Causal Analysis Is Needed to Evaluate Cardiorespiratory Interaction Alterations in Postural Orthostatic Tachycardia Syndrome Patients

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Abstract

Respiratory and cardiac activities are known to be linked by several mechanisms, resulting in a variety of patterns of heart rate variability. Cardiorespiratory interactions can be evaluated from spontaneous variability of heart period (HP) and respiration (R) through noncausal and causal approaches. The aim of this study is to describe cardiorespiratory interactions in a population known to feature an exaggerated sympathetic response to orthostatic stressors, such as patients affected by postural orthostatic tachycardia syndrome (POTS). Twelve female POTS patients (age: 36±10 yrs) and 14 female healthy controls (age: 37±8 yrs) underwent electrocardiogram and respiratory movement recordings while supine and during head-up tilt. Cardiorespiratory interactions were assessed via a model-based noncausal approach, squared coherence (K^2), and a model-based causal method, transfer entropy (TE). TE was found to be significantly decreased in POTS patients compared to healthy controls during head-up tilt, while K^2 was similar. We conclude that causal approaches are better suited than noncausal methods to evaluate modifications in the magnitude of HP-R variability interactions in POTS patients during orthostatic challenge, with possible future applications in post-acute COVID-19 patients exhibiting symptoms of dysautonomia.

1. Introduction

Signal processing analysis tools applied to spontaneous variability of heart period (HP) and respiration (R) allow the characterization of cardiorespiratory interactions [1]. Among these tools the class of noncausal approaches, such as squared coherence (K^2), are found to be useful to describe the degree of association between HP and R regardless of the temporal direction of interactions, while causal approaches, such as transfer entropy (TE), are superior when the strength of the HP-R coupling is needed to be estimated in a specific time direction [2].

Previous studies have demonstrated that cardiorespiratory interactions are under autonomic nervous system control [3,4]. While an augmented vagal control is responsible for an increased effect of respiration on HP variability, usually referred to as respiratory sinus arrhythmia [5], a sympathetic activation causes a decrease of the coupling between HP and R. Pathological situations that alter autonomic function might have a negative impact on cardiorespiratory interactions [1]. In particular, we hypothesize that patients who exhibit an exaggerated sympathetic response to orthostatic stressors [6,7], such as postural orthostatic tachycardia syndrome (POTS), might present alterations in the strength of cardiorespiratory interactions, especially during postural challenge.

The aim of the study is to estimate cardiorespiratory interactions between HP variability and R in dysautonomic patients compared to healthy (H) subject, at supine resting (REST) and during head-up tilt (TILT).

2. Methods

2.1. Squared Coherence

The degree of linear coupling between HP and R series can be computed as a function of the frequency f via K^2 as

$$K^2_{HP,R}(f)=\frac{|C_{HP-R}(f)|^2}{S_{HP}(f)\cdot S_R(f)}, \quad (1)$$

where $|C_{HP-R}(f)|$ represents the modulus of the cross-

Table 1. Time domain HP variability indexes in H subjects and POTS patients

Index	H		POTS	
	REST	TILT	REST	TILT
μ_{HP} [ms]	909±132	797±128*	828±168	646±65*
σ^2_{HP} [ms^2]	2211±1120	2079±1103	1859±1321	1421±881

H: healthy controls; POTS: postural orthostatic tachycardia syndrome patients; REST: at rest in supine position; TILT: head-up tilt; HP: heart period; μ_{HP}: HP mean; σ^2_{HP}: HP variance. Results are presented as mean±standard deviation. The symbol * indicates $p<0.05$ versus REST.

spectrum from R to HP, $S_{HP}(f)$ is the power spectrum of HP, and $S_R(f)$ is the power spectrum of R [8]. The cross-spectrum and power spectra were estimated according to a parametric approach based on a bivariate autoregressive (AR) model. The coefficients of the model were identified via a traditional least squares method and the model order was fixed at 10 [9]. $K^2_{HP,R}(f)$ is a symmetric function, i.e., $K^2_{HP,R}(f)=K^2_{R,HP}(f)$. Therefore, $K^2_{HP,R}$ can be high due to mechanisms that operate along either or both directions of HP-R interaction. The function $K^2_{HP,R}(f)$ was sampled in correspondence to the respiratory frequency f_R, estimated as the weighted average of the central frequency of the R spectral components in the high frequency band, namely 0.15-0.5 Hz [10].

2.2. Transfer Entropy

TE assesses the degree of linear association from a signal, taken as the cause, to another signal, designed as the effect, i.e., respectively R and HP in the present study. TE is defined as the amount of information carried by the effect that can be derived from the cause, above and beyond the amount of information carried by the effect that can derived exclusively from the past of the effect [11]. The information transferred from R to HP was estimated via a model-based approach, grounded on the separate identification of an AR model over HP with R taken as an exogenous (X) input, when both the HP and R series were considered, and on the identification of an AR model over HP when only HP was considered. The coefficients of the ARX and AR models were identified via traditional least squares approach and Cholesky decomposition method [12] and the ARX model order was optimized according to the Akaike's figure of merit [13]. The TE from R to HP, namely $TE_{R\rightarrow HP}$, is computed as

$$TE_{R\rightarrow HP}=\frac{1}{2}\log\left(\frac{\sigma^2_{AR}}{\sigma^2_{ARX}}\right), \qquad (2)$$

where the natural logarithm log was applied to the ratio between the prediction error variance of the AR model, i.e., σ^2_{AR}, to that of the ARX model, i.e., σ^2_{ARX} [2,14]. The prediction error is defined as the difference between the current value of the HP series and the prediction provided by the model, i.e., the portion of the variance of the HP dynamics that cannot be explained by the AR and ARX models respectively. $TE_{R\rightarrow HP}$ represents the predictability improvement observed when the restricted universe of knowledge formed solely by HP was completed with R.

3. Protocol and pre-processing

3.1. Experimental protocol

Twelve female POTS patients (age: 36±10 years) and 14 female H controls (age: 37±8 years) underwent electrocardiogram (lead II) and R recordings at REST and during TILT. R was monitored via a piezoresistive strain gauge belt (Marazza, Monza, Italy) recording thoracic movements. Recording sessions on the POTS group were carried out at the Syncope Unit of IRCCS Humanitas Research Hospital, Rozzano, Italy, while those on H subjects at IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy. Inclination of the TILT table was 75° for the POTS group and 70° for the H subjects. Both protocols adhered to the principles of the Declaration of Helsinki for medical research involving human subjects and were approved by the ethical review boards of the relevant institutions. Written informed consent was obtained from all subjects before taking part in the study.

3.2. Beat-to-beat series extraction

R-wave peaks were located according to a threshold-based algorithm working on the first derivative of the electrocardiogram. The time distance between two consecutive R-wave peaks was taken as HP. The identified R-wave peaks were then visually checked and manually corrected, if necessary. If isolated ectopic beats were detected, the abnormal values were substituted with their linear interpolation using the closest values unaffected by ectopic beats. R signal was sampled in correspondence to the first R-wave peak relevant to the current HP in order to obtain a R series synchronous with the HP series. Sequences of 256 consecutive values that satisfied the criteria of stationarity were selected in a random position within each experimental session. Selections avoided the transient period observed just after the onset of TILT.

3.3. Statistical analysis

Table 2. HP-R cardiorespiratory interaction markers in H subjects and POTS patients

Index	H		POTS	
	REST	TILT	REST	TILT
$K^2_{HP,R}(f_R)$	0.57±0.29	0.61±0.27	0.55±0.31	0.45±0.27
$TE_{R\rightarrow HP}$	0.16±0.11	0.18±0.12	0.11±0.07	0.08±0.04#

H: healthy controls; POTS: postural orthostatic tachycardia syndrome patients; REST: at rest in supine position; TILT: head-up tilt; HP: heart period; R: respiration; $K^2_{HP,R}$: squared coherence function; f_R: breathing rate; $K^2_{HP,R}(f_R)$: $K^2_{HP,R}$ at f_R; $TE_{R\rightarrow HP}$: transfer entropy from R to HP interval. Results are presented as mean±standard deviation. The symbol # indicates $p<0.05$ versus H subjects.

Data normality was tested with the Shapiro-Wilk test. Two-way repeated measures analysis of variance (one factor repetition, Holm-Sidak test for multiple comparisons) was performed to evaluate between-group differences in the same experimental condition (REST or TILT) and effects of the postural challenge in the same experimental group (H or POTS). Statistical analysis was carried out using a commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ was always considered as significant.

4. Results

Table 1 presents the results of time domain analysis of the HP variability series, namely HP mean (μ_{HP}) and HP variance (σ^2_{HP}), in H controls and POTS patients, both at REST and during TILT. μ_{HP} decreased during TILT in both populations, while σ^2_{HP} remained unchanged. Regardless of experimental condition, no significant difference was observed between groups within the same experimental session.

Table 2 shows the indexes of cardiorespiratory interactions, namely $TE_{R\rightarrow HP}$ and $K^2_{HP,R}(f_R)$, in H controls and POTS patients, both at REST and during TILT. Neither $TE_{R\rightarrow HP}$ nor $K^2_{HP,R}(f_R)$ were significantly affected by the orthostatic stimulus in either cohort. However, while the $K^2_{HP,R}(f_R)$ did not present any relevant difference between the two groups either at REST or during TILT, $TE_{R\rightarrow HP}$ decreased significantly in POTS patients compared to H subjects solely during TILT.

5. Discussion

The main findings of this study can be summarized as follows: i) the orthostatic stimulus did not affect cardiorespiratory interaction strength between HP variability and R in H subjects; ii) the decrease of HP-R cardiorespiratory interaction during TILT was more evident in the POTS population; iii) this decrease was only significant when assessed via a causal approach accounting for interactions directed from R to HP.

Our study suggests that HP-R cardiorespiratory interactions were not significantly affected by gravitational stimulus in H subjects. This result was unexpected, as it is well-known that cardiorespiratory coupling strength is significantly attenuated during a postural challenge [4]. A potential explanation for this observation might be the limited experimental protocol, which solely monitored ECG and R signal over time. Indeed, when only HP variability and R were studied in amateur athletes, no significant effect of standing was observed [15]. The effect of standing on cardiorespiratory interactions was visible only when the confounding factor of baroreflex mediation on the R to HP pathway was accounted for by explicit inclusion of systolic arterial pressure variability in the TE approach [15].

During TILT, the $TE_{R\rightarrow HP}$ was significantly smaller in POTS patients than in H subjects, thus indicating a lack of association from R to HP in the POTS group. A trend toward uncoupling between HP variability and R was observed in association with a graded postural challenge [4], during rapid eye movement sleep [16] and during sleep disordered breathing [17]. Since all these situations are accompanied by an increased sympathetic tone, our data support the clinical hypothesis that POTS patients feature a disproportionate cardiac sympathetic response to TILT compared to H individuals [6,7]. We propose the use of $TE_{R\rightarrow HP}$ as a noninvasive marker to quantify the adrenergic response of POTS patients to TILT.

The effect of TILT on cardiorespiratory interaction strength was visible exclusively when a causal approach, investigating the pathway from respiratory system to the heart, was applied. This finding suggests that causal tools are needed for a more appropriate assessment of the strength of HP-R cardiorespiratory interactions. It seems that the relation from HP to R along the reverse causal direction compared to that from R to HP could be a confounding factor for more traditional tools such as $K^2_{HP,R}$. Indeed, since $K^2_{HP,R}$ assesses the degree of linear association between HP variability and R regardless of the temporal direction of the interactions, $K^2_{HP,R}$ might remain high if the degree of R dependence on HP did not decrease during TILT. This situation was in fact observed in previous studies leading to the rejection of the hypothesis of an open loop relationship from R to HP [18]. Nonlinear tools for cardiorespiratory interactions assessment need to be applied to verify the relevance of nonlinear dynamics [19,20]. Multivariate approaches accounting for the effects of confounding factors such as baroreflex control might

add additional insight and provide new stratification possibilities [15,21].

6. Conclusions

In this study we evaluated cardiorespiratory interaction strength in patients characterized by an abnormal sympathetic response to an orthostatic stimulus (i.e., POTS group), via noncausal and causal approaches applied to HP variability and R series. Results showed a significant decrease of cardiorespiratory interactions along the pathway from the respiratory system to the heart in the POTS cohort during postural challenge. We conclude that the disproportionate sympathetic response to TILT of POTS patients influences HP-R dynamical interactions. In the future, electrocardiogram and respiratory activity recordings will be accompanied by simultaneous direct recordings of sympathetic activity (e.g., muscle sympathetic nerve activity via microneurography) for further confirmation of this hypothesis. Future studies should also test whether our findings could be simply the consequence of a hyperadrenergic response to TILT or could primarily contribute to their inability to cope with orthostatic stressors. The method proposed in this study will be applied to study the dysautonomia observed in a portion of patients recovering from COVID-19 syndrome.

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References

[1] M. Elstad et al., "Cardiorespiratory interactions in humans and animals: rhythms for life," *Am. J. Physiol.*, vol. 315, pp. H6–H17, 2018.

[2] A. Porta et al., "Paced breathing increases the redundancy of cardiorespiratory control in healthy individuals and chronic heart failure patients," *Entropy*, vol. 20, art. no. 949, 2018.

[3] C. Cogliati et al., "Acute β-blockade increases muscle sympathetic activity and modifies its frequency distribution," *Circulation*, vol. 110, pp. 2786–2791, 2004.

[4] A. Porta et al., "Model-based assessment of baroreflex and cardiopulmonary couplings during graded head-up tilt," *Comput. Biol. Med.*, vol. 42, pp. 298–305, 2012.

[5] J. A. Hirsch and B. Bishop, "Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate," *Am. J. Physiol.*, vol. 241, pp. H620–H629, 1981.

[6] R. Furlan et al., "Chronic orthostatic intolerance: a disorder with discordant cardiac and vascular sympathetic control," *Circulation*, vol. 98, pp. 2154–2159, 1998.

[7] F. Barbic et al., "Work ability assessment and its relationship with cardiovascular autonomic posture in postural orthostatic tachycardia syndrome," *Int. J. Environ. Res. Public Health*, vol. 17, art. no. 7836, 2020.

[8] J. P. Saul et al., "Transfer function analysis of the circulation: unique insights into cardiovascular regulation," *Am. J. Physiol.*, vol. 261, pp. H1231–H1245, 1991.

[9] A. Porta et al., "Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt," *J. Electrocardiol.*, vol. 44, pp. 662–668, 2011.

[10] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability - Standards of measurement, physiological interpretation and clinical use," *Circulation*, vol. 93, pp. 1043–1065, 1996.

[11] T. Schreiber, "Measuring information transfer," *Phys. Rev. Lett.*, vol. 85, pp. 461–464, 2000.

[12] G. Baselli et al., "Spectral decomposition in multichannel recordings based on multivariate parametric identification," *IEEE Trans. Biomed. Eng.*, vol. 44, 1092–1101, 1997.

[13] H. Akaike, "A new look at the statistical novel identification," *IEEE Trans. Autom. Control*, vol. 19, pp. 716–723, 1974.

[14] L. Barnett et al., "Granger causality and transfer entropy Are equivalent for gaussian variables," *Phys. Rev. Lett.*, vol. 103, art. no. 238701, 2009.

[15] R. M. de Abreu et al., "A transfer entropy approach for the assessment of the impact of inspiratory muscle training on the cardiorespiratory coupling of amateur cyclists," *Front. Physiol.*, vol. 11, art. no. 134, 2020.

[16] R. P. Bartsch, et al., "Phase transitions in physiologic coupling," *Proc. Natl. Acad. Sci. USA*, vol. 109, pp. 10181–10186, 2012.

[17] T. Penzel et al., "Modulations of heart rate, ECG, and cardio-respiratory coupling observed in polysomnography," *Front. Physiol.*, vol. 7, art. no. 460, 2016.

[18] A. Porta et al., "Cardiovascular control and time domain Granger causality: insights from selective autonomic blockade," *Phil. Trans. R. Soc. A*, vol. 371, art. no. 20120161, 2013.

[19] G. Nollo et al., "Evidence of unbalanced regulatory mechanism of heart rate and systolic pressure after acute myocardial infarction," *Am. J. Physiol.*, vol. 283, pp. H1200–H1207, 2002.

[20] B. Cairo et al., "Optimizing phase variability threshold for automated synchrogram analysis of cardiorespiratory interactions in amateur cyclists," *Phil. Trans. R. Soc. A*, 2021 (in press).

[21] A. Porta et al., "Effect of age on complexity and causality of the cardiovascular control: comparison between model-based and model-free approaches," *PLoS ONE*, vol. 9, art. no. e89463, 2014.

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