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No relationship between generalised anxiety symptoms and cardiovascular autonomic dysfunction

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ABSTRACT

Purpose: Patients with generalised anxiety symptoms generally complain of autonomic arousal symptoms. The present study examined the relationships between cardiovascular autonomic dysfunction and generalised anxiety symptoms.

Methods: Fifty-five participants including patients with generalised anxiety symptoms (n = 32) and healthy volunteers who served as controls (n = 23) were selected for this study. All participants completed the 7-item Generalised Anxiety Disorder Scale (GAD-7) questionnaire and underwent autonomic function tests, including the Ewing test battery and heart rate variability (HRV) test.

Results: Autonomic function parameters included low frequency (LF, 0.04–0.15 Hz) power of HRV, high frequency (HF, 0.15–0.4 Hz) power, power spectrum density (PSD), LF/HF ratio, 30:15 ratio, heart rate response to deep breathing, Valsalva ratio, root-mean square differences of successive R-R intervals (RMSSD), standard deviation of the NN interval (SDNN), stress index (SI) and the Alpha 1 index. There were no significant differences in these parameters between the participants with generalised anxiety symptoms and control participants.

Conclusions: The result of this study suggests that there is no statistically significant relationship between generalised anxiety symptoms and cardiovascular autonomic dysfunction.

1. Introduction

Generalised anxiety disorder (GAD) is a chronic and highly prevalent psychiatric disorder, in which the patient has excessive worry about everyday events and problems (Bandelow & Michaelis, 2015; Bandelow et al., 2013). According to a population-based European epidemiological study, over 8.9 million people (1.7%–3.4%) were affected by GAD in 2010, making it one of the most prevalent psychiatric conditions in the European Union (Wittchen, Jacobi, & Rehm, 2011). Patients with GAD usually have autonomic arousal symptoms such as palpitations, sweating, trembling and dry mouth (Gale & Davidson, 2007). Anxiety is associated with increased risk of cardiovascular events and mortality (Allgulander, 2015; Olafiranye, Jean-Louis, Zizi, Nunes, & Vincent, 2011). However the pathophysiology of GAD, its role in the autonomic nervous system (ANS) and relationship between GAD and cardiovascular disease are not fully understood (Craske and Michelle, 2016; Olafiranye et al., 2011). While some studies report lower high frequency (HF), power of heart rate variability (HRV), lower respiratory sinus arrhythmia (RSA) and lower mean successive differences in GAD patients, some report no differences in any HRV measure between GAD patients and controls (Hammel et al., 2011; Kollai & Kollai, 1992; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996). It is therefore clear that more studies are required to evaluate the relationship between GAD and the ANS.

The Ewing test battery is a standard for the diagnosis of autonomic dysfunction but requires much time, practice and patient cooperation; however, the HRV diagnostic tool is less invasive and simple to perform (Ewing & Clarke, 1986; Guo, Palmer, Strasser, Yusuf, & Bruera, 2013; Lee et al., 2016).

Patients with anxiety are often clinically diagnosed as having somatoform autonomic dysfunction (Jana, Praharaj, & Mazumdar, 2012). Somatoform autonomic dysfunction is a poorly defined and undifferentiated sub-diagnosis, which is easy-to-use and does not require instrumental tests (Rief & Isaac, 2007). Moreover, somatoform

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autonomic dysfunction is one the most frequently diagnosed mental disorders in primary care in Latvia (Leff, Vrubļevska, Lūse, & Rancāns, 2017).

The aim of the study was to determine the prevalence and pattern of cardiovascular autonomic abnormalities in patients with generalised anxiety symptoms by combining two methods: the Ewing test and HRV analysis.

2. Materials and methods

2.1. Subjects

Thirty-two patients with anxiety symptoms aged more than 18 years were selected from the emergency department of Riga Eastern Clinical University and Paul Stradins Clinical University hospitals. Twenty-three controls were selected from healthy volunteers. Healthy volunteers were recruited by placing advertisements in Rīga Stradiņš University and hospitals. The age of participants ranged from 22 to 56 years, with a mean age of 29.67 ± 8.08 years. Participants with generalised anxiety symptoms and control participants had minimal age difference, Me = 24 years (IQR = 23–30 years) versus Me = 29 years (IQR = 25–34 years) (p = 0.019). Of the 55 participants, 37 were women, and 18 were men. Of the 32 participants with generalised anxiety symptoms, 26 were females and 6 were males. Of the 23 control participants, 11 were females and 12 were males. Participants with the following criteria were excluded: the presence of other psychiatric disorders, substance use disorders (including alcohol), ischemic heart disease, atrial fibrillation, organic central nervous system disease, diabetes and other endocrinopathies. Participants were excluded for a self-reported history of psychotropic medications and medications which may affect cardiovascular autonomic system, such as beta blockers or other antiarrhythmic agents.

2.2. Generalized anxiety disorder scale

Generalised anxiety symptoms were recorded using the 7-item Generalized Anxiety Disorder Scale (GAD-7) (Spitzer, Kroenke, & Williams, 2006). The GAD-7 was developed to provide a brief self-reported measure to identify generalised anxiety in primary care. The GAD-7 has been validated within a large sample of patients in primary care and also in a general population sample in Germany (Löwe et al., 2008; Spitzer et al., 2006). The GAD-7 represents an anxiety measure based on 7 items that are scored from 0 to 3. The whole scale score can range from 0 to 21 and scores of 5, 10 and 15 were taken as the cut-off points for mild, moderate and severe anxiety, respectively (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007). Internal consistency of the GAD-7 was estimated at 0.92; moreover, there was good agreement between self-reported and interviewer-administered versions of the scale (Spitzer, Kroenke, Williams, Löwe et al., 2006). Patients who fulfilled the inclusion criteria were invited to complete the GAD-7 in Latvian. Previously, the GAD-7 scale was used within the framework of the Latvian National Research Program BIOMEDICINE (2014–2017) to assess the prevalence and detection of mental disorders in primary care settings in Latvia (Ivanovs et al., 2016). Participants were instructed to complete a paper and pencil form of the GAD-7 scale before autonomic testing. Patients from emergency department with a score of 5 and greater were included and formed the anxiety group. Healthy volunteers with a score below 5 formed the control group.

2.3. Ewing battery test

Quantitative and clinically validated protocols for the testing of autonomic functions were used. Normative data for the Valsalva ratio, 30:15 ratio and deep breathing test were age and gender dependent. The normal responses in heart rate during the tilt table test were defined as heart rate increment within 10–30 beats per minute and the maximal heart rate less than 120 beats per minute. Normal responses in the blood pressure during the tilt test were defined as a drop of the systolic blood pressure less than 30 mm Hg or drop of the mean blood pressure less than 20 mm Hg (Novak, 2011). The blood pressure response to tilt testing, heart rate response to deep breathing and the Valsalva manoeuvre were measured using a non-invasive Task Force Monitor (TFM; CN Systems, Graz, Austria). The static grip test was excluded because of its limited sensitivity and poorly established variables (Ewing, Irving, Kerr, Wildsmith, & Clarke, 1974; Lind, Taylor, Humphreys, Kennelly, & Donald, 1964; Vissing & Victor, 1989). Participants were asked to avoid night shift work for 48 h before performing tests; in addition, the participants were asked to avoid smoking, eating, and drinking coffee or tea for 2 h before performing tests. Measurements were recorded after 5 min of relaxation and adaptation to the environment. None of the subjects complained of an increase in anxiety during the testing. The Ewing test was performed anonymously with regard to the GAD-7 results. The Ewing test performer was blinded to the GAD-7 results. The standard Ewing's criteria were used to define normal, borderline and abnormal values (Ewing, Campbell, Burt, & Clarke, 1973).

Patients were evaluated as having normal autonomic function or parasympathetic, sympathetic, and combined dysfunction. Parasympathetic nervous system (PNS) abnormality was defined if participants had one or more abnormalities in 3 tests: Valsalva ratio, heart rate response to deep breathing, 30:15 ratio. Sympathetic nervous system (SNS) abnormality was defined if participants' blood pressure response to standing was found to be abnormal.

2.4. Heart rate variability testing

HRV was measured 10 min after the Ewing battery test using software programs ANS Analysis and TFM Monitor. Time and frequency domain HRV indices including root-mean square differences of successive R-R intervals (RMSSD), standard deviation of the NN interval (SDNN), stress index, Alpha 1 index, Low frequency (LF, 0.04-0.15 Hz) power of HRV, high frequency (HF, 0.15-0.4 Hz) power, power spectrum density (PSD) and LF/HF ratio were measured. Normative values from the manufacturer where used to define abnormalities. The approximate testing time was 40 min.

Analysis of HRV is used to describe the amount of fluctuations from the mean heart rate. HRV is considered a reliable indicator of cardiac autonomic dysfunction (Alvares, Quintana, Hickie, & Guastella, 2016). HRV analysis is possible in the time or frequency domain (Thayer, Yamamoto, & Brosschot, 2010).

2.4.1. Time domain indices

RMSSD index reflects parasympathetic influences on heart rate.

SDNN index reflects both sympathetic and parasympathetic influences.

Stress index reflects sympathetic activity.

Non-linear Alpha 1 parameter indicates compensation processes and quality of regulation.

2.4.2. Frequency domain indices

PSD represents the power distribution as a function of frequency.

LF (0.04-0.15 Hz) band reflects both parasympathetic and sympathetic impulses.

HF (0.15-0.4 Hz) band reflects parasympathetic input to the sinus node.

LF/HF ratio is used to express sympathovagal balance and sympathetic modulation (Lee et al., 2016; Thayer et al., 2010).

2.5. Statistical analysis

All statistical analyses were performed using SPSS Version 22 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel. The data were presented as