

Original Article

Evaluation of left ventricular systolic and diastolic functions in bipolar patients during lithium therapy

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Abstract: Background: Bipolar disorder (BD) is a chronic mental illness that is associated with substantial functional impairment, morbidity and mortality. Lithium is still considered as a first-line therapy in BD. In this study, systolic and diastolic function parameters were measured with echocardiography in BD during lithium therapy and compared to those of a control group. Methods: Thirty BD under lithium therapy and controls were included in our study. Blood samples were taken 12 hours after receiving the last dose of lithium treatment, in the meantime echocardiography were performed. Left ventricular systolic and diastolic function was assessed by conventional echocardiography and tissue Doppler imaging. Serum lithium level correlation between diastolic function parameters was measured. Results: Baseline demographic and laboratory results did not differ significantly between the groups. Left ventricular ejection fraction (LVEF) ($66.7 \pm 7.1\%$ vs $66.7 \pm 4.9\%$), E/A ratio (1.14 ± 0.41 vs 1.28 ± 0.29), and isovolumetric relaxation time (IVRT) (77.8 ± 14.5 cm/sec vs 75.9 ± 17.7 cm/sec) measured with conventional echocardiography showed no significant difference between the two groups. Em (14.8 ± 5.2 cm/sec vs 15 ± 4.6 cm/sec), Am (12.7 ± 4.0 cm/sec vs $11.1.0 \pm 2.4$ cm/sec) and E/Em (5.5 ± 1.8 vs 5.9 ± 2.4) measured with tissue Doppler echocardiography showed no significant difference between the two groups. Serum lithium levels were not correlated with LVEF, mitral inflow E velocity, mitral inflow A velocity, E/A ratio, deceleration time (DT), IVRT, or E/Em ratio. Conclusion: Left ventricular systolic and diastolic functions were preserved in BD during lithium therapy.

Keywords: Echocardiography, bipolar disorder, lithium, tissue Doppler, ventricular function

Introduction

Bipolar disorder (BD) is a chronic mental illness that is associated with substantial functional impairment, morbidity and mortality [1, 2]. Although suicide is a major cause of premature mortality in BD, most of the excess mortality rate is due to cardiovascular disorders [3, 4]. In a previous study, Correll et al. reported a 10-year coronary heart disease risk of 4.7% for patients with bipolar disorder and 19% of these had high risk ($\geq 10\%$) for coronary heart disease [5]. Therefore, individuals with BD die younger than the general population and cardiovascular disorders play an important role [1, 6, 7].

Lithium is still considered as a first-line therapy in BD [8]. However, its narrow therapeutic range

may lead to increased risk of intoxication [9]. It has been clearly established that lithium use is associated with cardiovascular side effects including, asymptomatic ECG changes, conduction defects, dysrhythmias, hypotension, myocarditis and circulatory failure [10-12]. Moreover, these cardiac side effects might occur at therapeutic levels among patients who are on lithium treatment.

Given this background, the effect of lithium use and BD on cardiac functions remains unclear. There is only one rat study that evaluates the effects of lithium on cardiac functions and concluded that lithium has no direct effect on cardiac function [13]. The purpose of the present study is to evaluate the cardiac both systolic and diastolic functions in patients with BD under lithium therapy.

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Table 1. Baseline characteristics

Variables	Bipolar disorder group (n = 30)	Control group (n = 30)	p value
Age (years)	37.2 ± 11.2	40.8 ± 17.4	0.34
Male/female n	13/17	18/12	0.30
Systolic blood pressure (mmHg)	118.4 ± 12.9	120.7 ± 18.2	0.57
Diastolic blood pressure (mmHg)	75.8 ± 8.3	74.8 ± 8.8	0.66
Hypertension n (%)	5 (17%)	1 (3%)	0.19
Diabetes mellitus n (%)	3 (10%)	1 (3%)	0.61
Hyperlipidemia n (%)	2 (7%)	3 (10%)	0.50
Smoking n (%)	8 (27%)	10 (30%)	0.77
Body mass index (kg/m ²)	29.0 ± 5.5	26.5 ± 4.8	0.06
Hemoglobin (g/dl)	13.5 ± 1.4	14.4 ± 1.7	0.06
Fasting blood glucose (mg/dl)	86.8 ± 25.8	96.8 ± 15.2	0.11
Total cholesterol (mg/dl)	175.1 ± 26.8	196.2 ± 39.4	0.06
High-density lipoprotein (mg/dl)	46.6 ± 14.5	53.5 ± 26.0	0.31
Low-density lipoprotein (mg/dl)	91.7 ± 27.4	111.5 ± 41	0.09
Triglyceride (mg/dl)	170.3 ± 100.6	148.2 ± 101.6	0.48
Blood urea nitrogen (mg/dl)	20.7 ± 5.9	20.4 ± 7.2	0.88
Creatinine (mg/dl)	0.76 ± 0.13	0.76 ± 0.11	0.99
Thyroid stimulating hormone (ng/dl)	1.92 ± 1.48	1.79 ± 0.75	0.72
Serum lithium (ng/dl)	0.74 ± 0.19		
Lithium dose (mg)	900 ± 192	-	-

Methods

This is a prospective, case-control study that performed between October 2013 and March 2014. The study sample was consisted of 30 healthy volunteers and 30 patients with BD according to DSM IV criteria who were on lithium therapy and in therapeutic range (0.74 ± 0.19 , mmol/l) since at least 6 months (mean follow-up 49.4 months). All of BD patients were BD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [14]. The healthy volunteers consisted of individuals who were admitted to cardiology outpatient unit for check-up.

Exclusion criteria for the study were presence of thyroid disorders, electrolyte imbalance, coronary artery disease, congestive heart failure, pulmonary hypertension, cardiomyopathy, moderate or severe valvular disease, and implantation of permanent or temporary pacemaker, atrial fibrillation, chronic obstructive pulmonary disease hepatic and renal failure. Blood pressure was measured after a 10 minute resting period before TTE with a random-zero sphygmomanometer by trained observers. Heart rate was recorded at the same time with blood pres-

sure measurement. Previous medical history was recorded from each patient's anamnesis and medical records. Informed consent was obtained from all participants (both patients and healthy volunteers) and the protocol was approved by the local Ethics Committee and the institutional review board.

Laboratory analysis

Blood sample was drawn in the morning approximately 8 h after fasting period and the last intake of the lithium capsules. Fasting glucose levels, lipid profile, serum lithium, renal, and hepatic function tests were measured by using Architect C8000 analyzer (Abbot Park, IL, USA). Complete blood

count was evaluated using Cell-Dyn Ruby analyzer System 1200® (Abbott Diagnostics).

Transthoracic echocardiography

Transthoracic echocardiography (TTE) was performed for each participants. Two-dimensional echocardiography was performed by using a commercially available machine Vivid 5 Dimension® (GE Vingmed Ultrasound AS N-3190 Horten, Norway) with a 2.5-MHz transducer for TTE during at least three consecutive cardiac cycles. All patients were studied in the left lateral recumbent position after a 10-min resting period.

The Teichholz method was used to assess left ventricular ejection fraction (LVEF) as recommended by guidelines [15]. As recommended by American Society of Echocardiography, from the parasternal long axis, via M-mode, left ventricle end diastolic diameter (LVEDD), the left ventricle end systolic diameter (LVESD), interventricular septum thicknesses, and posterior wall thicknesses were measured [15].

In the apical 4-chamber view, with pulse wave Doppler, mitral peak early filling (E wave) velocity, mitral late diastolic filling (A wave) velocity,

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Table 2. Echocardiographic properties of the study population

Variables	Bipolar disorder group (n=30)	Control group (n=30)	p value
LVSD (mm)	46.7 ± 4.6	44.7 ± 5.1	0.120
LVDD (mm)	29.6 ± 4.5	28.3 ± 4.2	0.286
Septum thickness (mm)	9.1 ± 1.4	8.7 ± 1.5	0.379
Posterior wall thickness (mm)	9.6 ± 1.1	9.1 ± 1.3	0.110
Ejection fraction (%)	66.7 ± 7.1	66.7 ± 4.9	0.966
Mitral inflow E velocity (cm/sec)	0.75 ± 0.17	0.79 ± 0.16	0.268
Mitral inflow A velocity (cm/sec)	0.63 ± 0.12	0.63 ± 0.16	0.132
E/A ratio	1.14 ± 0.41	1.28 ± 0.29	0.136
IVRT (cm/sec)	77.8 ± 14.5	75.9 ± 17.7	0.646
E wave deceleration time (m/sec)	200 ± 32	186 ± 44	0.185
Lateral wall Sm (cm/sec)	12.1 ± 3.5	11.9 ± 2.7	0.790
Lateral wall Em (cm/sec)	14.8 ± 5.2	15.0 ± 4.6	0.830
Lateral wall Am (cm/sec)	12.7 ± 4.0	11.1 ± 2.4	0.052
E/Em	5.5 ± 1.8	5.9 ± 2.4	0.136
Septum wall Sm (cm/sec)	9.5 ± 2.9	9.8 ± 2.0	0.621
Septum wall Em (cm/sec)	11.5 ± 3.7	12.4 ± 3.9	0.358
Septum wall Am (cm/sec)	12.1 ± 3.7	10.7 ± 2.7	0.099

LVSD: Left ventricular end systolic diameter, LVDD: Left ventricular end diastolic diameter, Am: Late diastolic myocardial velocity, Em: Early diastolic myocardial velocity, Sm: Early systolic myocardial velocity, IVRT: Isovolumetric relaxation time.

trans-mitral E/A ratio and mitral E wave deceleration time were calculated. The pulse wave tissue Doppler measurements were measured from septal and lateral wall velocities (including Sm, Em and Am) in apical 4 chamber images.

Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student t-test or Mann-Whitney U test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. A two tailed *p* value < 0.05 was considered significant. All statistical analyses were performed with the SPSS version 20 (SPSS, Inc., Chicago, Illinois).

Results

Baseline characteristics are shown in **Table 1**. There were 30 patients (mean age 37.2 ± 11.2 and 43% male) in BD group and 30 patients (mean age 40.8 ± 17.4 and 60% male) in con-

trol group. Mean age, coronary risk factors and blood sample parameters were not significantly different between groups. With respect to thyroid stimulating hormone, there was not significant differences between groups (*P* = 0.72). Serum lithium was 0.74 ± 0.19 (Range 0.451-1.182) in BD group.

The echocardiography values of the study population are given in **Table 2**. The LVEF was similar between groups (66.7 ± 7.1 vs. 66.7 ± 4.9, *P* = 0.966). LVSD, LVDD, septum and posterior wall thickness were also not significantly different between BD group and healthy volunteers (*P* = 0.120, *P* = 0.286, *P* = 0.379, *P* = 0.110, respectively). Mitral inflow E velocity was 0.75 ± 0.17 cm/sec in BD group, while 0.79 ± 0.16 in control

group (*P* = 0.268). Mitral inflow A velocity 0.63 ± 0.12 cm/sec in BD group and 0.63 ± 0.16 in control group (*P* = 0.132). Mitral E/A ration (1.14 ± 0.41 vs. 1.28 ± 0.29, *P* = 0.136), isovolumetric relaxation time (77.8 ± 14.5 vs. 75.9 ± 17.7 cm/sec, *P* = 0.646) were similar between groups. In respect of tissue Doppler parameters, left ventricular lateral wall wave's velocities, septal wall waves velocities, and E/Em ratio were also similar between groups (*P* > 0.05, for each).

In correlation analyses, we evaluated the relation of echocardiographic parameters that reflect the systolic and diastolic function of the myocardium to serum lithium levels in patients with BD. Ejection fraction (*r* = -0.115, *P* = 0.549), mitral inflow E velocity (*r* = -0.055, *P* = 0.774), mitral inflow A velocity (*r* = -0.085, *P* = 0.656), E/A ratio (*r* = -0.068, *P* = 0.721), E wave deceleration time (*r* = 0.066, *P* = 0.731), IVRT (*r* = -0.067, *P* = 0.726) and E/Em ratio (*r* = -0.136, *P* = 0.473) were not significantly correlated with serum lithium levels in patients with BD (**Table 3**).

Discussion

Lithium was introduced into psychiatry in 1949 for the treatment of mania [13]. After the

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Table 3. Correlation between serum lithium and echocardiographic parameters

Variables	Serum lithium	
	r value	p value
Ejection fraction (%)	0.114	0.549
Mitral inflow E velocity (cm/sec)	0.055	0.774
Mitral inflow A velocity (cm/sec)	-0.08	0.656
E/A ratio	0.068	0.721
E wave deceleration time (m/sec)	0.066	0.731
IVRT (cm/sec)	-0.067	0.726
E/Em ratio	0.136	0.473

E: Early mitral inflow velocity, Em: Early diastolic myocardial velocity, IVRT: Isovolumetric relaxation time.

approval by Food and Drug Administration, lithium has become more common preferred treatment in BD. Lithium has cardiotoxicity even in therapeutic dose range in most patients [16]. Lithium can be used safely if initiated at a low dose, increased gradually, and monitored closely. However prolonged use of lithium needs to be careful in terms of side effects in patients with BD. Known cardiovascular side effects of lithium are sinus node dysfunction, increase in ventricular irritability, reversible T wave changes (including inversion and flattening) on electrocardiogram, rhythm disturbance, hypotension, circulation failure and myocarditis [10-12]. There is insufficient data regarding the direct effect of lithium to the myocardial contraction and relaxation dynamics in the literature. The purpose of the present study is to investigate the effects of prolonged use of lithium in therapeutic dose range to the both myocardial systolic and diastolic properties. For this purpose, 30 patients with BD who are on lithium therapy and in normal therapeutic range were enrolled and followed up to 49.4 months on average (range 6-204 months). There are two major findings of this study. Lithium does not affect the systolic function of the myocardium. Secondly, Lithium also does not affect the relaxation dynamics of myocardium in the chronic use in patients with BD.

Evidence for both safety and efficacy of lithium salts in the treatment of BD and the prevention of recurrent attacks is convincing [17-19]. In recent years the limitations and adverse effects of lithium salts have become increasingly well appreciated. The risk for cardiovascular diseases is elevated and a standardized mortality rate

up to twice that of the general population in patients with bipolar disorder [20]. In a cohort of over 5.5 million from Denmark followed from either their fifteenth birthday or the beginning of 1973 through the beginning of 2001 found that 3,669 of the 11,648 patients with bipolar disorder had died by the end of the study period. The mortality rate for cardiovascular disease was 1.59 for men and 1.47 for women [21]. A similar study found a twofold increased cardiovascular mortality rate for those with bipolar disorder compared with a cardiovascular mortality rate for individuals with unipolar depression [22]. These studies clearly showed an elevated risk of cardiovascular mortality in patients with bipolar disorder. The effects of prolonged lithium use on cardiovascular mortality rate independent from bipolar disorder is little known. Lithium was used as a salt substitute for patients with congestive heart failure and hypertension, but its improper use caused lithium toxicity, including several which were fatal [10, 23]. In more recent years, it has been showed that lithium could cause a various cardiac abnormalities even at therapeutic dose including asymptomatic ECG changes, conduction abnormalities, dysrhythmias, hypotension, circulatory failure, myocarditis, and congenital heart disease [24-26]. There is only one published study that tested the hypothesis whether lithium has a direct toxic effect on cardiac functions in rats. They evaluated left ventricular peak systolic pressure, left ventricular end diastolic pressure, heart rate and coronary hemodynamic as cardiac functions. As a result, authors concluded that lithium use had no direct effects on cardiac functions [27]. However, effects of prolonged lithium use on both systolic and diastolic functions of myocardium remain unknown. Meanwhile, lithium could be used in patients with BD who have concomitant cardiovascular disorders. Therefore, it became more important in patients of BD who have such co-morbidities the effects of prolonged use of lithium on systolic and diastolic functions even in therapeutic dose. In the present study, we demonstrated that systolic functions were not deteriorated in patients with BD during follow-up to 49.4 months when compare to healthy volunteers. Therefore, prolonged lithium use is safe in terms of systolic functions in patients with BD.

Evaluation of diastolic function provides significant prognostic information in the cardiovascu-

lar disorders [28, 29]. In the generation of an effective stroke volume, not only a normal systolic function but also a normal diastolic function is essential [30]. Therefore, deteriorated left ventricular diastolic function is the main contributing factor for the development of heart failure with preserved ejection function [30]. Patients with diastolic heart failure show better long-term survival than patients with systolic heart failure. However, hospital readmission rates are similar [31]. Kane et al. found that, there is a relation between presence diastolic dysfunction and development of overt heart failure during a six-year follow-up period [28]. Tsutsui et al. showed in their study that even in the absence of heart failure, left ventricular diastolic dysfunction can be a sole cause of hospitalization and all-cause mortality [32]. Therefore, diastolic dysfunction is associated with poor prognosis and markedly increases all-cause mortality [33]. In the present study, we analyzed the association between prolonged lithium use and left ventricular diastolic function, measured using conventional Doppler techniques of mitral inflow and Tissue Doppler imaging-derived parameters in patients with BD and healthy volunteers. Accordingly, diastolic functions were similar in patients with BD when compared to healthy volunteers.

Conclusion

Although suicide is a major cause of premature mortality in bipolar disorder, most of the excess mortality rate is due to cardiovascular disorders. We showed that prolonged lithium use in patient with BD is a safe treatment option in terms of systolic functions of heart. As previously shown, even in patients with preserved systolic functions, diastolic dysfunction is associated with adverse outcomes and all-cause mortality. Therefore, we also evaluated the diastolic functions in patients with BD and demonstrated that diastolic properties did not differ in patients with BD when compared to healthy volunteers. In conclusion, prolonged lithium use does not impair both systolic and diastolic functions of heart in patients with BD.

Disclosure of conflict of interest

None.

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