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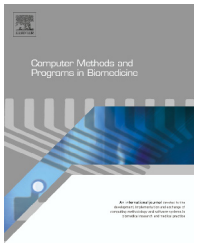

Orthostatic stress causes immediately increased blood pressure variability in women with vasovagal syncope

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ABSTRACT

The cardiovascular and respiratory autonomic nervous regulation has been studied mainly by hemodynamic responses during different physical stressors. In this study, dynamics of autonomic response to an orthostatic challenge was investigated by hemodynamic variables and by diverse linear and nonlinear indices calculated from time series of beat-to-beat intervals (BBI), respiratory cycle duration (RESP), systolic (SYS) and diastolic (DIA) blood pressure. This study included 16 young female patients (SYN) with vasovagal syncope and 12 age-matched female controls (CON). The subjects were enrolled in a head-up tilt (HUT) test, breathing normally, including 5 min of baseline (BL, supine position) and 18 min of 70° orthostatic phase (OP). To increase the time resolution of the analysis the time series were segmented in five-minute overlapping windows with a shift of 1 min. Hemodynamic parameters did not show any statistical differences between SYN and CON. Time domain linear analysis revealed increased respiratory frequency and increased blood pressure variability (BPV) in patients during OP meaning increased sympathetic activity and vagal withdrawal. Frequency domain analysis confirmed a predominance of sympathetic tone by steadily increased values of low over high frequency power in BBI and of low frequency power in SYS and DIA in patients during OP. The nonlinear analysis by symbolic dynamics seemed to be highly suitable for differentiation of SYN and CON in the early beginning of OP, i.e., 5 min after tilt-up. In particular the index SYS_plvar3 showed less patterns of low variability in patients reflecting a steadily increase in both BPV and sympathetic activity. The proposed dynamical analysis could lead to a better understanding of the temporal underlying mechanisms in healthy subjects and patients under orthostatic stress.

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1. Introduction

Vasovagal syncope (VVS) is a temporal loss of consciousness due to a reduction in cerebral blood flow by an orthostatic stress being the women the more probably population to report syncopal episodes [1]. In clinical practice evaluation of autonomic function associated with VVS is routinely performed by means of the head-up tilt (HUT) test. The HUT test, in which the subject undergoes a change of position very quickly from supine to certain tilt or orthostatic phase (OP), causes a reduction in venous return leading to diminished stroke volume and cardiac output. To maintain blood pressure, the reduction in stroke volume must be compensated for by reflex mechanisms that increase total peripheral resistance. Otherwise, blood pressure falls leading to cerebral hypoperfusion and syncope [2]. VVS has been studied from different points of view using unmedicated or medicated HUT to understand its underlying physiological mechanisms or to predict possible syncopal episodes. In 2013, Forleo et al. published a review of HUT experimental protocols for diagnosing VVS where among other issues it is reported that the sensitivity of the test increases as the duration of the OP increases [3]. From the signal processing point of view, acquired cardiovascular and respiratory time series have been analyzed mainly by linear techniques and by some nonlinear techniques using one temporal window at supine, tilt and recovery phases. Furthermore, in analysis of cardiovascular variability, indices derived from linear techniques have been standardized [4] but in the case of nonlinear indices their usefulness is still under research.

In 1997, Lipsitz et al. [5] studied a cohort of healthy subjects, in a HUT test protocol, with a maneuver of paced breathing followed by spontaneous breathing. The authors found highly periodic blood pressure rhythms in those healthy subjects that later developed syncope, suggesting an unstable physiological control network that predisposes individuals to circulatory collapse. Nowadays, researches point out that clinicians should be aware of the prognostic implications of the variability in blood pressure [6]. In fact, Rickards et al. in 2014 published a review focused on blood pressure and cerebral flow variability in different health status as risk of stroke, myocardial infarction and end-organ damage from hypertension, among others [7]. In the review, blood pressure variability analysis was performed just close to the syncope event and for healthy subjects. Consequently, more research needs to be done to validate the usefulness of BP variability to improve health outcomes to avoid detrimental consequences on vital organs [7–9].

We hypothesize that univariate linear and nonlinear analysis of segmented cardiovascular and respiratory time series, as performed in this study, may reveal changes in the dynamic of the autonomic regulation response in healthy females and in female patients with VVS, facing an orthostatic challenge. Accordingly, in the present study, under an unmedicated HUT test protocol and including healthy subjects and VVS patients, the aim is three-fold: first, to increase the temporal resolution of the analysis of the HUT test response by a segmentation procedure of cardiovascular and respiratory time series; second, to find representative indices by diverse linear and nonlinear techniques that evidence the time course of fluctuations of sympathetic and vagal activities in both subject groups and third, to elucidate the importance of changes in blood pressure variability for VVS patients and healthy subjects.

2. Methods

2.1. Subjects and experimental protocol

In this study, 16 female patients diagnosed with vasovagal syncope with a mean age of 26 ± 8 years and 12 age-matched female controls with a mean age of 26 ± 5 years were enrolled. All SYN cases were patients of the National Institute of Cardiology (NIC), at Mexico City, with at least 2 syncope or presyncope episodes within the previous 12 months. Presyncope was determined if the subject experienced weakness, diaphoresis, chills, dizziness and nausea without loss of consciousness. VVS was confirmed by the HUT test. Controls were healthy volunteers with no syncope or presyncope history and negative HUT test. In this study the phase of the menstrual cycle was not controlled; there is a controversy about its influence on the autonomic regulation [10,11]. Studies were approved by the Ethics Committee of the NIC and performed under informed consent according to the Declaration of Helsinki. High-resolution ECG (1000 Hz sampling frequency), continuous non-invasive arterial pressure (CNAP) and impedance cardiography (ICG) were simultaneously recorded using a Task Force Monitor (CNSystems, Graz, Austria). The subject was first adjusted to a tilting table and allowed to accommodate to supine position to guarantee a stable condition. Data recording started with a rest period of 5 min in the supine position (baseline – BL). During one minute, the subject underwent a 70° head-up tilt. The duration of the following orthostatic phase (OP) varied between 30 and 40 min in case of the controls. Regarding patients, the HUT test was aborted by returning the tilt table back to supine positions if the patient developed symptoms of presyncope during orthostatic phase. This reduced the maximal comparable duration of orthostatic phase between patients and controls down to 18 min, see Fig. 1.

2.2. Data acquisition and pre-processing

Time series of successive beat-to-beat intervals (BBI, tachogram), the time interval between two successive breaths (RESP, respirogram), systolic (SYS, systogram) and diastolic (DIA, diastogram) blood pressure values were extracted from ECG, ICG and CNAP, respectively. All extracted time series were manually reviewed and subsequently corrected for by interpolation of ventricular premature beats and artifacts using an adaptive filter to obtain normal-to-normal beat time series (NN) [12]. Data analysis was performed twofold: in the first analysis we used 20 five-minute overlapping windows with a shift of one minute to investigate the dynamical changes from baseline to and during orthostatic phase, comparing in each window female controls (CON) with female VVS patients (SYN). The 20 windows referred to the following stages: window 1 (baseline – BL), windows 2–6 (transition including one minute of tilt-up to orthostatic phase) and

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