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ORIGINAL ARTICLE

Cardiovascular and cardiorespiratory phase synchronization in normovolemic and hypovolemic humans

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Abstract We investigated whether and how cardiovascular and cardiorespiratory phase synchronization would respond to changes in hydration status and orthostatic stress. Four men and six women were tested during graded head-up tilt (HUT) in both euhydration and dehydration (DEH) conditions. Continuous R–R intervals (RRI), systolic blood pressure (SBP) and respiration were investigated in low (LF 0.04–0.15 Hz) and high (HF 0.15–0.4 Hz) frequency ranges using a phase synchronization index (λ) ranging from 0 (complete lack of interaction) to 1 (perfect interaction) and a directionality index (*d*), where a positive value of *d* reflects oscillator 1 driving oscillator 2, and a negative value reflects the opposite driving direction. Surrogate data analysis was used to exclude relationships that occurred by chance. In the LF range, respiration was not synchronized with RRI or SBP, whereas RRI and SBP were phase synchronized. In the HF range, phases among all variables were synchronized. DEH reduced λ among all variables in the HF and did not affect λ between RRI and SBP in the LF region. DEH reduced *d* between RRI and SBP in the LF and did not affect *d* among all variables in the HF region. Increasing λ and decreasing *d* between SBP and RRI were observed in the LF range during HUT. Decreasing λ between SBP and RRI, respiration and RRI, and decreasing *d* between respiration and SBP were observed in the HF range during HUT. These results show that orthostatic stress disassociated interactions among RRI, SBP and respiration, and that DEH exacerbated the disconnection.

Keywords Cardiovascular coupling · Cardiorespiratory coupling · Phase synchronization · Orthostatic stress · Hypovolemia

Introduction

The cardiovascular system is influenced by several feedback and feed-forward mechanisms regulating cardiovascular homeostasis (Malpas 2002). It is well known that heart rate (HR) and systolic blood pressure (SBP) interact with each other in a closed loop via the baroreflex feedback and the mechanical feed-forward mechanisms (Faes et al. 2011, 2013a; Porta et al. 2011; Nollo et al. 2005). Cardiovascular interaction is also perturbed by respiration (RESP) via mechanical effects on intrathoracic pressure and stroke volume (Toska and Eriksen 1993), and effects on cardiac vagal motoneurons (Gilbey et al. 1984). Different physiological (Faes et al. 2011; Nollo et al. 2005; Pereda et al. 2005; Porta et al. 2012; Bartsch et al. 2012; Cysarz et al. 2004; Lackner et al. 2011; Moertl et al. 2013; Mrowka et al. 2003; Niizeki and Saitoh 2012) and pathological (Porta et al. 2011; Wang et al. 2006; Ocon et al. 2011; Riedl et al. 2010; Nollo et al. 2009; Faes et al. 2013a, b; Lipsitz et al. 1998; Krishnamurthy et al. 2004) states have been shown to alter cardiovascular coupling and/or cardiorespiratory coupling. Therefore, it is essential to assess cardiovascular and cardiorespiratory interactions using these output signals (e.g., HR, SBP and RESP) to provide important information concerning physiological mechanisms involved in regulation of cardiovascular and respiratory systems.

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For a more detailed understanding of regulation of cardiovascular and respiratory systems, it is essential not only to detect interactions but also to identify causal relationships (Nollo et al. 2009; Rosenblum et al. 2006). Since cardiovascular and respiratory systems very likely interact with each other in a non-linear way, it is more appropriate to analyze the interactions using non-linear approaches (Schulz et al. 2013) in addition to conventional linear methods (Badra et al. 2001; Krishnamurthy et al. 2004). Several non-linear methods (Schulz et al. 2013), such as higher-order statistics (Wang et al. 2006), non-linear Granger causality (Riedl et al. 2010), non-linear prediction (Nollo et al. 2009), entropy (Faes et al. 2013a; Porta et al. 2011), and phase synchronization approach (Bartsch et al. 2012; Mrowka et al. 2003; Rosenblum et al. 2002; Lackner et al. 2011; Moertl et al. 2013; Schafer et al. 1998; Ocon et al. 2011; Cysarz et al. 2004; Niizeki and Saitoh 2012; Karavaev et al. 2009), have been applied to analyze cardiovascular and cardiorespiratory couplings in health and disease conditions.

Orthostatic stress is known to increase the pooling of blood in the lower body, resulting in reduction in venous return and central blood volume. Consequently, baroreflex-mediated increase in HR and vasoconstriction are evoked to compensate the reduction in central blood volume and to maintain blood pressure (Rowell 1993). Ineffective reflex mechanisms may induce bradycardia and vasodilation, and result in orthostatic intolerance, i.e., the inability to maintain blood pressure with the eventual loss of consciousness upon upright posture. Cardiovascular and cardiorespiratory coupling have been explored during orthostatic stress (Faes et al. 2011; Nollo et al. 2005; Porta et al. 2011, 2012) and preceding syncope (Wang et al. 2006; Ocon et al. 2011; Nollo et al. 2009; Faes et al. 2013a, b) using different non-linear methods, with an aim of understanding and preventing orthostatic intolerance. However, there are limitations in those studies, such as lack of respiratory variability information (Nollo et al. 2005, 2009; Porta et al. 2011; Faes et al. 2013a, b), lack of coupling direction (Wang et al. 2006), and that require prior assumptions of the cardiovascular system (Porta et al. 2012). In addition, reduction in blood volume has been considered contributing to the occurrence of orthostatic intolerance (Fu et al. 2005; Zhang et al. 2014), particularly in astronauts following long-term spaceflight; however, studies concerning the effects of combining orthostatic stress and DEH on cardiovascular and cardiorespiratory interactions are rare. Furthermore, none of the previous studies investigating causal relationship among cardiovascular and respiratory oscillations (Faes et al. 2011; Ocon et al. 2011) have addressed the effects of DEH.

In this study, we applied the phase synchronization approach to investigate effects of different gravitational environments and reduced blood volume on cardiovascular and cardiorespiratory couplings in a ground-based simulation of space exploration to obtain more information concerning spaceflight-induced orthostatic intolerance. Changes in phase relationships among SBP, R–R intervals (RRI) and RESP were tested during graded head-up tilt (HUT) with normal [euhydration (EUH)] and reduced [dehydration (DEH)] blood volume using the phase synchronization approach. We hypothesized that both DEH and orthostatic stress, as physiological stressors, would reduce cardiovascular and cardiorespiratory couplings.

Methods

Subjects

Six men (24.2 ± 0.5 years in age, 171.8 ± 3.1 cm in height, and 74.2 ± 8.9 kg in weight) and six women (24.7 ± 0.5 years in age, 159.1 ± 1.5 cm in height, and 59.3 ± 2.1 kg in weight), who were non-smokers and normotensive, were recruited. None was a trained athlete. Each subject gave informed written consent to the experimental protocol, approved by the University of Kentucky Institutional Review Board and the NASA Johnson Space Center Committee for Protection of Human Subjects. Selection of subjects was based on a screening evaluation that consisted of a medical history questionnaire, a 12-lead electrocardiogram, and blood pressure (BP) measurement.

Experimental protocol

This study was part of a broader experimental design testing whether upright lower body positive pressure would be comparable to HUT in modeling physiological responses to partial gravities during both EUH and DEH. Details of experimental protocols and results concerning cardiovascular responses to HUT and upright lower body positive pressure were reported elsewhere (Zhang et al. 2014). For the present study, only HUT data were used. Briefly, the experimental protocol was as follows. Subjects participated in two experimental sessions separated by 7 days. Subjects were euhydrated during one session and dehydrated during the other. Acute DEH was induced by intravenous furosemide administration (0.5 mg furosemide per kg body weight). The order of EUH and DEH sessions was counterbalanced. During each session, subjects were tilted from supine (T0) to 10° (T10), 20° (T20) and 80° (T80) to simulate standing in the gravitational environments of 0 g (spaceflight), 1/6 g (Moon), 3/8 g (Mars) and 1 g (Earth), respectively. Tests were terminated when experimental protocols were completed or subjects developed presyncopal symptoms (SBP <70 mmHg, HR drop >20 beats per minute, lightheadedness, dizziness or nausea).

Instrumentation and data acquisition

Standard lead II electrocardiogram (Model 90623A, SpaceLabs Inc., Redmond, WA) was continuously monitored and recorded. Continuous BP was obtained at the middle finger using photoplethysmography (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands) with the hand positioned at heart level. In addition, brachial artery BP was measured periodically using a manometer (UA-767, A&D Medical, San Jose, CA) placed around the upper arm for the calibration of continuous BP. Respiration was derived from thoracic impedance (UFI Model 2994D, Morro Bay, CA). The angle of the tilt table was recorded by an accelerometer (Crossbow, Jameco, CA). All data were collected by computer acquisition software (WinDAQ, DATAQ Instruments, Akron, OH) at 1,000 Hz with subsequent analysis using MATLAB (R2012b, Mathworks, Natick, MA).

Data analysis

In contrast to approaches investigating signal amplitudes, the phase synchronization approach investigates phases of oscillations directly (Schulz et al. 2013). The concept of phase synchronization is taken from the studies of two weakly interacting oscillators (Rosenblum et al. 2006; Rosenblum and Pikovsky 2001; Pikovsky et al. 2001). Generally, weak or moderate interaction only affects phases of oscillators but not their amplitudes, and as the interaction strength increases, phases of oscillators are affected first, followed by correlation between amplitudes (Rosenblum et al. 2006; Pikovsky et al. 2001; Rosenblum and Pikovsky 2001). Therefore, the phase synchronization approach is appropriate to study coupling between cardiovascular and respiratory systems, in which case, coupling is usually weak or moderate (Schafer et al. 1998; Prokhorov et al. 2003), in terms of both strength (Rosenblum et al. 2006) and direction (Rosenblum and Pikovsky 2001) of the interactions. In addition, since parameters of the physiological system cannot be assessed and only measurements under free-running conditions are possible, the feasibility of a posterior estimation of coupling direction makes phase synchronization approach more attractive (Rosenblum and Pikovsky 2001). The steps of this approach are described in detail below.

Preprocessing

Data were summarized as three min averages at each tilt angle during both EUH and DEH. The times of occurrence of R wave peaks were calculated using the Pan-Tompkins algorithm (Pan and Tompkins 1985). Then RRI was calculated as the duration between successive R peaks. The local maximum within each heartbeat was designated as SBP. After removing artifacts by visual inspection, the resulting RRI and SBP time series were resampled at 4 Hz using the cubic spline interpolation method. Respiratory rate (f_R) was determined by identifying local minima of the respiratory waveform (i.e., the start of expiration). The respiratory signal was then down-sampled to 4 Hz to obtain corresponding sampling times as in the RRI and SBP time series. To estimate phase coupling in sympathetic and vagal branches of the autonomic nervous system, time series were band-pass filtered in low- (LF 0.04–0.15 Hz) and high- (HF 0.15–0.4 Hz) frequencies, respectively (Malliani et al. 1991). A Butterworth forward and backward zero phase shift filter was used to avoid altering the phase of the time series. It is worth noting that by obtaining LF and HF components separately, we were able to analyze synchronization among RESP, SBP and RRI in both LF and HF components, an outcome that would not be possible when defining phases from raw signals.

Phase extraction via the Hilbert transform approach

The Hilbert transform (Pikovsky et al. 2001; Gabor 1946) was used to extract phase, resulting in time series of phases of RRI, SBP and RESP signals, $\varphi(t)_{\mathrm{RRI}}$, $\varphi(t)_{\mathrm{SBP}}$ and $\varphi(t)_{\mathrm{RESP}}$. An illustration of this procedure is as follows: let $x(t)$ be the filtered physiological signal at the given frequency range, then the complex analytic extension of $x(t)$ is given by

$$\vartheta(t) = x(t) + i\hat{x}(t), \tag{1}$$

where the imaginary part, $\hat{x}(t)$, is generated by the Hilbert transform of the signal $x(t)$

$$\hat{x}(t) = H(t) = \frac{1}{\pi}\mathrm{PV}\int_{-\infty}^{+\infty}\frac{x(\tau)}{t-\tau}d\tau, \tag{2}$$

where PV is the Cauchy principal value of the integral. The analytic signal, $\vartheta(t)$ is then projected on the unit circle

$$z(t) = \frac{\vartheta(t)}{\|\vartheta(t)\|} = e^{i\varphi(t)}, \tag{3}$$

where $\|\vartheta(t)\|$ is the modulus of $\vartheta(t)$. The phase $\varphi(t)$ can be extracted as the angle of $z(t)$.

Phase synchronization index

A phase synchronization analysis (Rosenblum et al. 2006) was performed between SBP and RRI (SBP–RRI), RESP and RRI (RESP–RRI), and RESP and SBP (RESP–SBP). Firstly, phase differences between each pair of parameters were constructed: $\Delta\varphi(t)_{\mathrm{SBP\text{-}RRI}} = \varphi(t)_{\mathrm{SBP}} - \varphi(t)_{\mathrm{RRI}}$; $\Delta\varphi(t)_{\mathrm{RESP\text{-}RRI}} = \varphi(t)_{\mathrm{RESP}} - \varphi(t)_{\mathrm{RRI}}$; $\Delta\varphi(t)_{\mathrm{RESP\text{-}SBP}} = \varphi(t)_{\mathrm{RESP}} - \varphi(t)_{\mathrm{SBP}}$. A phase synchronization index (λ) was then defined as

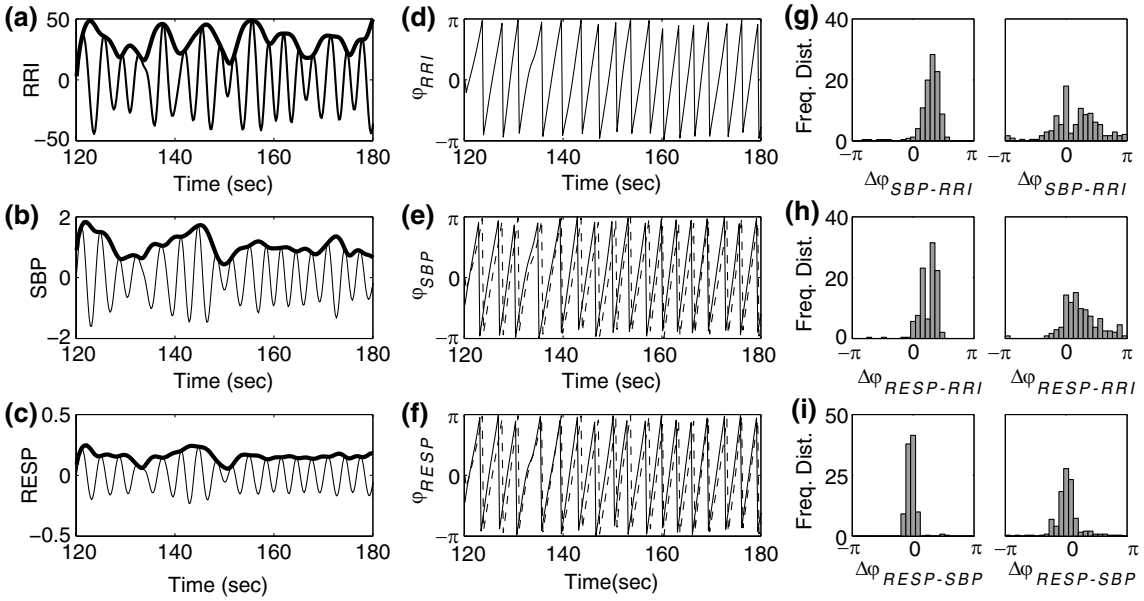

Fig. 1 A representative illustration of phase synchronization analysis procedure. One minute, filtered data in the high-frequency (0.15–0.4 Hz) range (*thin line*, **a**–**c**), the instantaneous amplitudes (*thick line*, **a**–**c**) and instantaneous phases (**d**-**f**) after the Hilbert transform, and the phase difference distributions at supine rest (**g**–**i**, *left*), as well as the phase difference distributions at 80° head-up tilt (**g**–**i**, *right*) of one euhydrated male subject are shown. *Dotted lines* in (**e**) and (**f**) indicate instantaneous phase of RRI. *SBP* systolic blood pressure (mmHg), *RESP* respiration (a.u.), φ_{RRI} phase of R–R intervals (radians), φ_{SBP} phase of systolic blood pressure (radians), φ_{RESP} phase of respiration (radians), $\Delta\varphi_{SBP\text{–}RRI}$ phase differences between R–R intervals and systolic blood pressure (radians), $\Delta\varphi_{RESP\text{–}RRI}$ phase differences between respiratory trace and R–R intervals (radians), $\Delta\varphi_{RESP\text{–}SBP}$ phase differences between respiratory trace and systolic blood pressure (radians), *Freq Dist* frequency distribution (%)

$$\lambda = \sqrt{\langle \sin \Delta\varphi(t) \rangle^2 + \langle \cos \Delta\varphi(t) \rangle^2}, \tag{4}$$

where $\Delta\varphi(t)$ describes the phase differences and $\langle\rangle$ denotes the averaging over time. In the present study, the phase synchronization index was calculated from 40 s moving average windows with 50 % overlap, which were then averaged over each three min segment. $\lambda = 0$ indicated independent phases, i.e., a complete lack of interaction, and $\lambda = 1$ indicated perfect interaction (Rosenblum et al. 2006).

Figure 1 shows an example of the analysis procedure above. The filtered 1 min data (thin line, a–c) in the HF range, the instantaneous amplitudes (thick line, a–c) and instantaneous phases (d–f) of the Hilbert transform of one euhydrated male subject at supine rest are shown. The sawtooth-shaped traces (d–f) indicate phase evolution of physiological signals, where φ_{RESP} slightly precedes φ_{RRI}, and φ_{SBP} slightly leads φ_{RRI}. In addition, the frequency distributions of cyclic relative phase differences among RRI, SBP and RESP at supine (g–i, left) and at T80 (g–i, right) are shown for the same subject in EUH. The narrow distributions of phase differences at supine imply high synchronization between each pair of signals; while the wide, uniform distributions of phase differences at T80 demonstrate that upright posture reduced the synchronization among RRI, SBP and RESP.

Directionality index

A directionality index (d) was also calculated to determine which parameter influenced the coupling relationship more strongly (Rosenblum and Pikovsky 2001; Mrowka et al. 2003). Generally, let $\varphi_1(t)$ and $\varphi_2(t)$ be phases of two signals. The basic idea behind this method is that phase increments over a certain temporal window of length τ

$$\Delta_{1,2} = \varphi_{1,2}(t+\tau) - \varphi_{1,2}(t), \tag{5}$$

can be considered as being generated by an unknown two-dimensional noisy map

$$\Delta_{1,2} = \omega_{1,2}\tau + \tilde{F}_{1,2}\left(\varphi_{2,1}, \varphi_{1,2}\right) + \varepsilon_{1,2}, \tag{6}$$

where $\omega_{1,2}$ are the natural frequencies, $\tilde{F}_{1,2}$ the coupling term, and $\varepsilon_{1,2}$ the noisy perturbations. To estimate the deterministic term $\tilde{F}_{1,2}$ of the two-dimensional noisy map, a finite Fourier series,

$$F_{1,2} = \sum\nolimits_{n,m} e^{i(n\varphi_1 + m\varphi_2)}, \tag{7}$$

is used to fit the function $\tilde{F}_{1,2}$ in a least mean square sense. In our calculation, we chose $n, m < 4$. To measure how strongly an oscillator is driven and how sensitive it is to being driven, the cross-dependency coefficients are then computed by

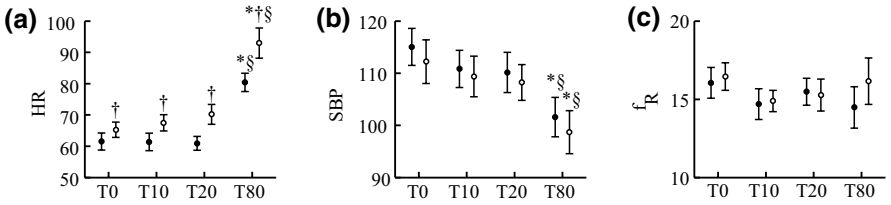

Fig. 2 Heart rate (**a**), systolic blood pressure (**b**) and respiratory rate (**c**) at supine rest [0° (T0)] and in response to head-up tilt [10° (T10), 20° (T20) and 80° (T80)] under euhydration (*filled circle*) and dehydration (*open circle*) conditions. *HR* heart rate (beats per minute), *SBP* systolic blood pressure (mmHg), f_R respiratory rate (breaths per minute). *Asterisk* significantly different from T0, $p < 0.05$; *section sign* significantly different from adjacent stress, $p < 0.05$; *dagger* significantly different from euhydration, $p < 0.05$

$$c_{1,2}^2 = \int_0^{2\pi} \int_0^{2\pi} \left(\partial F_{1,2}/\partial \varphi_{2,1}\right)^2 d\varphi_1 d\varphi_2. \quad (8)$$

And finally, a directionality index is obtained as

$$d_{1,2} = (c_2 - c_1)/(c_1 + c_2), \quad (9)$$

which ranges from 1 (oscillator 1 drives oscillator 2) to −1 (oscillator 2 drives oscillator 1) (Rosenblum et al. 2002; Rosenblum and Pikovsky 2001; Ocon et al. 2011; Pereda et al. 2005). Therefore, in our study, a positive value of $d_{\text{SBP–RRI}}$ indicates that SBP drives RRI (i.e., feedback control) and a negative value indicates that RRI drives SBP (i.e., feed-forward control). The same interpretation can also be applied to $d_{\text{RESP–RRI}}$ and $d_{\text{RESP–SBP}}$.

Data analysis with surrogate data

To exclude the possibility that the synchronization patterns detected for different orthostatic stress levels (i.e., T0, T10, T20 and T80) and plasma volume conditions (i.e., EUH vs. DEH) appeared by chance, surrogate data analysis (Schreiber and Schmitz 2000) was conducted. Specifically, we analyzed the phase synchronization between the original physiological signals (λ_{ori}) and the phase synchronization between one original signal and one surrogate signal (λ_{surr}). The surrogate signal was obtained by substituting the Fourier phases in the original signals with random phases in the range $[0, 2\pi]$ with a uniform distribution, while preserving the amplitude of the Fourier coefficients (Schreiber and Schmitz 2000). One hundred surrogate datasets were generated from each original signal. The phase synchronization indices between the 100 surrogate datasets of one original signal and each of the other two original signals were computed using the method described above. The 95th percentile of the phase synchronization indices was chosen as the surrogate phase synchronization index for subsequent statistical analysis.

Statistical analysis

The normality of the distribution was assessed using the Kolmogorov–Smirnov test. A two-tailed, paired *t* test was used to determine the significance of phase synchronization indices computed using original signals over those computed using surrogate signals. A two-way mixed model ANOVA was used to determine the effects of stress (T0, T10, T20 and T80) and condition (EUH vs. DEH) on cardiovascular variables, phase synchronization indices and directionality indices. When significant effects were observed, Tukey's post hoc analysis was performed to estimate differences between pairwise comparisons. Significance was accepted at $p < 0.05$. Analyses were completed using SAS 9.3 (SAS Institute Inc., Cary, NC). Values are shown as mean ± standard error of the mean (SE).

Results

One male subject was not involved in DEH sessions since his BP after furosemide infusion was above 140/90 mmHg, and another male subject was excluded due to the development of orthostatic intolerance symptoms during low level of orthostatic stress in DEH. Therefore, data from 10 subjects (four men, six women) are reported. Data from one male and one female subject at T80 during DEH were excluded because shortly after starting data collection at T80, these subjects developed presyncopal symptoms.

Hemodynamic parameters and respiration

Figure 2 shows hemodynamic responses to HUT during both EUH and DEH. Heart rate (main effect of stress, $p < 0.0001$) increased, and SBP decreased (main effect of stress, $p < 0.0001$) with increase in tilt angle. DEH significantly elevated HR at each stress (main effect of condition, $p < 0.0001$).

Surrogate data analysis

Table 1 shows differences between the phase synchronization index computed using original and surrogate data

Table 1 Differences (Δ) of phase synchronization index computed from orignal (λ_{ori}) and surrogate data (λ_{surr})

$\lambda_{ori} - \lambda_{surr}$	Euhydration				Dehydration			
	*T*0	*T*10	*T*20	*T*80	*T*0	*T*10	*T*20	*T*80
$\Delta\lambda_{SBP-RRI,LF}$	$0.24 \pm 0.04^{\dagger}$	$0.26 \pm 0.04^{\dagger}$	$0.21 \pm 0.04^{\dagger}$	$0.31 \pm 0.04^{\dagger}$	$0.22 \pm 0.05^{*}$	$0.21 \pm 0.04^{*}$	$0.19 \pm 0.04^{*}$	$0.27 \pm 0.07^{*}$
$\Delta\lambda_{RESP-RRI,LF}$	0.09 ± 0.05	0.13 ± 0.04	0.08 ± 0.04	0.03 ± 0.02	0.02 ± 0.07	0.04 ± 0.04	0.03 ± 0.03	-0.00 ± 0.03
$\Delta\lambda_{RESP-SBP,LF}$	0.15 ± 0.04	0.09 ± 0.05	0.06 ± 0.03	0.08 ± 0.03	0.09 ± 0.04	0.06 ± 0.03	0.03 ± 0.04	0.11 ± 0.04
$\Delta\lambda_{SBP-RRI,HF}$	$0.42 \pm 0.03^{\dagger}$	$0.42 \pm 0.03^{\dagger}$	$0.48 \pm 0.02^{\dagger}$	$0.38 \pm 0.05^{\dagger}$	$0.41 \pm 0.04^{\dagger}$	$0.44 \pm 0.05^{\dagger}$	$0.46 \pm 0.03^{\dagger}$	$0.27 \pm 0.06^{*}$
$\Delta\lambda_{RESP-RRI,HF}$	$0.43 \pm 0.04^{\dagger}$	$0.38 \pm 0.03^{\dagger}$	$0.41 \pm 0.03^{\dagger}$	$0.24 \pm 0.05^{*}$	$0.39 \pm 0.03^{\dagger}$	$0.41 \pm 0.02^{\dagger}$	$0.32 \pm 0.04^{\dagger}$	$0.24 \pm 0.04^{\dagger}$
$\Delta\lambda_{RESP-SBP,HF}$	$0.39 \pm 0.04^{\dagger}$	$0.41 \pm 0.03^{\dagger}$	$0.41 \pm 0.05^{\dagger}$	$0.35 \pm 0.06^{\dagger}$	$0.33 \pm 0.04^{\dagger}$	$0.40 \pm 0.05^{\dagger}$	$0.34 \pm 0.05^{\dagger}$	$0.38 \pm 0.08^{*}$

Values are mean ± SE

RRI R–R intervals, *SBP* systolic blood pressure, *RESP* respiratory trace, *LF* low frequency (0.04–0.15 Hz), *HF* high frequency (0.15–0.4 Hz)

Significant greater phase synchronization index when computed using original data compared with that using surrogate data, * $p < 0.01$; † $p < 0.001$

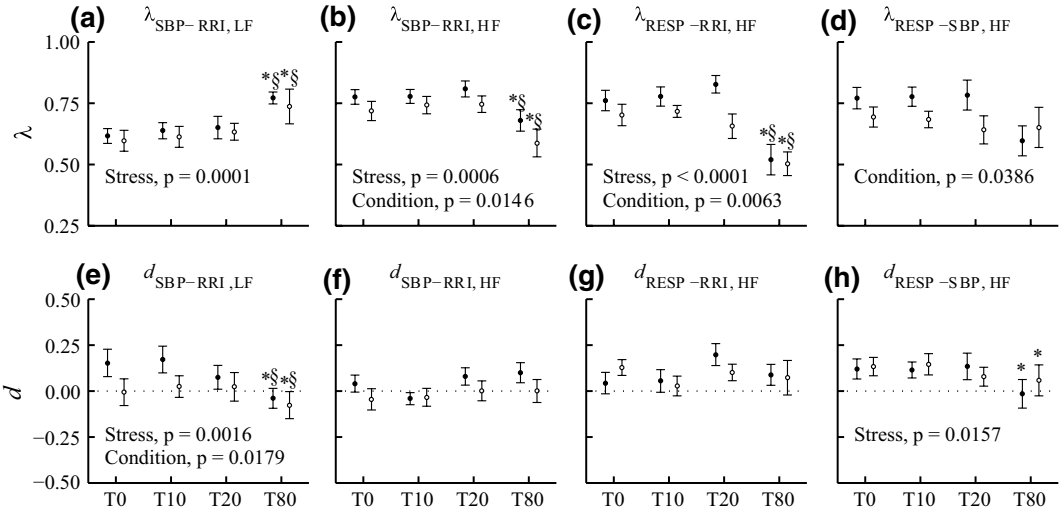

Fig. 3 Phase sychronization index (λ, **a**–**d**) and directionality index (*d*, **e**–**h**) between systolic blood pressure and R–R interval (SBP–RRI), respiration and R–R interval (RESP–RRI) and respiration and systolic blood pressure (RESP–SBP) in low- (LF 0.04–0.15 Hz) and high-frequency (HF 0.15–0.4 Hz) ranges in response to head-up tilt [0° (T0), 10° (T10), 20° (T20) and 80° (T80)] under euhydration (*filled circle*) and dehydration (*open circle*) conditions. *Stress* main effect of stress level; *Condition* main effect of condition (euhydration vs. dehydration). *Asterisk* significantly different from T0, $p < 0.05$; *section sign* significantly different from adjacent stress, $p < 0.05$

($\lambda_{ori} - \lambda_{surr}$). Phase synchronization indices related to the LF component of RESP, i.e., $\lambda_{RESP-RRI,LF}$ and $\lambda_{RESP-SBP,LF}$, were not significantly greater than those computed using surrogate data. However, significantly greater phase synchronization indices were obtained for signals related to the HF component of RESP, i.e., $\lambda_{RESP-RRI,HF}$ and $\lambda_{RESP-SBP,HF}$. In addition, $\lambda_{SBP-RRI,LF}$ and $\lambda_{SBP-RRI,HF}$ generated from original data were significantly greater than those computed using surrogate data. Therefore, in the remainder of the text, we report only those parameters that quantify cardiovascular coupling in LF and HF ranges, and those that quantify cardiorespiratory (i.e., cardiac-respiratory and vascular-respiratory) coupling in the HF range.

Phase synchronization index and directionality index in low- and high-frequency ranges

Figure 3 shows phase synchronization index (λ, a–d) and directionality index (λ, e–h) of SBP–RRI, RESP–RRI and RESP–SBP in LF and HF regions. Compared to T0, increasing tilt angle increased $\lambda_{SBP-RRI,LF}$ (main effect of stress, $p = 0.0001$) and decreased $\lambda_{SBP-RRI,HF}$ (main effect of stress, $p = 0.0006$) and $\lambda_{RESP-RRI,HF}$ (main effect of stress, $p < 0.0001$) during both EUH and DEH. Orthostatic stress tended to reduce $\lambda_{RESP-SBP,HF}$ (main effect of stress, $p = 0.0513$). With respect to T0, $d_{SBP-RRI,LF}$ (main effect of stress, $p = 0.0016$) and $d_{RESP-SBP,HF}$ (main effect of stress, $p = 0.0157$) decreased; while $d_{RESP-RRI,HF}$ remained

unchanged throughout graded HUT during both EUH and DEH. In addition, HUT appeared to have different effects on $d_{SBP–RRI,HF}$ in different hydration conditions (condition by stress interaction, $p = 0.0298$). However, post hoc tests indicated that neither HUT nor hydration status affected $d_{SBP–RRI,HF}$. With respect to EUH, DEH reduced $\lambda_{SBP–RRI,HF}$ (main effect of condition, $p = 0.0146$), $\lambda_{RESP–RRI,HF}$ (main effect of condition, $p = 0.0063$) and $\lambda_{RESP–SBP,HF}$ (main effect of condition, $p = 0.0386$), and had no significant effect on $\lambda_{SBP–RRI,LF}$. In addition, DEH had no significant effects on $d_{SBP–RRI,HF}$, $d_{RESP–RRI,HF}$ and $d_{RESP–SBP,HF}$, but significantly decreased $d_{SBP–RRI,LF}$ (main effect of condition, $p = 0.0179$).

Discussion

We made use of two non-linear indices, the phase synchronization index (λ) and the directionality index (d), to determine the presence and causal relationship of cardiovascular and cardiorespiratory couplings at rest and in response to orthostatic stress and to DEH. The main findings of the present study are (1) the phase synchronization of variables related to respiration did not exceed that occurring by chance in the LF range; (2) DEH reduced phase synchronization indices among all variables in the HF range and $d_{SBP–RRI}$ in the LF range; and (3) orthostatic stress increased $\lambda_{SBP–RRI}$ and decreased $d_{SBP–RRI}$ in the LF range, and decreased $\lambda_{SBP–RRI}$, $\lambda_{RESP–RRI}$ and $d_{RESP–SBP}$ in the HF range.

Validity of utility of the phase synchronization approach in cardiovascular coupling analysis

In the present study, phase synchronization between SBP and RRI oscillations was studied in both LF and HF ranges, based on the assumption that SBP oscillations and RRI oscillations are generated by different central neural structures involved in autonomic cardiovascular regulation. Concerns may exist since some investigators assumed that RRI oscillations are just produced by resonance phenomenon due to SBP oscillations. Specifically, it is assumed that respiratory sinus arrhythmia is caused by blood pressure oscillations in the HF range (Karemaker 2009). However, the findings that respiratory SBP oscillations are resulted almost entirely from the direct effect of centrally mediated heartbeat fluctuations in dogs (Akselrod et al. 1985), and that respiratory sinus arrhythmia can actually contribute to respiratory arterial pressure fluctuations in humans (Taylor and Eckberg 1996) support our hypothesis, i.e., RRI oscillations in the HF range is not simply a baroreflex buffering of SBP oscillations. Some facts also support a central origin for LF fluctuations of RRI. Cooley et al. (1998) found that LF component of RRI oscillations were restored without any change in the LF component of SBP oscillations, using the left ventricular assist device in severe heart failure patients. Taylor and Eckberg (1996) found that elimination of LF component of RRI oscillations by fixed-rate cardiac pacing did not change LF blood pressure oscillations. These different responses of SBP and RRI to external stimuli indicate that different centers are responsible for generation of LF cardiovascular oscillations. In addition, an inconsistent relationship between LF oscillations of SBP and RRI in response to lower body negative pressure (Hamner et al. 2001) suggests that a complex interaction of regulatory mechanisms determines the link between LF fluctuations.

Surrogate data analysis

Respiration did not synchronize with RRI and SBP in the LF range, which is consistent with other studies (Lackner et al. 2011; Moertl et al. 2013). Cysarz et al. (2004) indicated that the respiratory oscillations did not contain a LF component during spontaneous breathing, and therefore, the cardiorespiratory interaction was desynchronized. Badra et al. (2001) also found that respiratory frequency had no effect on LF autonomic rhythms, indicating that LF rhythms are generated by mechanisms independent of respiratory rhythm generators. Thus, the cardiorespiratory desynchronization in the LF range was expected since our subjects were allowed to breathe spontaneously, and therefore, the breathing frequency was mainly in the HF band. Coupling between SBP and RRI, however, significantly exceeded those occurring by chance in both LF and HF ranges. The significantly high value of phase synchronization index between SBP and RRI in the LF range indicated a high correlation within the cardiovascular system in healthy humans, which is consistent with other studies (Lackner et al. 2011; Moertl et al. 2013; Karavaev et al. 2009). In addition, it has been shown that partialization of respiratory effects using a partial coherence method reduced coherence between RRI and SBP in the HF range (Badra et al. 2001); therefore, the significant phase synchronization between RRI and SBP in the HF range indicated that cardiovascular interaction could be respiratory driven (Lackner et al. 2011; Moertl et al. 2013).

Cardiovascular coupling analysis

The analysis of causal relationships (Ocon et al. 2011; Faes et al. 2011, 2013a; Nollo et al. 2005, 2009; Porta et al. 2011) and coupling strength (Lackner et al. 2011; Moertl et al. 2013; Ocon et al. 2011; Porta et al. 2012) between SBP and RRI provides information concerning the cardiovagal baroreflex, which is essential to maintain blood

pressure in response to orthostatic stress. Using a cross-conditional entropy method, Porta et al. (2011) reported that the causal relationship changed from RRI leading SBP at supine rest, to SBP driving RRI during HUT. Ocon et al. (2011) also illustrated a dominant feed-forward relationship at supine in healthy subjects using the phase synchronization method. Similar results have been reported using other mathematical approaches (Nollo et al. 2005, 2009; Faes et al. 2013a). In contrast, our results indicate a causal relationship from SBP to RRI in the LF range, but a bidirectional relationship in the HF range, at supine rest. Although similar bivariate methods were used in the present study and other studies (Nollo et al. 2005, 2009; Porta et al. 2011; Ocon et al. 2011; Faes et al. 2013a), we explored the coupling strength and causal relationship in the LF and HF ranges separately. Results from other studies (Badra et al. 2001; Lackner et al. 2011; Moertl et al. 2013; Cysarz et al. 2004) and the present study indicated that respiration did not interact with RRI and SBP in the LF range. Faes et al. (2011) demonstrated that cardiovascular feed-forward and feedback mechanisms were balanced at supine rest by excluding respiratory effects using a multivariate information domain approach, which is not consistent with their previous studies using similar protocols, but with different bivariate analysis methods (Porta et al. 2011; Nollo et al. 2005, 2009). Faes et al. (2011) pointed out that respiration may induce a feed-forward mechanism contributing to the observed RRI driving SBP in those studies (Porta et al. 2011; Nollo et al. 2005, 2009). Therefore, the predominance of the feedback causal relationship we observed in the LF range may reflect a relationship that is independent of the main rhythms of respiration.

Previous studies (Nollo et al. 2005, 2009; Porta et al. 2011; Ocon et al. 2011; Faes et al. 2011, 2013a) have shown increased SBP driving RRI with increased tilt angle, in contrast, we observed that the moderate unidirectional SBP driving RRI in the LF range was reduced and converted to bidirectional driven by both HUT and DEH, while bidirectional relationship in the HF range was maintained throughout HUT and DEH. Pereda et al. (2005) previously indicated that parasympathetic blockade via atropine administration increased the dependency of SBP on RRI in the LF range, but had no effect on the bidirectional causal relationship between SBP and RRI in the HF range, in male rats. Therefore, results from the present study and those from our previous report (Zhang et al. 2014), indicated reduced vagal outflow in response to both HUT and DEH. Different responses of the causal relationship between SBP and RRI with HUT in the present study and other studies (Nollo et al. 2005, 2009; Porta et al. 2011; Ocon et al. 2011; Faes et al. 2011, 2013a) might be due to differences in experimental protocols. In our study, subjects were exposed to orthostatic stress for a much longer time period (~45 min) compared with other studies (~10 min). It has been shown that a prolongation of passive HUT may lead to orthostatic intolerance (Faes et al. 2013a, b; Lipsitz et al. 1998; Ocon et al. 2011; Wang et al. 2006). Indeed, significant SBP drop was observed throughout HUT during both EUH and DEH in our study, and seven of our ten subjects had presyncopal symptoms by the end of HUT test during DEH. It has been shown that patients with a history of vasovagal syncope demonstrated diminished SBP driving RRI using a directionality index (Ocon et al. 2011), or reduced information transferred from SBP to RRI using a corrected conditional entropy method (Faes et al. 2013a) and an information decomposition strategy (Faes et al. 2013b), indicating a loss of baroreflex regulation preceding syncope. Therefore, our results are more applicable to the situations where stability of circulation is challenged to the point of approaching faintness and thus may be more relevant in prediction of orthostatic intolerance. In addition, it is possible that differences in the causal relationship between SBP and RRI in the present study, compared to previous studies (Nollo et al. 2005, 2009; Porta et al. 2011; Ocon et al. 2011; Faes et al. 2011, 2013a), might arise from methodological differences. The application of our phase focused method on filtered signal components may affect the interdependence between signals, since interactions between LF and HF components of each signal were not considered. Therefore, further research should be performed to assess effects of different methodologies.

In addition to the changes in causal relationships, changes in coupling strength between SBP and RRI have been observed in subjects approaching syncope using different methods. Ocon et al. (2011) reported that the coupling strength between SBP and RRI reduced preceding faint in patients with a history of vasovagal syncope, revealed by the phase synchronization approach, indicating an impaired cardiovagal integrity. Wang et al. (2006) utilized a bispectral analysis to observe that the coupling between SBP and RRI decreased during tilt, and was smaller in tilt-positive with respect to tilt-negative healthy subjects. It has been suggested that LF oscillations are determined by both sympathetic and parasympathetic activities, with HF oscillations determined by vagal activity only (Malliani et al. 1991). Thus, in our study, the augmentation of $\lambda_{SBP-RRI,LF}$ reflected a case in which sympathetic compensation overwhelmed the parasympathetic effects before the collapse of cardiovascular regulation; while the reduction of $\lambda_{SBP-RRI,HF}$ indicated vagal withdrawal.

Cardiorespiratory coupling analysis

In normal, unstressed, physiological conditions (e.g., at supine in EUH), the cardiovascular system is closely tied to the respiratory system, as indicated by high phase

synchronization indices related to the HF component of RESP. Decreased cardiac-respiratory coupling (i.e., RESP–RRI) has been observed during stressful conditions, such as orthostatic stress (Faes et al. 2011; Porta et al. 2012), mental challenge (Lackner et al. 2011; Niizeki and Saitoh 2012) and pregnancy (Moertl et al. 2013). However, decreased (Lackner et al. 2011; Moertl et al. 2013), unchanged (Faes et al. 2011) and increased (Porta et al. 2012) vascular-respiratory coupling (i.e., RESP–SBP), have been obtained during different physiological conditions. Our results indicated that HUT reduced cardiac–respiratory and did not alter vascular–respiratory coupling, which is consistent with Faes et al. (2011), while DEH significantly reduced both cardiac– and vascular–respiratory interactions. Bartsch et al. (2012) found that cardiac–respiratory phase synchronization was high when sympathetic activity was reduced and weak when sympathetic tone was dominant during different sleep stages using a phase synchrogram method. Niizeki and Saitoh (2012) indicated that the phase synchronization index of cardiac-respiratory coupling was positively related to parasympathetic status. The decreased cardiac-respiratory coupling, i.e., $\lambda_{RESP–RRI,HF}$, during DEH and HUT is consistent with DEH- and HUT-induced sympathetic excitation and vagal withdrawal determined in our previous report (Zhang et al. 2014) and also consistent with cardiorespiratory decoupling before syncope (Lipsitz et al. 1998). The DEH-induced, but not HUT-induced, reduction in vascular–respiratory interaction, i.e., $\lambda_{RESP–SBP,HF}$, indicated that the respiratory effect on stroke volume was more detectable in response to DEH-induced acute overall reduction compared with tilt-induced caudal shift of blood volume. The difference between HUT- and DEH-induced changes in $\lambda_{RESP–SBP,HF}$ imply that DEH exacerbated the orthostatic stress-induced desynchronization among RESP, RRI and SBP by reducing mechanical effects of respiration on SBP. In addition, we observed that the causal relationship was always from RESP to RRI and SBP in response to both HUT and DEH, consistent with the fact that RESP interacts with cardiovascular variables as an external oscillator (Faes et al. 2011; Ocon et al. 2011).

Limitations

A limitation of the approach used in the present study is that it requires windowing of the original data and therefore, choice of window size can affect the exact value of the synchronization indices. To eliminate a bias induced by choice of window size, we used several different windows ranging from 10 to 100 s. Analysis using these different window sizes all resulted in the same conclusion, although the exact values were different. In addition, in the case of perfect synchrony (i.e., $\lambda = 1$), it is not possible to separate the effect of interaction from the internal dynamics of autonomous systems (Rosenblum and Pikovsky 2001); therefore, the directionality index cannot be obtained in this situation. However, none of the oscillations in our study were perfectly synchronized.

Significance and perspective

We assessed the causal relationship and coupling strength of cardiovascular, cardiac-respiratory, vascular–respiratory interactions in response to orthostatic stress and DEH by a thorough analysis of interactions among RRI, SBP and RESP, respectively. Results of the present study indicate that loss of causality from SBP to RRI seems to be able to early identify the onset of presyncope. In addition, the method we used can deal with closed-loop interactions without priori assumptions and is able to capture both linear and non-linear interactions without specifying a model of the observed interactions. This is important in furthering our understanding of mechanisms contributing to neurally mediated syncope and assessing interventions for preventing orthostatic intolerance. Effects of several interventions to orthostatic intolerance, especially in the field of space medicine, such as lower body compression (Zhang et al. 2014; Evans et al. 2013) and artificial gravity (Evans et al. 2004), have been analyzed using conventional methods. Future studies may be needed to assess the effects of existing interventions on causal relationship and strength of interactions among cardiovascular and respiratory oscillations to gain more insight into the question.

Conclusions

In summary, we utilized the phase synchronization method to quantify cardiovascular and cardiorespiratory coupling in response to orthostatic stress and DEH. We found that orthostatic stress resulted in desynchronization among heart rate, blood pressure and respiration, and DEH exacerbated this disassociation. DEH also reduced involvement of baroreflex regulation, which may contribute to the increased occurrence of orthostatic intolerance following acute blood volume reduction.

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Conflict of interest The authors declare that they have no conflict of interest.

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