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 [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 (≥ 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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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 pressure 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bipolar disorder group (n=30)</th>
<th>Control group (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSD (mm)</td>
<td>46.7 ± 4.6</td>
<td>44.3 ± 5.1</td>
<td>0.120</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>29.6 ± 4.5</td>
<td>28.3 ± 4.2</td>
<td>0.286</td>
</tr>
<tr>
<td>Septum thickness (mm)</td>
<td>9.1 ± 1.4</td>
<td>8.7 ± 1.5</td>
<td>0.379</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>9.6 ± 1.1</td>
<td>9.1 ± 1.3</td>
<td>0.110</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66.7 ± 7.1</td>
<td>66.7 ± 4.9</td>
<td>0.966</td>
</tr>
<tr>
<td>Mitral inflow E velocity (cm/sec)</td>
<td>0.75 ± 0.17</td>
<td>0.79 ± 0.16</td>
<td>0.268</td>
</tr>
<tr>
<td>Mitral inflow A velocity (cm/sec)</td>
<td>0.63 ± 0.12</td>
<td>0.63 ± 0.16</td>
<td>0.132</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.14 ± 0.41</td>
<td>1.28 ± 0.29</td>
<td>0.136</td>
</tr>
<tr>
<td>IVRT (cm/sec)</td>
<td>77.8 ± 14.5</td>
<td>75.9 ± 17.7</td>
<td>0.646</td>
</tr>
<tr>
<td>E wave deceleration time (m/sec)</td>
<td>200 ± 32</td>
<td>186 ± 44</td>
<td>0.185</td>
</tr>
<tr>
<td>Lateral wall Sm (cm/sec)</td>
<td>12.1 ± 3.5</td>
<td>11.9 ± 2.7</td>
<td>0.790</td>
</tr>
<tr>
<td>Lateral wall Em (cm/sec)</td>
<td>14.8 ± 5.2</td>
<td>15.0 ± 4.6</td>
<td>0.830</td>
</tr>
<tr>
<td>Lateral wall Am (cm/sec)</td>
<td>12.7 ± 4.0</td>
<td>11.1 ± 2.4</td>
<td>0.052</td>
</tr>
<tr>
<td>E/Em</td>
<td>5.5 ± 1.8</td>
<td>5.9 ± 2.4</td>
<td>0.136</td>
</tr>
<tr>
<td>Septum wall Sm (cm/sec)</td>
<td>9.5 ± 2.9</td>
<td>9.8 ± 2.0</td>
<td>0.621</td>
</tr>
<tr>
<td>Septum wall Em (cm/sec)</td>
<td>11.5 ± 3.7</td>
<td>12.4 ± 3.9</td>
<td>0.358</td>
</tr>
<tr>
<td>Septum wall Am (cm/sec)</td>
<td>12.1 ± 3.7</td>
<td>10.7 ± 2.7</td>
<td>0.099</td>
</tr>
</tbody>
</table>

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.

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 control 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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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 disease 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.

Table 3. Correlation between serum lithium and echocardiographic parameters

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

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