European Psychiatry 30 (2015) 228–232

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Heart rate variability and Omega-3 Index in euthymic patients with bipolar disorders

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ARTICLE INFO

Article history:
Received 4 August 2014
Received in revised form 17 November 2014
Accepted 17 November 2014
Available online 30 December 2014

Keywords:
Bipolar disorder
Heart rate variability
Omega-3 Index
Cardiovascular disease

ABSTRACT

Background: Affective disorders are associated with an increased risk of cardiovascular disease, which, at least partly, appears to be independent of psychopharmacological treatments used to manage these disorders. Reduced heart rate variability (SDNN) and a low Omega-3 Index have been shown to be associated with increased risk for death after myocardial infarction. Therefore, we set out to investigate heart rate variability and the Omega-3 Index in euthymic patients with bipolar disorders.
Methods: We assessed heart rate variability (SDNN) and the Omega-3 Index in 90 euthymic, mostly medicated patients with bipolar disorders (Bipolar-I, Bipolar-II) on stable psychotropic medication, free of significant medical comorbidity and in 62 healthy controls. Heart rate variability was measured from electrocardiography under a standardized 30 minutes resting state condition. Age, sex, BMI, smoking, alcohol consumption and caffeine consumption as potential confounders were also assessed.
Results: Heart rate variability (SDNN) was significantly lower in patients with bipolar disorders compared to healthy controls (35.4 msec versus 60.7 msec; $P < 0.0001$), whereas the Omega-3 Index did not differ significantly between the groups (5.2% versus 5.3%). In a linear regression model, only group membership (patients with bipolar disorders versus healthy controls) and age significantly predicted heart rate variability (SDNN).
Conclusion: Heart rate variability (SDNN) may provide a useful tool to study the impact of interventions aimed at reducing the increased risk of cardiovascular disease in euthymic patients with bipolar disorders. The difference in SDNN between cases and controls cannot be explained by a difference in the Omega-3 Index.

1. Introduction

Bipolar disorders (BD) are lifelong lasting affective disorders, manifesting themselves, in general, in early adulthood and characterized by episodes as well as subsyndromal symptoms of depression, hypomania and mania, associated with significant impairment in psychosocial, interpersonal and occupational functioning [29]. The life-time prevalence is around 1–5%, dependent on the definition used, with both sexes being equally affected [25]. The available data suggest, that life expectancy in patients with bipolar disorders is decreased by around 12 to 13 years [21]. This is partly due to the increased risk of suicide, but also a result of the increased medical burden associated with bipolar disorders [35], with cardiovascular disease playing a prominent role [20]. The increased risk of cardiovascular mortality among patients with bipolar disorders, compared to the general

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http://dx.doi.org/10.1016/j.eurpsy.2014.11.010
0924-9338/

population, may be accounted for by a higher prevalence of established cardiovascular risk factors in patients with bipolar disorders [42], but also due to depressive symptoms themselves [34].

Measurement of heart rate variability (HRV), with the standard deviation of all NN intervals (SDNN) as key parameter, can serve as a tool for cardiovascular risk stratification [16]. Decreased HRV has been associated with increased cardiac morbidity and mortality, especially in post-MI patients [6]. In a meta-analysis patients with SDNN below 70 ms on 24 hours ECG recording had an almost 4 times greater probability of death within the next 3 years compared to those with an SDNN > 70ms [5]. Interestingly, preliminary data suggest that point-process heart rate variability non-linear methodology may even help to successfully recognize mood states in patients with bipolar disorders [39]. One of the modulators of heart rate variability is the content of eicosapentaenoic + docosahexaenoic acids (EPA + DHA) in erythrocytes, i.e. the Omega-3 Index [15]. Although not entirely consistent, a positive correlation between cellular content of omega-3 polyunsaturated fatty acids (PUFA) and HRV, specifically SDNN, has been found, with intervention studies with EPA + DHA supporting causality [7,10]. A recent meta-analysis suggested that adjunctive omega-3 fatty acids might improve depressive symptoms in bipolar disorders [31]. Taken together these data are compatible with the hypothesis that a deficiency of omega-3 fatty acids may be a risk factor for both depression and cardiovascular mortality [33].

Up to now there are few studies examining HRV (SDNN) in bipolar disorders. So far, the available data point to a decreased HRV compared to healthy controls [22,23,26], even when euthymic [11]. However, none of these studies incorporated the content of Omega-3 Index as a potentially modulating variable. Therefore, we set out to investigate SDNN and the Omega-3 Index in euthymic patients with bipolar disorders, as compared to healthy volunteers. We hypothesized that HRV (SDNN) would be lower in euthymic patients with bipolar disorders, as compared to healthy controls, and that this difference would be, at least partly, explained by a lower Omega-3 Index in the bipolar patient group.

2. Methods

The data used in this study were derived from 2 separate studies both approved by the institutional review board of the faculty of medicine of the Ludwig-Maximilians-Universität München and carried out at the department of psychiatry and psychotherapy, Ludwig-Maximilians-Universität München, in collaboration with preventive cardiology, Ludwig-Maximilians-Universität München, from 04/2009–03/2012.

Patient data were derived from the baseline assessment of the randomized, double-blind, placebo-controlled trial "Omega-3 Fatty Acids in Bipolar Patients with a low Omega-3 Index and Reduced Heart Rate Variability: the 'BIPO-3' Trial" (NCT00891826). Recruitment for this study took place between 04/2009–03/2012. To be enrolled in this study, patients had to meet the DSM-IV criteria for bipolar disorders, in remission (Structured Clinical Interview for DSM-IV, SCID). In addition they had to be between 18–65 years old, be free of psychotropic medication or on stable medication for at least 2 weeks and be able to give written informed consent. Exclusion criteria included, among others, significant medical comorbidity (e.g. cardiovascular disease), any acute and life-threatening condition, a current significant suicidal or homicidal risk or current substance use, apart from smoking and caffeine consumption.

Healthy controls were recruited through postings at the Ludwig-Maximilians-Universität München as well as mailing lists of employees and students of the Ludwig-Maximilians-Universität München. Recruitment for this study took place between 06/2011–11/2011. The group consisted of healthy volunteers who did neither meet at the time of the assessment nor in the past any DSM-IV criteria for a mental disorder, as judged by the SCID (DSM-IV). Furthermore, they had never received any kind of formal psychotherapy. In addition, they had to be able to give written informed consent. Exclusion criteria included, among others, significant medical comorbidity (e.g. cardiovascular disease), any acute and life-threatening condition, a current significant suicidal or homicidal risk or current substance use, apart from smoking and caffeine consumption.

After having signed informed consent, healthy controls as well as patients underwent a structured medical history as well as a physical and neurological examination.

Continuous electrocardiographic (ECG) recordings (ProSciCard III, CPS medical) were obtained from all study participants during a 30 minutes interval. This 30 minutes time interval was chosen as preliminary data suggested, that shorter-term (5 minutes) recordings yield intolerably high intra-individual variability with regard to the primary outcome parameter (SDNN). In contrast, 24 hours recordings proved unacceptable for the majority of our outpatients and healthy controls and would have limited the external validity of our findings. SDNN was chosen as standard parameter for HRV as it can be applied to any short- or long-term recording [41] and provides better prognostic information than any single other HRV parameter [37]. Continuous ECG recordings were done in a supine position, during normal breathing, after a short rest. The room was slightly darkened and had a comfortable room temperature. Participants were asked to relax and stay awake during the test period. Careful considerations were made to ensure subjects were not disturbed by noise. The recordings took place at the same time of the day, commonly between 10 am and 2 pm, with few exceptions being equally distributed between the groups. The ECG recordings were transferred continuously to the monitor. ProSciCard computer system (ProSciCard III) was installed for analyzing HRV. By using the recorded NN intervals, the standard deviation of the NN interval (SDNN) (as a statistical time domain measure) was calculated [12]. The system's internal check of the data was performed by Task Force Analysis, artifacts were marked. Before elimination of the artifacts, the investigator herself (A.L.) double-checked if the artifacts set by the software were correct and could, in addition, mark artifacts herself [12], if overlooked by the software. Artifacts were defined as a fluctuation range of more than 15% of the RR intervals.

Blood was drawn from all study participants to determine the Omega-3 Index. To this end, erythrocyte fatty acid composition was analyzed according to the HS-Omega-3 Index® methodology as previously described [15]. Results are given as EPA plus DHA expressed as a percentage of total identified fatty acids after response factor correction. The coefficient of variation for EPA plus DHA was 5%. Analyses were quality-controlled according to DIN ISO 15189 [15].

To determine whether age, sex, smoking status, body mass index (BMI), caffeine consumption, omega-3 fatty acids, or HRV differed between healthy controls and patients with bipolar disorders, we performed univariate tests (Fisher's exact test and Mann-Whitney test for categorical and continuous variables, respectively). In order to test for associations with HRV, we used Mann-Whitney tests (categorical variables) and Spearman correlation coefficients (continuous variables) on all study participants. No corrections for multiple tests have been applied. Multivariate analyses comprised linear models on HRV, which was transformed using the Box-Cox Transformation to attend normal distribution of the residuals.

3. Results

For the bipolar disorders group, 110 consecutively screened patients of the BIPO-3 intervention trial were included, of whom