $p_{FDR} = 0.01$), 30 s ($d = 0.72$, $p_{FDR} < 0.001$), and 40 s ($d = 0.91$, $p_{FDR} < 0.001$) post-hyperventilation youth with BD had a significantly lower T_2 relaxation time *v.* controls.

Within-group analyses found that the breathing-paradigm induced a significant change in T_2 relaxation time in both the control group ($\beta = 0.46$, $p < 0.001$) and the BD group ($\beta = 0.25$, $p = 0.002$). In the control group, post-hoc tests compared to baseline found that T_2 relaxation time was lower 10 s post-hyperventilation ($d = 2.3$, $p_{FDR} < 0.001$), and higher 20-, 30-, and 40-s post-hyperventilation ($d = 3.25$, $d = 3.7$, $d = 3.6$ respectively; all $p_{FDR} < 0.001$). In the BD group post-hoc tests compared to baseline, found that T_2 relaxation time was lower 10 s post-hyperventilation ($d = 4.58$, $p_{FDR} < 0.001$), and higher 20-, 30-, and 40-s post-hyperventilation ($d = 1.35$, $d = 1.83$, $d = 1.69$ respectively; all $p_{FDR} < 0.001$). Finally, for descriptive purposes, we also compared the effect that the breathing-paradigm had on T_2 relaxation time in males *v.* females. However, there were no significant differences in CMVR in males *v.* females ($\beta = -0.01$, $p = 0.75$).

Sensitivity analyses

We undertook four sensitivity analyses focused on differences of medication usage in BD *v.* controls, specifically the current use of second-generation antipsychotics, lithium, stimulants, and any medication use. Additionally, we also conducted sensitivity analyses to control for racial differences and duration of illness in BD. All analyses remained significant after controlling for these confounds.

Discussion

This study examined an established measure of coronary microvascular function (i.e. CMVR), alongside clinical metrics of gross cardiac structure and function, in relation to BD in youth. Clinical CMR metrics of gross LV structure and function were normal in both youth with BD and controls, and did not differ between the groups. Additionally, the breathing-paradigm successfully assessed CMVR in a sample of youth without CVD, which is noteworthy as this paradigm does not require the administration of an exogenous pharmacological agent. As hypothesized, this study found evidence of coronary microvascular dysfunction in youth with BD. Importantly, this finding occurred in the context of otherwise normal cardiac structure and function and appears to be independent of BMI or psychotropic medication, including SGA. These findings provide preliminary evidence that coronary microvascular dysfunction is present in youth with

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Table 1. Demographic and clinical characteristics of participants

	Mean,± s.d. or no. (%)				
Demographics	Bipolar disorder ($n = 39$)	Controls ($n = 47$)	Statistical test	Effect size	p Value
Age (Years)	17.9 ± 1.6	18.0 ± 1.7	$t = -0.15$	$d = 0.03$	$p = 0.88$
Socio-economic status	4.0 ± 1.1	4.5 ± 0.6	$U = 551.0$	$d = 0.90$	$p = 0.09$
Sex (Female)	27 (69)	21 (45)	$\chi^2 = 5.21$	$V = 0.25$	$p = 0.02$
Race (Caucasian)	28 (72)	22 (50)	$\chi^2 = 4.10$	$V = 0.22$	$p = 0.04$
Intact family	20 (53)	30 (68)	$\chi^2 = 2.07$	$V = 0.16$	$p = 0.15$
Tanner stage	4.5 ± 0.6	4.3 ± 0.7	$U = 566.5$	$d = 0.65$	$p = 0.12$
Bipolar subtype					
Bipolar subtype: BDI	19 (49)	—	—	—	—
Bipolar subtype: BDII	8 (21)	—	—	—	—
Bipolar subtype: BDNOS	12 (31)	—	—	—	—
Age of onset of BD (Years)	15.5 ± 2.0	—	—	—	—
Physiological characteristics					
Body mass index (kg/m^2)	23.28 ± 3.42	21.29 ± 2.84	$U = 1226.0$	$d = 0.64$	$p = 0.004$
Clinical characteristics					
Lifetime psychosis	13 (33)	0 (0)	$\chi^2 = 18.46$	$V = 0.46$	$p < 0.001$
Lifetime suicide attempts	9 (23)	0 (0)	$\chi^2 = 8.21$	$V = 0.34$	$p = 0.004$
Lifetime self-injurious behavior	21 (54)	0 (0)	$\chi^2 = 23.85$	$V = 0.58$	$p < 0.001$
Lifetime suicidal ideation	27 (69)	3 (10)	$\chi^2 = 25.01$	$V = 0.6$	$p < 0.001$
Legal history (Police contact/Arrest)	15 (38)	3 (9)	$\chi^2 = 8.59$	$V = 0.34$	$p = 0.003$
Lifetime physical abuse	3 (8)	2 (4)	$\chi^2 = 0.46$	$V = 0.07$	$p = 0.5$
Lifetime sexual abuse	5 (13)	1 (2)	$\chi^2 = 3.75$	$V = 0.21$	$p = 0.05$
Lifetime any abuse (Physical and/or Sexual)	5 (13)	1 (2)	$\chi^2 = 3.75$	$V = 0.21$	$p = 0.05$
Lifetime psychiatric hospitalization	24 (62)	0 (0)	$\chi^2 = 38.09$	$V = 0.68$	$p < 0.001$
Current depression rating score	13.51 ± 12.22	1.36 ± 3.31	$U = 1431.5$	$d = 1.39$	$p < 0.001$
Most severe past depression rating score	30.31 ± 12.17	3.3 ± 4.0	$U = 1687.5$	$d = 3.06$	$p < 0.001$
Current mania rating score	6.56 ± 9.08	0.2 ± 0.88	$U = 1282.0$	$d = 1.02$	$p < 0.001$
Most severe lifetime mania rating score	33.79 ± 9.31	0.45 ± 1.59	$U = 1716.0$	$d = 5.15$	$p < 0.001$
CGAS most severe past episode	43.54 ± 10.72	83.52 ± 7.98	$U = 0.5$	$d = 4.25$	$p < 0.001$
CGAS past year highest level of functioning	71.67 ± 10.56	88.57 ± 4.62	$U = 93.5$	$d = 2.12$	$p < 0.001$
CGAS current episode (Past month)	66.59 ± 11.93	87.43 ± 6.57	$U = 94.0$	$d = 2.2$	$p < 0.001$
Lifetime comorbid diagnosis					
ADHD	15 (38)	4 (9)	$\chi^2 = 11.11$	$V = 0.36$	$p < 0.001$
Any anxiety	35 (90)	5 (11)	$\chi^2 = 53.61$	$V = 0.79$	$p < 0.001$
CD	0 (0)	0 (0)	—	—	—
OCD	6 (15)	1 (2)	$\chi^2 = 5.01$	$V = 0.24$	$p = 0.03$
ODD	11 (28)	0 (0)	$\chi^2 = 15.2$	$V = 0.42$	$p < 0.001$
PTSD	4 (10)	0 (0)	$\chi^2 = 5.06$	$V = 0.24$	$p = 0.02$
SUD	13 (33)	1 (2)	$\chi^2 = 15.23$	$V = 0.42$	$p < 0.001$
Family history (1st or 2nd degree)					
Mania/Hypomania lifetime	20 (51)	0 (0)	$\chi^2 = 31.41$	$V = 0.6$	$p < 0.001$
Depression lifetime	31 (79)	11 (23)	$\chi^2 = 26.83$	$V = 0.56$	$p < 0.001$

(*Continued*)

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Table 1. (*Continued.*)

Demographics	Mean,± s.d. or no. (%)		Statistical test	Effect size	*p* Value
	Bipolar disorder (*n* = 39)	Controls (*n* = 47)			
Suicide attempts lifetime	11 (28)	2 (4)	$\chi^2 = 9.53$	$V = 0.33$	$p = 0.002$
Anxiety lifetime	27 (69)	5 (11)	$\chi^2 = 31.32$	$V = 0.6$	$p < 0.001$
ADHD lifetime	14 (36)	1 (2)	$\chi^2 = 16.88$	$V = 0.44$	$p < 0.001$
Psychosis lifetime	10 (26)	0 (0)	$\chi^2 = 13.64$	$V = 0.4$	$p < 0.001$
Current medications					
Second generation antipsychotics	22 (56)	0 (0)	$\chi^2 = 35.63$	$V = 0.64$	$p < 0.001$
Lithium	11 (28)	0 (0)	$\chi^2 = 15.2$	$V = 0.42$	$p < 0.001$
SSRI antidepressants	7 (18)	0 (0)	$\chi^2 = 9.18$	$V = 0.33$	$p = 0.002$
Non-SSRI antidepressants	2 (5)	0 (0)	$\chi^2 = 2.47$	$V = 0.17$	$p = 0.12$
Stimulants	2 (5)	0 (0)	$\chi^2 = 2.47$	$V = 0.17$	$p = 0.12$
Valproate	0 (0)	0 (0)	—	—	—
Lamotrigine	7 (18)	0 (0)	$\chi^2 = 9.18$	$V = 0.33$	$p = 0.002$
Any medications	31 (82)	1 (2)	$\chi^2 = 56.5$	$V = 0.82$	$p < 0.001$
Lifetime medications					
Second generation antipsychotics	34 (87)	0 (0)	$\chi^2 = 67.77$	$V = 0.89$	$p < 0.001$
Lithium	14 (36)	0 (0)	$\chi^2 = 20.15$	$V = 0.48$	$p < 0.001$
SSRI antidepressants	23 (58)	0 (0)	$\chi^2 = 37.84$	$V = 0.66$	$p < 0.001$
Non-SSRI antidepressants	11 (28)	0 (0)	$\chi^2 = 15.2$	$V = 0.42$	$p < 0.001$
Stimulants	8 (21)	2 (4)	$\chi^2 = 5.48$	$V = 0.25$	$p = 0.02$
Valproate	3 (8)	0 (0)	$\chi^2 = 3.75$	$V = 0.21$	$p = 0.05$
Lamotrigine	11 (28)	0 (0)	$\chi^2 = 15.2$	$V = 0.42$	$p < 0.001$
Any medications	38 (97)	2 (4)	$\chi^2 = 74.39$	$V = 0.93$	$p < 0.001$

ADHD, attention deficit/hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; SUD, substance use disorder; SSRI, selective serotonin reuptake inhibitor; CGAS, Children's Global Assessment Scale; s.d., standard deviation.

BD, even in the early stages of their course of illness, and prior to any detectable abnormalities and/or differences in gross cardiac structure and function.

Coronary microvascular reactivity

Consistent with our hypothesis, we found that youth with BD had blunted CMVR compared to the control youth. These results align with prior research that found that psychological stressors (Arrighi et al., 2000; Hasegawa et al., 2005) and psychiatric disorders (e.g. major depressive disorder (Vaccarino et al., 2009), post-traumatic stress disorder (Vaccarino et al., 2013, 2021b)) are associated with impaired coronary microvascular function. While impaired coronary microvascular function has been observed in children and adolescents with Kawasaki disease (Furuyama et al., 2003; Hamaoka et al., 1992; Muzik et al., 1996; Noto et al., 2002), and congenital heart disease (Aburawi & Pesonen, 2011; Bengel et al., 1998), this topic has not been previously studied in a youth psychiatric sample.

The mechanisms underlying microvascular dysfunction are multifactorial (Choi & Kim, 2021). While the current study was not designed to elucidate mechanisms, we speculate that biological processes known to be relevant to both BD and CVD may be contributory. For example, inflammation, which is elevated in youth with BD (Karthikeyan et al., 2022), is independently associated with coronary microvascular dysfunction in adults with angina who do not have coronary artery disease or other cardiovascular risk factors (Recio-Mayoral, Rimoldi, Camici, & Kaski, 2013). Similarly, oxidative stress is evident in youth with BD (de Sousa et al., 2014), and is associated with microvascular dysfunction in young, otherwise healthy, adults with major depressive disorder (Greaney, Saunders, Santhanam, & Alexander, 2019). While compelling evidence supports that endothelial dysfunction is mediated by inflammation and oxidative stress (Cai & Harrison, 2000; Clapp et al., 2005), other mechanisms relevant to both BD and endothelial function, such as brain-derived neurotrophic factor (Donovan et al., 2000; Goldstein et al., 2020; Totoson, Pedard, Marie, & Demougeot, 2018), and vascular endothelial growth factor (Goldstein et al., 2020; Kliche & Waltenberger, 2001) may have played a role in the observed findings.

The present findings build upon prior evidence from adult studies demonstrating that coronary microvascular function can be assayed non-invasively using OS-CMR with a breathing-paradigm, extending similar findings to a sample of youth without CVD. In this age group, the non-invasiveness of a breathing-

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Table 2. Left ventricular parameters in youth

Left ventricle parameters	BD ($n = 39$) Mean ± S.D.	Controls ($n = 47$) Mean ± S.D.	p Value[a]	Males ($n = 38$) Mean ± S.D.	Females ($n = 48$) Mean ± S.D.	p Value[b]
LV-EDV (ml)	135 ± 28	145 ± 35	0.99	160 ± 34	126 ± 21	<0.001
LV-EDV index (ml/m^2)	76 ± 13	82 ± 15	0.58	87 ± 15	74 ± 10	<0.001
LV-ESV (ml)	50 ± 12	56 ± 16	0.72	62 ± 15	47 ± 10	<0.001
LV-ESV index (ml/m^2)	28 ± 6	31 ± 7	0.36	34 ± 7	27 ± 5	<0.001
LV-SV (ml)	85 ± 17	89 ± 21	0.84	98 ± 21	79 ± 14	<0.001
LV-SV index (ml/m^2)	48 ± 8	50 ± 10	0.79	53 ± 10	46 ± 7	<0.001
LV mass diastole (g)	101 ± 21	111 ± 25	0.86	123 ± 21	94 ± 18	<0.001
LV mass diastole index (g/m^2)	58 ± 10	63 ± 11	0.83	67 ± 10	55 ± 9	<0.001
LV-EF (%)	63 ± 3	62 ± 4	0.45	61 ± 4	63 ± 4	0.06
T_1 relaxation (ms)	1153 ± 80	1157 ± 60	0.25	1116 ± 159	1182 ± 65	0.007
Baseline T_2 relaxation (ms)	40 ± 2	40 ± 2	0.25	39 ± 2	40 ± 2	<0.001

LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, systolic volume; LV-EF, left ventricle ejection fraction; a, analyses with age and sex as covariates; b, analyses with age as a covariate.

paradigm relative to the administration of an exogenous pharmacological agent such as adenosine is beneficial in a research setting. Furthermore, the present findings provide evidence that OS-CMR is sensitive to detecting differences in CMVR in an otherwise healthy sample of youth with BD who are at an elevated risk of developing future CVD.

Left ventricular parameters in youth

In contrast to prior echocardiography and CMR studies in adults, which have found that depression, schizophrenia, and BD are associated with poorer measures of LV function and structure (Andreou et al., 2020; Chen et al., 2021; Chen & Chung, 2018; Kim et al., 2012; Korkmaz, Korkmaz, Özer, & Atmaca, 2016; Pillinger et al., 2019), there were no significant differences in LV volumes or mass between youth with BD and controls. However, this could be expected, given that this is an otherwise healthy youth sample with a relatively short duration of illness. While BD is associated with a premature onset of CVD and predisposes youth to accelerated atherosclerosis (Goldstein et al., 2015a, 2015b), the onset of CVD still does not usually occur until adulthood (Goldstein et al., 2015b). It is likely that changes in clinical measures of cardiac structure and function take decades to manifest and are not yet evident during youth. Therefore, it is important to investigate novel indicators of early coronary microvascular dysfunction that may precede changes in gross cardiac structure and function.

Aside from the focus on BD, the current study addresses an important gap in the knowledge regarding cardiovascular MRI in youth, a topic that focuses thus far, almost exclusively on congenital heart disease and Kawasaki disease. This is unfortunate, as normative modeling of CMR in populations of youth at an increased risk for CVD, and amongst youth in general, offers potential insights regarding the genesis and early precursors of CVD. The current study found that measures of gross cardiac structure and function were normal in both the youth with BD and controls. Additionally, males also had larger LV volumes and mass, even after indexing for body-surface area, when compared to females. This aligns with both youth and adult literature, which has shown that males have up to 40% larger LV volumes

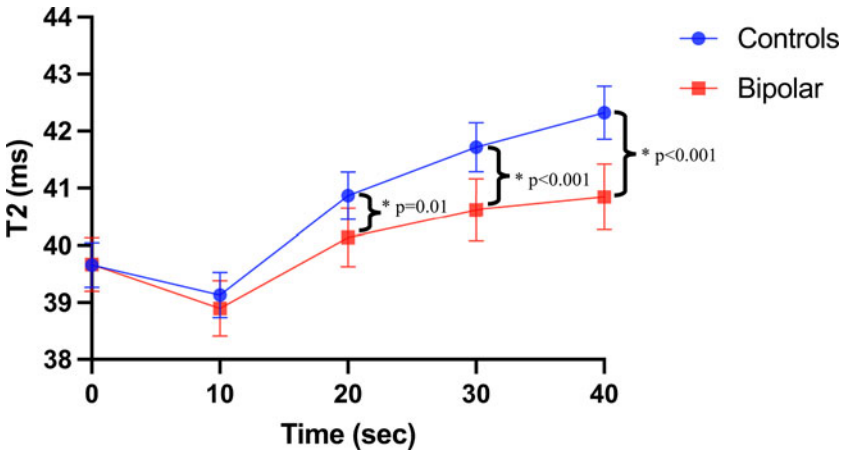

Figure 2. CMVR in youth with BD and HC. Visual representation of *T2* relaxation time from quantitative *T2* scans at baseline, and 10-, 20-, 30-, and 40-s post hyperventilation in youth with bipolar disorders and controls controlling for age, sex, and BMI. Youth with bipolar disorder had significantly lower CMVR than controls ($\beta = -0.11$, $p = 0.002$). Post-hoc tests revealed that at 20 s ($d = 0.48$, $p_{FDR} = 0.01$), 30 s ($d = 0.72$, $p_{FDR} < 0.001$), and 40 s ($d = 0.91$, $p_{FDR} < 0.001$) post-hyperventilation youth with bipolar disorder had a significantly lower *T2* relaxation time v. controls. Error bars = 95% confidence intervals.

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and mass (Kawel-Boehm et al., 2015; Salton et al., 2002; Sandstede et al., 2000; van der Ven et al., 2020). Importantly, our CMR measures of clinical cardiac structure and function showed good agreement with reference CMR values reported in a recent multicenter study based on youth between the ages of 12–18 (van der Ven et al., 2020). Lastly, our study also found that females had significantly higher T_1 and T_2 relaxation times than males, which aligns with the prior adult literature (Bönner et al., 2015; Granitz et al., 2019; Piechnik et al., 2013; Rauhalammi et al., 2016).

Potential clinical applications and generalizability of findings

Generating insights and knowledge regarding the genesis and early precursors of CVD in youth, particularly among those at increased risk for CVD, is essential to inform future clinical practices. The rates of premature and excessive CVD observed in BD exceed what can be explained by traditional cardiovascular risk factors (Goldstein et al., 2015b), which provides motivation for a focus on microvessels. By demonstrating coronary microvascular dysfunction in youth early in their course of BD, independent of obesity and medications, the current study adds important preliminary evidence that microvessels may be implicated in the excess and premature onset of CVD in BD. There is a small but growing body of literature showing that microvascular dysfunction is present in BD and has psychiatric clinical correlates (Fiedorowicz, Coryell, Rice, Warren, & Haynes, 2012; Kennedy et al., 2023a, 2023b; Mio et al., 2021; Urback, Metcalfe, Korczak, MacIntosh, & Goldstein, 2019). While BD is listed as a tier II moderate-risk condition for future CVD by the American Heart Association (Goldstein et al., 2015a), current guidelines for screening and intervention focus solely on traditional cardiovascular risk factors (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011; de Ferranti et al., 2019). As a result, microvascular dysfunction has not yet been integrated into the appraisal of CVD risk and related screening and prevention approaches.

While additional research is needed to change future clinical practices, it is possible that, in the future, microvascular metrics may guide prevention and treatment strategies, and inform more personalized CVD risk assessment among individuals with BD and other illnesses characterized by microvascular dysfunction. For example, thresholds for CVD-related intervention may be reduced, given the knowledge that both microvascular and macrovascular risk factors contribute to the excess risk of CVD among individuals with BD. Another implication is the potential for repurposing of microvascular-focused medications focused on improving microvascular and endothelial function. Phosphodiesterase inhibitors (e.g. sildenafil), and nitric oxide synthase inhibitors (e.g. nitroarginine, aminoguanidine) target the microvascular endothelium, leading to vasodilation (Cheitlin et al., 1999; Melikian, Seddon, Casadei, Chowienczyk, & Shah, 2009). Given that both clinical and animal studies have demonstrated that sildenafil (Duarte-Silva et al., 2020) and nitric oxide synthase inhibitors (Wegener & Volke, 2010) have antidepressant effects, the benefit-to-risk ratio of using these drugs in individuals with mood disorders may be enhanced.

It is essential to discuss the generalizability of this study's findings to other populations of youth with BD. The clinical characteristics of the current sample, including psychosis, suicidality, physical/sexual abuse, treatment, comorbid psychiatric diagnoses, and family psychiatric history, closely resembled those reported in the COBY study (Birmaher et al., 2006; Birmaher et al., 2009; Esposito-Smythers et al., 2010). Moreover, adolescents with BD in the Canadian Community Health Survey (CCHS), the most directly comparable community-based epidemiological study, also exhibit high rates of psychiatric comorbidity and suicidality (Kozloff et al., 2010). However, it is important to note that while our clinical sample consisted of treatment-seeking individuals, less than half of the adolescents with BD in the CCHS had accessed mental health services. Finally, the lifetime prevalence of ADHD and anxiety within our control group aligns with the prevalence reported in large national surveys and epidemiological studies in both the United States and Canada (Bitsko et al., 2022; Merikangas et al., 2010; Wiens et al., 2020). Taken together, the similarity of our study's clinical characteristics to those of large and epidemiological studies indicates that our findings would likely translate to the general population.

Limitations

Several limitations of this study require consideration. First, the cross-sectional design of the study precludes inferences regarding the temporal relationship between BD and CMVR. Future studies with repeated measures are necessary to inform our understanding of the life-course relationships of CMVR in youth in general and specifically in BD. Second, the efficacy and reliability of the breathing-paradigm is subject to participant compliance. Even though participants practiced with a trained staff member and their compliance was monitored, there may be unexplained variance related to pulmonary function, and/or depth of inhalation and exhalation during the breathing-paradigm. Relatedly, a thorough assessment of respiratory diseases, such as asthma, was not included in the study. The efficacy and reliability of the breathing-paradigm may be lower in the presence of such conditions. Third, CMVR was assessed on a single midventricular slice to achieve the temporal and spatial resolutions required for monitoring changes in T_2 relaxation. This local measurement may not be reflective of CMVR across the entire LV. Finally, while we investigated the potential confounding effects of select covariates in this proof-of-principle study (age, sex, obesity, second-generation antipsychotics, stimulants, lithium, any medication, race), we cannot rule out the possibility of residual confounding and effects related to other factors (e.g. psychiatric comorbidity, lifestyle, early adversity).

Conclusion

We present evidence that microvascular function is impaired among youth with BD early in their course of illness and precedes changes in the clinical metrics of cardiac structure and function. These findings converge with prior findings in adults with major depressive disorder and post-traumatic stress disorder. Heuristically, studying a youth sample is beneficial, as it can inform our understanding of the role of microvascular dysfunction in the genesis of BD, offering the advantage that youth have not been exposed to decades of BD symptoms, medications, and other cardiovascular risk factors that are often comorbid. While the current study focused on BD, the approach undertaken here can be similarly applied to studying youth with other conditions associated with an increased risk of CVD and accelerated atherosclerosis, such as juvenile inflammatory arthritis, diabetes, and inflammatory bowel disease (de Ferranti et al., 2019).

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Future studies integrating larger samples, prospective follow-up, and blood-based biomarkers are warranted.

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