Interactive Effects of Simultaneously Varying Respiratory Frequency and Tidal Volume on Respiratory Sinus Arrhythmia

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Abstract

The effects of respiratory frequency (RF) and tidal volume (TV) on respiratory sinus arrhythmia (RSA) have been established separately. We assessed the interactive effects of simultaneously varying RF and TV on high-frequency power of RR intervals (HF_{RR}). 25 subjects performed three 30-s breathing protocols: linearly increasing RF (RF_{LI}) at fixed TV; linearly increasing TV (TV_{LI}) and decreasing TV (TV_{LD}) at fixed RF, and RF_{LI} with TV_{LI}-TV_{LD}. From time-frequency spectra, HF_{RR} and instantaneous RF were computed. RF_{LI}-HF_{RR} correlations were strong in separated and combined conditions, with greater regression slope in combined ($p<0.001$). Three types of TV_{LI}-HF_{RR} relations were found: negative linear, no change and positive linear. Combined protocol transformed this inconsistent response into a systematic negative linear relation with greater slope ($p<0.001$). TV_{LD}-HF_{RR} correlations were strong in separated and combined conditions, with steeper slope in combined ($p<0.001$). Our fast, non-fatiguing and linearly varying protocols document that: 1) RF_{LI} consistently attenuates RSA, 2) the separate effects of TV_{LI}-TV_{LD}, especially TV_{LI}, on RSA, are ambiguous and present hysteresis, and 3) RF_{LI} combined with TV_{LI}-TV_{LD} induce greater attenuating effects on RSA. The nonlinear effect of TV on RSA questions the usual practice of normalizing RSA for TV.

1. Introduction

Voluntary control of respiratory movements is a powerful procedure that has permitted to explore the independent effects of respiratory frequency (RF) and tidal volume (TV) on respiratory sinus arrhythmia (RSA) magnitude, knowledge required for a comprehensive understanding of its underlying mechanisms [1,2].

Hirsch & Bishop [2] published one of the most influential studies that documented the effects of RF and TV on RSA magnitude, in which two different controlled-breathing protocols were employed: one to examine the effect of about 16 different RF at fixed TV, and the other to assess the effect of six levels of TV, at constant RF. Their results demonstrated that RSA amplitude presents an inverse relation with RF and a positive linear relation with TV, the latter being a necessary condition for normalizing RSA by TV. The findings of that study on the separated effects of each respiratory parameter on RSA have been confirmed repeatedly [3], more often for RF than for TV. However, there are no reports available documenting the effects of the simultaneous variation of the two respiratory variables on RSA amplitude. Therefore, our aim was to assess the interactive effects of the joint variation of RF and TV on the high-frequency power of RR intervals (HF_{RR}).

2. Methods

2.1. Subjects

Twenty five healthy and sedentary subjects, 13 men and 12 women, participated. Mean age, height and weight were 23.5±1.5 years, 168±7 cm and 65.4±8.0 kg respectively. Their written informed consent was requested to participate.

2.2. Protocol

In a first visit to the laboratory health status of the subjects was assessed and they were trained to execute breathing maneuvers correctly. In a second visit, subjects performed three 30-s breathing maneuvers in random order, with 5-min resting periods in between. They were: linearly increasing RF (RF_{LI}) from 0.15 to 0.5 Hz at a constant TV of 1L; linearly increasing TV (TV_{LI}) from 1 to 2.5L followed by linearly decreasing TV (TV_{LD}) from 2.5 to 1L at a fixed RF of 0.2Hz, and the simultaneous performance of RF_{LI} and TV_{LI}-TV_{LD}. Maneuver execution was visually guided by displaying on a screen the target respiratory pattern and the TV of the subject.

2.3. Recorded variables and signal acquisition

ECG was detected at the thoracic bipolar derivation CM5 with a bioelectric amplifier (Biopac Systems). TV was computed by a set of pneumotachometer (Hans Rudolph), pressure transducer (Validyne), carrier demodulator (Validyne) and integrator (Validyne). CO_2 concentration was measured with an infrared analyzer (Biopac Systems). Signals were digitized at 500 Hz via an acquisition and display system (Biopac Systems).

2.4. Data processing

R-wave peaks were detected to form RR interval series (RRi), which, together with the TV series, were cubic-spline interpolated, resampled at 8 Hz and detrended. RRi and TV time-frequency spectra were estimated via the smoothed pseudo-Wigner-Ville distribution to compute HF_{RR} power and instantaneous RF in the 0.15-0.5 Hz frequency band. From maximum values of CO_2 recordings end-tidal CO_2 levels were computed. For visualization purposes the individual continuous dynamics and relationships were ensemble-averaged.

2.5. Statistical analysis

For classification and comparison purposes, the relations of HF_{RR} with TV were divided into the increasing and decreasing parts. After natural logarithmic transformation, linear regressions and correlation coefficients were computed for the individual RF_{LI}-$lnHF_{RR}$, TV_{LI}-$lnHF_{RR}$ and TV_{LD}-$lnHF_{RR}$ relationships, in both separated and combined conditions. Student's paired *t*-test was employed to compare the slopes and intercepts. Statistical significance was accepted at $p < 0.05$.

3. Results

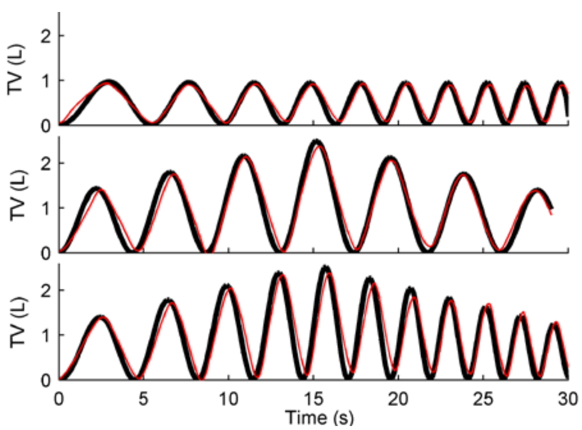

Figure 1. Time course of the ensemble averages of the TV (thin line) during the three breathing protocols in relation to their respective target respiratory patterns (thick line): (A) RF_{LI} at fixed TV, (B) TV_{LI}-TV_{LD} at fixed RF and (C) RF_{LI} and TV_{LI}-TV_{LD} combined.

Figure 1 depicts the ensemble averages of the TV of the subjects, superimposed to the breathing patterns they followed during RF_{LI} alone, TV_{LI}-TV_{LD} alone and the combined maneuver. The differences between the target pattern and the TV traces produced by the subjects are noticeably small.

The time-frequency distributions of the RRi series obtained during the three controlled breathing protocols showed distinctive effects on the HF_{RR} component: progressive decrease during RF_{LI} (Fig. 2A), progressive increase during TV_{LI} followed by progressive decrease during TV_{LD} (Fig. 2B) and greater decrease during the combined protocol (Fig. 2C).

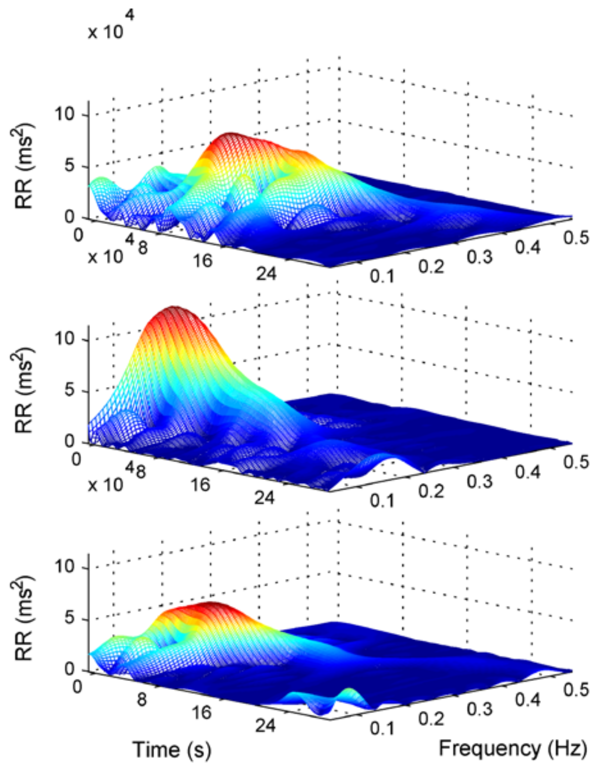

Figure 2. Representative time-frequency distributions of RRi series during the three protocols: (A) RF_{LI} at fixed TV, (B) TV_{LI}-TV_{LD} at fixed RF and (C) RF_{LI} and TV_{LI}-TV_{LD} combined.

RF_{LI}-$lnHF_{RR}$, TV_{LI}-$lnHF_{RR}$ and TV_{LD}-$lnHF_{RR}$ relations showed strong correlations in both the independent and combined protocols (Table 1), which were greater for the latter ($p<0.001$). The effect of RF_{LI} on $lnHF_{RR}$ was a systematic linear decrease in both the independent and combined protocols, with greater slope ($p<0.001$) in the latter (Table 1, Fig. 3 A).

The effect of TV_{LI}-TV_{LD} on $lnHF_{RR}$ was complex, especially during the TV_{LI} part of the independent protocol, which produced three types of responses: in 34% of the recordings $lnHF_{RR}$ presented a progressive increase (Fig. 3B), in 24% $lnHF_{RR}$ power did not change (Fig. 3C) and in 42% a linear decrease was observed (Fig.

3D). These diverse effects contrast with the systematic linear decrease of $lnHF_{RR}$ during the TV_{LD} part.

Table 1. Mean ± SD of correlations, slopes and intercepts of the HF_{RR} -respiratory variables relations during the independent (I) and combined (C) protocols. N=25.

Relation	Protocol	Correlation	Slope	Intercept
RF_{LI}-$lnHF_{RR}$	I	-0.8±0.2	-6.0±3.2	9.1±0.9
	C	-0.9±0.1*	-12.5±4.5*	10.7±1.4
TV_{LI}-$lnHF_{RR}$	I 1st	-0.8±0.2	-0.9±0.7	9.0±1.6
	2nd	-0.0±0.1		
	3rd	0.7±0.2	0.6±0.4	7.4±1.0
	C	-0.9±0.1*	-1.9±1.2*	10.5±1.9*
TV_{LD}-$lnHF_{RR}$	I	0.7±0.2	0.9±0.5	6.3±1.4
	C	0.8±0.1*	1.8±1.0*	3.0±2.3*

*p<0.001 between I and C protocols

The simultaneous variation of RF and TV provoked a complex response on $lnHF_{RR}$ power, particularly because of the much greater hysteresis it produced, reflected by the intercept differences (Table 1, Fig. 3).

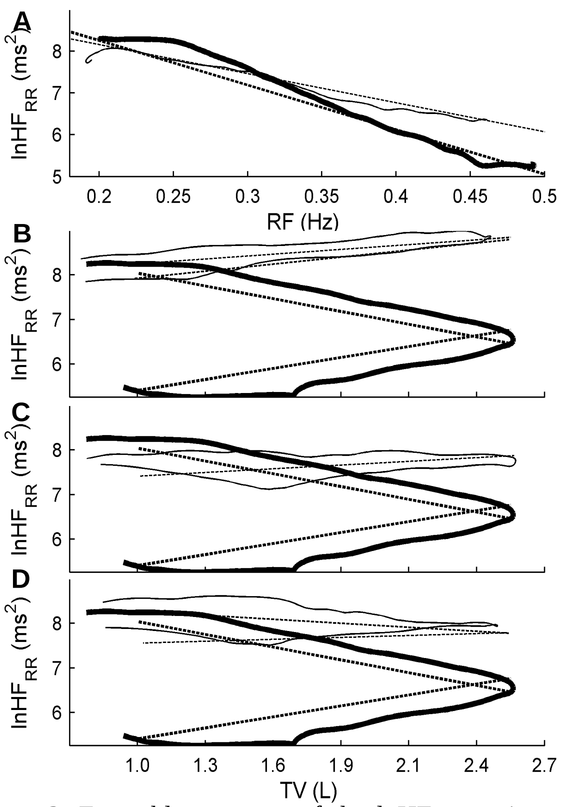

Figure 3. Ensemble averages of the $lnHF_{RR}$-respiratory variables relations in the independent (thin solid lines) and combined (thick solid lines) protocols with their respective regressions (dotted lines). (A) Effects of RF_{LI}. The three effects of TV_{LI} alone (upper traces) on $lnHF_{RR}$: (B) linear increase, (C) no change and (D) linear decrease, each compared to the combined protocol response.

The linear regression of $lnHF_{RR}$ in the TV_{LI} part of the combined protocol presented a negative slope, while the slope of the regression during the TV_{LD} section was positive (Table 1, Fig. 3B,C,D). The combined protocol induced a steeper slope (p<0.001) on the RF_{LI}-$lnHF_{RR}$ regression than the independent ones (Table 1, Fig. 3A). The combined maneuver produced a systematically negative slope on the TV_{LI}-$lnHF_{RR}$ regression, steeper (p<0.001) than any of the slopes corresponding to the diverse cases of the independent protocol (Table 1). The TV_{LD}-$lnHF_{RR}$ slope of the combined protocol was also greater (p<0.001) than the independent one (Table 1).

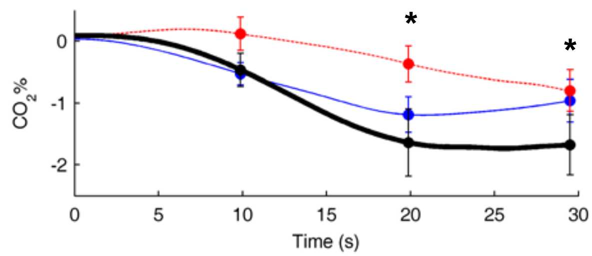

Figure 4. Ensemble averages and mean±SD values every 10 s of the end-tidal CO_2 in RF_{LI} (dotted line), TV_{LI}-TV_{LD} (thin line) and RF_{LI}-TV_{LI}-TV_{LD} (thick line) protocols. *p<0.001 between protocols.

Statistical comparison of the end-tidal CO_2 levels at 10-second intervals showed differences (p<0.001) among protocols. The greatest hypocapnia corresponded to the combined protocol (Fig. 4).

4. Discussion and conclusions

The main findings of the present study are: 1) The continuous linear and inverse RF_{LI}-$lnHF_{RR}$ relationship presents a steeper slope in the combined breathing protocol than in the independent one. 2) The effect of TV_{LI}-TV_{LD} independent protocol on the $lnHF_{RR}$ power shows a complex relationship with hysteresis. While the TV_{LI}-$lnHF_{RR}$ relationship presents three different cases, the effect of TV_{LD} is a systematic positive linear relationship. 3) The effects of the simultaneous variation of RF and TV on $lnHF_{RR}$ are systematic, presenting a pattern that consists on a linearly decreasing section corresponding to TV_{LI} followed by a positive linear part associated to TV_{LD}. The hysteresis is much greater than that of the independent effect, indicating a much greater attenuation of the $lnHF_{RR}$ power during the simultaneous variation of TV_{LD} with RF_{LI}.

The independent effects of RF on RSA have been studied with protocols that change RF within a range in two modalities: pseudo-random fluctuations [4] and stepwise increments [5]. In the first type of protocol, which is difficult to perform, TV is not controlled. The second protocol is very fatiguing, since up to 13 discontinuous RF are maintained for several minutes [6]. In contrast, the RF_{LI} protocol used in the present study is easy to perform and includes a wide range of continuous- and linearly varying RF in a short time, thus minimizing the hyperventilation and fatigue.

The studies aimed at establishing the effect of TV on RSA have used similar protocols, which consist in at least six maneuvers with increasing TVs at fixed RF, each maintained for several minutes [1,7] In contrast, in our fixed RF protocol, TV is linearly increased until a maximum, and then linearly decreased, in a breath-by-breath manner. Given its short duration it is non-fatiguing and relatively easy to perform. Even more, by increasing then decreasing TV, this maneuver is capable to establish the hysteresis of the response of the system.

All the breathing protocols we used are associated to slight but significant hypocapnia, greatest for the combined protocol. Although it is unlikely that such levels of CO_2 could have affected the autonomic function [8], we cannot discard its effect.

The inversely proportional relationship between HF_{RR} and RF, referred to as the low-pass filter effect of the autonomic-sinus node system, is well documented [3,4]. The continuous relationship found with our RF_{LI} protocol is similar to the reported ones. Therefore, the attenuation of RSA amplitude caused by increasing RF is a markedly consistent effect.

It is commonly accepted that RSA increases in proportion to TV increment. The linearity of this relationship is the supporting premise of the normalization of RSA amplitude with TV, which is performed using various techniques [3,7]. With our TV_{LI}-TV_{LD} at fixed RF protocol we did not find a systematic behavior for the TV_{LI}-$lnHF_{RR}$ relation. The participants of this study responded to the independent TV_{LI} either with linear increase, no change or linear decrease on $lnHF_{RR}$ power. This inconsistent response contrasts with the systematic linear decrease of RSA obtained with TV_{LD}. Additionally, in all subjects we observed that, for a given TV, the $lnHF_{RR}$ level corresponding to the increasing path was greater than the decreasing one, that is, these relations present hysteresis. The strikingly ambiguous effect of the independent TV_{LI}-TV_{LD} protocol on RSA we found has the following implications: 1) it questions the usually accepted linear effect of TV on RSA, therefore 2) it questions the normalization of RSA amplitude by TV and 3) it encourages to control both TV and RF in studies that employ controlled breathing, which usually control RF [8] but not TV.

To our knowledge this is the first study to explore, under controlled conditions, the effects of linearly varying RF and TV both independently and simultaneously on RSA magnitude. The interactive effect documented by the present study is greater attenuation of $lnHF_{RR}$ power in relation to the independent effect of each variable. Furthermore, the simultaneous variation of both respiratory variables transforms their effect on $lnHF_{RR}$ into a response pattern: a linear attenuation of RSA with TV_{LI} (negative slope) and a linear decrease with TV_{LD} (positive slope), which presents much greater hysteresis. These may reflect that the inhibitory effect of RF_{LI} on $lnHF_{RR}$ first predominates over the effects of TV_{LI} and after is added to the inhibitory effect of TV_{LD}.

In conclusion our fast, non-fatiguing and linearly varying controlled breathing protocols allowed us to document that: 1) RF_{LI} consistently attenuates RSA, whether applied alone or in simultaneous variation with TV; 2) the independent effects of TV_{LI}-TV_{LD} on RSA are ambiguous, especially for TV_{LI}, and present hysteresis, and 3) RF_{LI} and TV_{LI}-TV_{LD} combined induce greater attenuating effects on RSA than separately. The non linear effect of TV upon RSA we found questions the usual practice of normalizing RSA amplitude with TV.

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