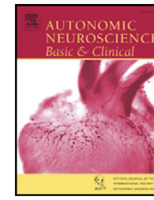
Autonomic Neuroscience: Basic and Clinical 186 (2014) 69–76

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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



Additive effect of simultaneously varying respiratory frequency and tidal volume on respiratory sinus arrhythmia

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ARTICLE INFO

Article history:
Received 29 November 2013
Received in revised form 29 May 2014
Accepted 12 August 2014

Keywords:
Controlled breathing
Gender differences
Heart rate variability
Respiratory frequency
Respiratory sinus arrhythmia
Tidal volume
Time–frequency distribution

ABSTRACT

Our aims were to assess, in healthy young females and males, the effects of the linear joint variation of respiratory frequency (RF) and tidal volume (VT) on the logarithmic transformation of high-frequency power of RR intervals (lnHF).

ECG and VT were recorded from 18 females and 20 males during three visually guided 30-s breathing maneuvers: linearly increasing RF (RF_{LI}) at constant VT; linearly increasing VT (VT_{LI}) followed by decreasing VT (VT_{LD}) at fixed RF, and RF_{LI} and VT_{LI}–VT_{LD} combined. VT of females was 20% smaller. Instantaneous RF and lnHF were computed from the time–frequency distributions of respiratory series and RR intervals.

LnHF–RF and lnHF–VT relations were similar between genders. LnHF and RR intervals control-maneuver differences during combined maneuver were approximately equal to the sum of those of the independent maneuvers. LnHF–RF_{LI} relation showed strong negative correlations in separated and combined conditions, with steeper slope in the latter ($p < 0.001$). LnHF–VT_{LI} and lnHF–VT_{LD} relations presented, in the independent maneuvers, three combinations of slopes of different sign, all with hysteresis, and in the combined maneuver, strong correlations with negative slope for VT_{LI} and positive slope for VT_{LD}, steeper ($p < 0.001$) and with greater hysteresis ($p < 0.001$) than the independent ones.

LnHF responses to our fast, non-fatiguing and non-steady-state breathing maneuvers are: similar between genders; consistent attenuation due to RF_{LI}, whether applied alone or combined; ambiguous and with hysteresis to independent VT_{LI}–VT_{LD} variations; systematic greater attenuation during RF_{LI} combined with VT_{LI}–VT_{LD}, equal to the sum of the independent effects, indicating that there is no interference between them.

1. Introduction

Voluntary control of respiratory movements is a valuable procedure that has permitted to explore the effects of respiratory frequency (RF) and tidal volume (VT) on respiratory sinus arrhythmia (RSA). This knowledge is required for a comprehensive understanding of its underlying mechanisms (Hirsch and Bishop, 1981; Larsen et al., 2010).

One of the most used and powerful tools to assess RSA is the spectral analysis of RR interval (RR) series, in particular its high frequency component (HF) (Larsen et al., 2010), whose amplitude and central frequency changes are easily measured. Spectral analysis also allows the estimation of the coherence between RR and respiratory series.

Few studies have searched for gender differences in RSA basal levels (Snieder et al., 2007) or in its response to changes in the respiratory variables (Sébert, 1983; Stark et al., 2000) or to other provocative maneuvers (Ruiz et al., 2006). Therefore, this issue remains unresolved.

Hirsch and Bishop (1981) published one of the most influential studies that documented the effects of RF and VT on RSA magnitude, in which two different controlled-breathing protocols were employed: one to examine the effect of more than 10 different RF at fixed VT, and the other to assess the effect of six levels of VT at constant RF. They reported that RSA amplitude presents an inverse relation with RF and a positive linear relation with VT. The latter is assumed by many authors for normalizing RSA for VT, a procedure deemed necessary to avoid respiratory confounds and minimize interindividual variations to improve its comparability. The findings of that study on the separated influences of each respiratory parameter on RSA have been confirmed repeatedly (Grossman and Taylor, 2007), more often for the effect of RF than for VT. However, there are no reports available documenting the effects of the continuous and simultaneous variation of the two respiratory variables on RSA amplitude. To shed new light on how the autonomic nuclei integrate the effects of simultaneous and voluntary variations of VT and RF, we devised an innovative methodological approach comprising the following strategies: 1) Comparing between the effects provoked by the independent and by the simultaneous variations of RF and VT on

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http://dx.doi.org/10.1016/j.autneu.2014.08.003
1566-0702/

autonomic activity may suggest that the integration of the respiratory afferences by autonomic nuclei is facilitatory or inhibitory, analogously to studies that compare between the cortical effects of separate and simultaneous somatosensory stimuli to explore the degree of overlap of the responsive areas (Biermann et al., 1998; Hamada and Suzuki, 2003). 2) Using continuous and linearly varying VT and RF over a wide range as respiratory stimuli to explore the linearity of the autonomic-cardiac response. 3) Non-invasively assessing the autonomic-cardiac response by means of the most consistent index obtained from the spectral analysis of heart rate variability (HRV), the HF power (Parati et al., 2006), and the mean values of RR intervals (RRm). 4) Performing the spectral analysis of HRV with a time–frequency distribution, an analysis tool capable of tracking the instantaneous variations of the spectral components of non-stationary signals over time (Mainardi, 2009). Therefore, the aim of the present study was to assess, in healthy young females and males, the effects of the voluntary linear joint variations of RF and VT on HF and RRm. We hypothesize that the autonomic nervous system regions that participate in the generation of RSA integrate the afferences from VT and RF separately. Hence, the effect of the simultaneous changes of both variables will be equal to the sum of their independent effects.

2. Materials and methods

2.1. Subjects

Thirty-eight long-term residents of Mexico City (altitude 2240 m) participated voluntarily in this study. Inclusion criteria were: healthy (as established by clinical examination, resting ECG, and spirometry), young, normotensive, non-overweight, non-smoker and sedentary males and females (Table 1). They were asked to refrain from eating large meals, drinking alcoholic or stimulating beverages, and performing intense physical activity in the 12 h prior to the study. Written informed consent of the volunteers was requested to participate. This study was approved by the Ethics Committee of our university and was performed in accordance with the Declaration of Helsinki.

2.2. Protocol

In a first visit to the laboratory the health status of each subject was assessed. When subjects met the inclusion criteria, they were trained to ensure the correct execution of the controlled breathing maneuvers. In a second visit, subjects performed the three controlled-breathing maneuvers in random order and in sitting position, with 5-min resting periods between maneuvers to allow their physiological status return to baseline. Since vital capacity and VT of women are usually 20% smaller than those of men (Hankinson et al., 1999), two sets of controlled breathing maneuvers were used to ensure that the respiratory effort was similar for all subjects. The maneuvers were: 1) Independent RF condition: linearly increasing RF (RF_{LI}) from 0.15 to 0.5 Hz while keeping a constant VT of 1.0 l for males and of 0.8 l for females; 2) Independent VT maneuver: linearly increasing VT (VT_{LI}) followed immediately by linearly decreasing VT (VT_{LD}) at a fixed RF of 0.2 Hz, from 1.5 to 2.5 l for men and from 1.0 to 2.0 l for women; and 3) Combined condition: the simultaneous performance of RF_{LI} and VT_{LI}–VT_{LD}. Each maneuver was preceded by three control respiratory cycles at a RF of 0.2 Hz and a VT of 0.8 l for women and 1.0 l for men. Maneuver execution was visually guided by overlapping the VT signal of the subject and the target respiratory pattern, displayed on a monitor.

Table 1
Means ± S.D. of the anthropometric characteristics of the subjects.

	Females	Males
N	18	20
Age (years)	20.7 ± 1.7	21.3 ± 1.8
Height (cm)	158.4 ± 5.8	171.8 ± 7.6
Weight (kg)	59.8 ± 10.1	71.3 ± 15.4
Body mass index (kg/m^2)	23.8 ± 3.4	23.9 ± 3.7

ECG, VT and tidal CO_2 signals were recorded throughout the entire protocol. Subjects were studied between 10:00 and 13:00 h. Mean barometric pressure in the laboratory was 591 ± 2 mmHg.

2.3. Recorded variables and signal acquisition

ECG was detected at the thoracic bipolar derivation CM5 with a bioelectric amplifier (ECG100, Biopac Systems). None of the participants presented ectopic beats. VT was recorded by a set composed of pneumotachometer (HR100, Hans Rudolph), pressure transducer (MP45, Validyne), carrier demodulator (CD19A, Validyne) and integrator (FV156, Validyne). Air was continuously sampled from the mouthpiece and tidal CO_2 concentration was measured with an infrared analyzer (CO2100, Biopac Systems), calibrated with gases of known concentration. Signals were digitized at a sampling rate of 500 Hz via an acquisition and display system (MP150, Biopac Systems).

2.4. Data processing

All data processing was performed offline using customized algorithms written in the MATLAB (R2012a, MathWorks) programming environment. Maximum values of R waves were detected from ECG to generate RR series. VT was measured from each respiratory cycle. Breath-by-breath end-tidal CO_2 ($ETCO_2$) levels were computed from the maximum values of tidal CO_2 recordings to construct the respective time series. RR, $ETCO_2$ and VT series were cubic-spline interpolated, resampled at 8 Hz, and detrended using the smoothness priors method (Tarvainen et al., 2002). The trend of RR series, obtained from the smoothness priors filter with a cutoff frequency of 0.04 Hz, was employed as RRm.

Time–frequency spectra of the RR and VT series were estimated with the smoothed pseudo-Wigner-Ville distribution, a representation of the Cohen's class widely used in physiological studies (Cottin et al., 2004). This methodology allows tracking the evolution of the spectral components of non-stationary signals while providing excellent time and frequency resolution due to its independent smoothing windows (Mainardi, 2009).

Instantaneous HF in absolute units and instantaneous RF were computed as the first two-order moments of the RR and VT time-frequency distributions in the 0.15–0.5 Hz frequency band, respectively (Monti et al., 2002). Pulmonary ventilation (PV) was derived from the VT series and instantaneous RF.

To facilitate their mathematical characterization and statistical analysis, the HF responses to VT_{LI}–VT_{LD} were divided into the increasing and decreasing parts in the independent and combined maneuvers. For visualization purposes, the individual continuous dynamics of the variables and their relationships were ensemble-averaged.

2.5. Statistical analysis

Data are expressed as means ± standard deviation. Because of the skewed distribution of HF power, logarithmic transformation was used (lnHF). Linear regressions and correlation coefficients were computed to assess the lnHF–RF_{LI}, lnHF–VT_{LI} and lnHF–VT_{LD} relations of each subject, in both separated and combined conditions.

The integral of the instantaneous values of PV, RRm, and lnHF was used to compute their mean values during the control period and during the breathing maneuver. For $ETCO_2$, the mean control and end of maneuver values were considered. To provide a measure of the maneuver effect, control-maneuver mean values differences of these variables were obtained. The difference between the intercepts (ΔI) of the increasing and decreasing lnHF–VT regressions was taken as a measure of hysteresis. Student's paired t-test was employed to compare the