ARTICLE IN PRESS

Autonomic Neuroscience: Basic and Clinical xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Temporal stability and drivers of change in cardiac autonomic nervous system activity

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A R T I C L E I N F O

Keywords:
Autonomic nervous system
Temporal stability
Longitudinal
Lifestyle
Antidepressants
Cardiac medication

A B S T R A C T

Objectives: This study determined temporal stability of ambulatory measured cardiac autonomic activity for different time periods and investigated potential drivers of changes in this activity.
Methods: Data was drawn from baseline (n = 2379), 2-year (n = 2245), and 6-year (n = 1876) follow-up from the Netherlands Study of Depression and Anxiety. Cardiac autonomic activity was measured with heart rate (HR), respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP). Autonomic temporal stability was determined across 2, 4, and 6 year intervals. We subsequently examined the association between socio-demographics, lifestyle, mental health, cardiometabolic health, and the use of antidepressant and cardiac medication with change in cardiac autonomic activity.
Results: Over 2 years, stability was good for HR (ICC = 0.703), excellent for RSA (ICC = 0.792) and moderate for PEP (ICC = 0.576). Stability decreased for a 4- (HR ICC = 0.688, RSA ICC = 0.652 and PEP ICC = 0.387) and 6-year interval (HR ICC = 0.633, RSA ICC = 0.654 and PEP ICC = 0.355). The most important determinants for increase in HR were (increase in) smoking, increase in body mass index (BMI) and (starting) the use of antidepressants. Beta-blocking/antiarrhythmic drug use led to a decrease in HR. Decrease in RSA was associated with age, smoking and (starting) antidepressant use. Decrease in PEP was associated with age and (increase in) BMI.
Conclusions: Cardiac autonomic measures were rather stable over 2 years, but stability decreased with increasing time span. Determinants contributing to cardiac autonomic deterioration were older age, (increase in) smoking and BMI, and (starting) the use of antidepressants. (Starting) the use of cardiac medication improved autonomic function.

1. Introduction

The autonomic nervous system (ANS) plays a key role in cardiovascular regulation, and is a major determinant of resting heart rate (HR) and blood pressure (BP), two independent risk factors for coronary artery disease (MacMahon et al., 1990; Palatini & Julius, 2004). Indicators of cardiac sympathetic and parasympathetic activity can be non-invasively and unobtrusively measured by electrocardiography (ECG) and impedance cardiography (ICG) (De Geus et al., 1995; De Geus & Van Doornen, 1996). In order to draw conclusions from longitudinal studies on indices of cardiac autonomic activity, these indices are assumed to remain rather stable within individuals. Since there are many factors in a person's life that may influence autonomic measures, it is impossible to achieve 100% agreement within a person over time. Therefore, it is useful to determine the temporal stability of cardiac autonomic activity when interpreting the results of longitudinal studies. In addition, it is necessary to investigate which factors contribute to cardiac autonomic change, so that these factors are accounted for in longitudinal studies.

Temporal stability has been investigated for HR, stroke volume, cardiac output, pre-ejection period (PEP), total peripheral resistance, systolic BP, and heart rate variability (HRV) (Bertsch et al., 2012; Barnes et al., 2004; Sloan et al., 1995; Vrijkotte et al., 2004; Goedhart et al., 2007, 2008; Colloca et al., 2006; Mukherjee et al., 2012; Burleson et al., 2003). These studies generally yielded moderate to high stability. However, found correlation coefficients showed variations among

Abbreviations: ANS, autonomic nervous system; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; ECG, electrocardiogram; HR, heart rate; HRV, heart rate variability; IAT, implicit association task; IBI, interbeat interval; ICG, impedance cardiography; METmin, multiple of resting metabolic rate times minutes of physical activity per week; NESDA, Netherlands Study of Depression and Anxiety; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; SNRI, selective serotonin and noradrenalin reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; VU-AMS, Vrije Universiteit Ambulatory Monitoring System

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http://dx.doi.org/10.1016/j.autneu.2017.07.005
Received 27 March 2017; Received in revised form 21 July 2017; Accepted 24 July 2017
1566-0702/

studies, likely caused by differences in methodology. For instance, studies differ in time span (ranging from a couple of days to a couple of years), sample size (ranging from tens of participants to over a hundred participants) and sample population (population versus clinical samples). While it would be intuitively appealing for temporal stability to decrease with increasing time span, this was not inferred from the literature. To our knowledge, Goedhart and colleagues conducted the longest study in this research field across 3.3 years and still found moderate to high stability for both cardiac sympathetic and parasympathetic activity (Goedhart et al., 2007, 2008). Regarding sample population, it has been suggested that HRV, for instance, has significantly worse stability in clinical populations than in healthy controls, as shown for populations with chronic heart failure (Ponikowski et al., 1996) and cardiac transplant recipients (Lord et al., 2001).

ANS dysregulation has been associated with unfavorable health outcomes, such as the metabolic syndrome (Hu et al., 2016a; Koskinen et al., 2009) and cardiometabolic health (Curtis & O'Keefe, 2002; Grassi et al., 2015; Carnethon et al., 2006). This can partly reflect a causal role of ANS activity in the onset of these diseases, but it is possible that in parallel changes in cardiac ANS activity over time might themselves be affected by these health issues, for instance through the effects of cardiac medication (MacFadyen, 1997; Harada et al., 2003). Many more factors have been suggested to influence the ANS. Sociodemographics such as age (Pfeifer et al., 1983), sex (Dart, 2002) and social economic status (Sloan et al., 2005) have been linked to autonomic activity. In addition, several lifestyle factors have been associated with ANS activity (Hu et al., 2017), including physical activity (Rennie et al., 2003), alcohol use (Ohira et al., 2009), smoking behavior (Middlekauff et al., 2014), and unhealthy dietary patterns as indexed by e.g. body mass index (BMI) (Molfino et al., 2009). Patients with psychiatric disorders, such as depression and anxiety, have been suggested to have altered ANS (re)activity, with causal effects possible in both directions (Phillips et al., 2011; Hu et al., 2016b). Importantly, there is increasing evidence that the use of antidepressants might negatively impact autonomic balance (Kemp et al., 2010; Licht et al., 2010, 2012). For many of these factors, studies mostly investigated cross-sectional relationships with ANS and occasionally short-term longitudinal relationships. Longitudinal studies over the course of years are scarce.

The current study aims to establish the temporal stability of ambulatory measured cardiac autonomic activity during several laboratory conditions over a 2-, 4- and 6-year time period in a large cohort of the Netherlands Study of Depression and Anxiety (NESDA). We used the following indicators of cardiac ANS activity: HR (controlled by both sympathetic and parasympathetic activity) (De Geus & Van Doornen, 1996), respiratory sinus arrhythmia (RSA: an indicator of parasympathetic activity) (De Geus et al., 1995) and PEP (indicative of sympathetic activity) (De Geus & Van Doornen, 1996). We investigated whether sociodemographics or (changes in) lifestyle, mental health, cardiometabolic health, and the use of antidepressant or cardiac medication were significant drivers of changes in cardiac autonomic activity over time.

2. Methods

2.1. Subjects

Data was obtained from NESDA, an ongoing longitudinal cohort study to examine the long-term course of depression and anxiety. Participants were recruited from community, primary care and mental health care in The Netherlands. The NESDA sample includes 2981 participants aged 18–65 years with a current diagnosis of depression and/or anxiety disorder, a prior history of these disorders, and healthy controls. A four-hour baseline measurement was conducted between September 2004 and February 2007, and follow-up assessments took place after two, four and six years. A detailed description of the rationale, objectives and methods of the NESDA study can be found elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of each participating center, and all participants provided written informed consent. The study was performed conform the declaration of Helsinki.

Data for the present study were drawn from baseline (n = 2981), 2-year (n = 2596) and 6-year (n = 2256) follow-up assessments (cardiac autonomic activity was not measured during 4-year follow-up). Subjects were included when they had measurement of either HR, RSA or PEP during at least two assessments, so that temporal stability could be determined. This resulted in a total of 2379 subjects at baseline, 2245 subjects at 2-year follow-up and 1876 subjects at 6-year follow-up. Missing physiological data was due to telephone or at-home interviews without ANS recording, equipment failure during assessment or poor electrocardiogram quality.

2.2. Procedures

The clinic visits consisted of biological assessment including a supine blood pressure measurement, a psychiatric interview, a general interview and a computer task. The psychiatric interview included questions about various indicators of anxious and depressive symptoms, as well as suicide ideation, mood disorder symptoms and experience of adverse life events. The general interview contained questions about somatic health, smoking behavior, use of medication, daily functioning and health care utilization. The computer task was an implicit association task (IAT) (Greenwald et al., 1998).

2.3. Determinants of change in autonomic activity

Determinants of autonomic instability were measured at all three waves and described in detail below.

2.3.1. Sociodemographics

The following sociodemographic factors were investigated: age (years), sex (1 = male, 2 = female), and education (years) as a proxy for social economic status.

2.3.2. Lifestyle factors

Physical activity was measured by the short IPAQ (Booth et al., 2003), a 7-item instrument assessing the amount of habitual vigorous activity, moderate and walking activities over the last 7 days. A continuous score is calculated in Metabolic Equivalent Total (MET)-minutes per week: MET level ∗ minutes of activity ∗ events per week. Alcohol use was assessed by the Alcohol Use Disorder Identification Test questionnaire (Babor et al., 1992) from which the number of alcoholic drinks per week was derived. A drink was defined as follows: 1) a single small (8 oz) glass of beer, 2) a single shot/measure of liquor/spirits, 3) a single glass of wine. Smoking was indicated by the current number of cigarettes/day. Body mass index (BMI) was measured in kg/m^2.

2.3.3. Mental health

Participants were considered to have a current psychopathology when they had a 6-month diagnosis of major depressive disorder and/or anxiety disorder (panic disorder, social phobia and/or generalized anxiety disorder) according to the DSM-IV-based Composite International Diagnostic Interview, version 2.1.

2.3.4. Antidepressant use

Participants were requested to bring their medication containers to the assessments so that medication use could be determined. We investigated the use of tricyclic antidepressants (TCAs: ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs: ATC code N06AB), and selective serotonin and noradrenalin reuptake inhibitors (SNRIs: ATC code N06AX). Previous research on NESDA data has indicated that TCAs and SNRIs have a different effect on ANS activity than SSRIs, with detrimental effects of TCAs and SNRIs on HR, RSA and PEP, while SSRIs