Med Biol Eng Comput
DOI 10.1007/s11517-016-1517-6

ORIGINAL ARTICLE

Effects of slow and regular breathing exercise on cardiopulmonary coupling and blood pressure

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Received: 5 November 2015 / Accepted: 2 May 2016

Abstract Investigation of the interaction between cardiovascular variables and respiration provides a quantitative and noninvasive approach to assess the autonomic control of cardiovascular function. The aim of this paper is to investigate the changes of cardiopulmonary coupling (CPC), blood pressure (BP) and pulse transit time (PTT) during a stepwise-paced breathing (SPB) procedure (spontaneous breathing followed by paced breathing at 14, 12.5, 11, 9.5, 8 and 7 breaths per minute, 3 min each) and gain insights into the characteristics of slow breathing exercises. RR interval, respiration, BP and PTT are collected during the SPB procedure (48 healthy subjects, 27 ± 6 years). CPC is assessed through investigating both the phase and amplitude dynamics between the respiration-induced components from RR interval and respiration by the approach of ensemble empirical mode decomposition. It was found that even though the phase synchronization and amplitude oscillation of CPC were both enhanced by the SPB procedure, phase coupling does not increase monotonically along with the amplitude oscillation during the whole procedure. Meanwhile, BP was reduced significantly by the SPB procedure (SBP: from 122.0 ± 13.4 to 114.2 ± 14.9 mmHg, $p < 0.001$, DBP: from 82.2 ± 8.6 to 77.0 ± 9.8 mmHg, $p < 0.001$, PTT: from 172.8 ± 20.1 to 176.8 ± 19.2 ms, $p < 0.001$). Our results demonstrate that the SPB procedure can reduce BP and lengthen PTT significantly. Compared with amplitude dynamics, phase dynamics is a different marker for CPC analysis in reflecting cardiorespiratory coherence during slow breathing exercise. Our study provides a methodology to practice slow breathing exercise, including the setting of target breathing rate, change of CPC and the importance of regular breathing. The applications and usability of the study results have also been discussed.

Keywords Cardiorespiratory interaction · Phase coupling · Blood pressure · Pulse transit time · Stepwise-paced breathing

1 Introduction

There is growing interest in investigating the interaction between cardiovascular and cardiorespiratory systems [34, 40]. Analysis of cardiopulmonary coupling (CPC) provides information about the coupling dynamics between the cardiorespiratory systems [3], leading to improved knowledge of the interacting regulatory mechanisms under different physiological and pathophysiological conditions [34]. Amplitude and phase dynamics are two major aspects of the investigation for CPC, and amplitude dynamics was mainly considered in most of studies [3]. In the past three decades, a large number of papers have been published using the analysis of heart rate (HR), blood pressure (BP) and respiration as a quantitative, indirect and noninvasive

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approach to assess the autonomic control of cardiovascular function [13, 29, 39].

To keep respiration a narrow-band signal to eliminate respiratory confounds (e.g., power spectral analysis [12, 26]), paced breathing (PB) procedure is commonly performed [8, 21, 29]. It has been demonstrated that PB procedure can lead to increased amplitude oscillations in both HR and BP when breathing rate becomes lower [36, 37]. The change of phase dynamics during PB procedure, however, has rarely been explored simultaneously. As coupled oscillators interact both through their phases and amplitudes, analysis of phase dynamics has been used to investigate the strength and direction of CPC [3, 27, 30, 34]. Compared with amplitude-based coupling analysis, phase dynamics are more sensitive to the subtle change of coupling strength [25]. Small perturbations will have a large impact on the phase, but only a very small effect on the amplitude [3]. Therefore, phase dynamics are potentially more effective than amplitude dynamics in reflecting the subtle changes of CPC during the PB procedure.

Slow breathing exercises have been used across cultures and centuries to provide health benefits [35]. Based on the phenomena that CPC at slow breathing rate can increase heart rate variability and improve arterial baroreflex sensitivity [15, 19], breathing control techniques have been employed to improve cardiovascular autonomic balance and reduce BP [2, 33]. An FDA (the Food and Drug Administration, USA) approved device, Resperate (InterCure Ltd, Lod, Israel), has been developed for the treatment of hypertension by PB technology [35]. However, recent studies suspected the effectiveness of this device to lower BP [1, 17, 20, 22]. Some fundamental questions on practicing slow breathing exercise have not been well answered, such as the setting of target breathing frequency and the importance of breathing regularity. Resperate states that the target breathing frequency of 10 breaths per minute (BPM) or less should be achieved for this device to generate favorable clinical effects on cardiovascular system [33, 35]. Regular breathing is described as a key factor either by Resperate or many other slow breathing exercises such as yogic and Taoist breathing. Surprisingly, current literatures have provided little direct evidence on these importance issues.

The aim of this study was to investigate the change of CPC and cardiovascular variables during a stepwise-paced breathing (SPB) procedure and explore the characteristics and effectiveness of slow breathing exercises. Several fundamental issues about practicing slow breathing exercises to benefit cardiovascular system were analyzed. To simulate the process of slow breathing exercise and observe the cumulative effects of slow and regular breathing on cardiovascular system, an SPB protocol with six-fixed breathing rates of [14, 12.5, 11, 9.5, 8 and 7] BPM was performed. For the investigation of CPC, both amplitude and phase dynamics were quantified and explored simultaneously during the SPB procedure.

Through the SPB procedure, detailed information on the variation of amplitude and phase dynamics, BP, pulse transit time (PTT) and breathing regularity during slow breathing exercise can be acquired. Issues about adopting slow breathing exercises to benefit the cardiovascular system, such as effectiveness of the slow breathing exercise, the setting of target breathing rate, change of CPC in terms of amplitude and phase dynamics, and the importance of breathing regularity, can be effectively addressed. Our study provides a methodology to practice slow breathing exercise, and results from this study can be used for cardiovascular biofeedback training.

2 Materials and methods

2.1 Participants and protocol

This study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital. All participants received detailed verbal and written information about the study objectives and procedure and gave written informed consent. Fifty-five healthy subjects were recruited in this experiment and were abstained from caffeine-containing beverages for at least 4 h before the study. Volunteers were excluded when they had a known history of respiratory, cardiovascular or neurological diseases. During the experiment, each subject underwent a SPB procedure in a sitting position at rest. The SPB procedure consisted of one 3-min spontaneous breathing (SB) section and six PB sections. Each PB section had a pre-defined breathing rate with a constant inspiration to expiration ratio (1:2), lasting 3 min. The six PB sections were arranged in a stepwise order with breathing rate changing from high to low in a protocol of [14, 12.5, 11, 9.5, 8 and 7] BPM. To observe the cumulative effects of the PB on cardiovascular system, there was no recovery period during the whole SPB procedure.

After 10 min of quiet rest and familiarization with the laboratory and instruments, we obtained recordings of ECG (lead II), respiration of rib cage (RC) and abdomen (AB) (by respiratory inductive plethysmography: RIP), continuous BP (by CNAP Monitor 500) and pulse wave (detected at the radial artery) by Biopac MP150 data acquisition system through the whole SPB procedure. All signals were sampled at 1000 Hz. During the PB procedure, the breathing was controlled by six melodies corresponding to six different PB rates. Each melody comprises two different tones, with a rising tone guiding inhalation while a lower tone accompanying exhalation. Before the experiment, instructions on how to perform the breathing exercise was given, and each subject had 1 min to get familiar with the guiding music to conduct correct breathing maneuvers.

2.2 Signal preprocessing

2.2.1 QRS complex detection

A 50 Hz notch filter was first implemented to remove the power line interference from the ECG waveform. Then, each heartbeat was detected by using an automated QRS complex detection algorithm [11], and the detection result was verified by visual inspection. Consequently, the peak of each R wave was located and RR interval (RRI) time series from each subject was derived. Abnormal beats (e.g., ectopic), which occurred occasionally, were identified by a moving window filter with a window duration of 1 min. In each moving window, if a RRI differs from the mean value of the window by more than three standard deviations, it was removed. Finally, normal-to-normal sinus intervals were extracted from the RRI time series. In this study, since the volunteers are healthy and the ECG signal quality is good, less than 1 % of heart beats were removed as abnormal beats.

2.2.2 PTT calculation

PTT is the time delay for the pressure wave to travel between two arterial sites [23]. In our study, to simplify the measurement of PTT, the time interval from the R-spike of the ECG to the arterial pulse wave recorded by a pressure sensor at the radial artery was calculated to approximate PTT (which is actually called pulse arrival time: PAT [23]). There are several methods to determine the arrival point of the pulse wave, such as the peak or valley point on the raw waveform. In our study, we took the peak of the second derivative of the pulse wave as the arrival point (see Fig. 1). The peak point on the second derivative is more accurate in recognition of the inflection points of the pulse wave. To guarantee reliable detection of the arrival points, we used each R wave to locate the associated pulse wave and searched the peak on the second derivative in the same cardiac cycle. This method improves the detection accuracy and has a high level of motion artifact and baseline wonder tolerance. Manual inspection was also performed to confirm the correctness of the detection.

2.2.3 Extraction of respiration-induced oscillations

The PB procedure, to some extent, increases the reproducibility of parameter estimation [16]. However, as HR and BP can be affected by complex interactions through different feedback mechanisms [9, 28], there are nonlinear interactions underlying the physiological feedback control systems [26, 34, 40]. Therefore, for the reliable investigation of CPC, signal analysis techniques capable of dealing with non-stationary and nonlinear signals should be adopted. In this study, ensemble empirical mode decomposition (EEMD) [24] was applied to decompose cardiorespiratory signals of RRI and respiration. Respiration-induced oscillations were extracted from each signal, and both phase and amplitude dynamics were studied.

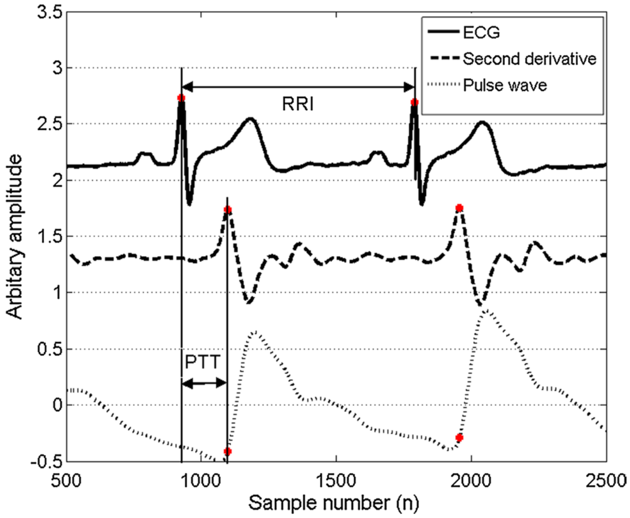


Fig. 1 Illustration of the PTT definition and calculation

Firstly, RRI time series were linearly interpolated at an even interval of 0.125 s (i.e., 8 Hz), and respiratory signal (sum of rib cage and abdomen recorded by RIP) was down-sampled to 8 Hz through a decimation method. Then, EEMD was applied to each series. EEMD is a noise-assisted data analysis method to overcome mode mixing problem encountered in EMD approach [24]. EMD is the core algorithm of Hilbert–Huang transform, which was developed to extract dynamical information from non-stationary and nonlinear signals at different timescales [14]. Details of the algorithm can be found in the original articles [24]. Briefly, the EEMD decomposes a complex data into a finite number of intrinsic modes of oscillations. Each mode of oscillation, termed intrinsic mode function (IMF), is decomposed sequentially from the original time series by identifying the intrinsic modulations at different timescales. By EEMD, time series of RRI and respiration is decomposed into multiple IMFs so that the fluctuations caused by respiration process can be represented in corresponding empirical modes.

The normal breathing frequency of heathy subjects ranges from 0.15 to 0.40 Hz, and the RRI oscillations induced by normal breathing should be within this frequency range. For the PB rates ([14–12.5–11–9.5–8–7] BPM) performed in this study, each PB frequency is constant. Therefore, the respiratory oscillations presented in

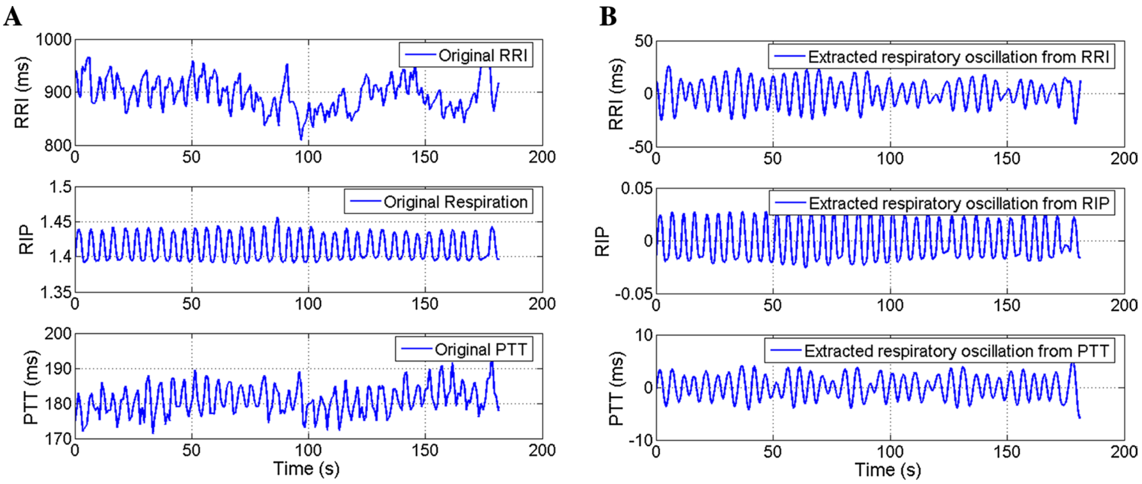


Fig. 2 Respiration-induced oscillations during one PB section. **a** Original RRI, RIP and PTT signals; **b** respiratory oscillations extracted from each time series

corresponding IMF are easy to be identified for both the respiration and the RRI time series decomposed by EEMD. It is observed that, in the SPB dataset, the respiration-induced oscillations in both the RRI and the respiration time series all lie in the IMFs 3–6, but the dominant respiratory IMF differs between different PB sections. Generally speaking, the lower the PB rate, the higher the level of dominant respiratory IMF. Therefore, after applying EEMD to each time series, we further segmented each decomposed series into seven subsections (corresponding to one SB section and six PB sections) according to the SPB protocol. In each subsection, power spectrum analysis was conducted to calculate the dominant frequency component of each IMF from IMFs 3–6. The IMF within the respiratory band was identified as the respiration-induced oscillation in each series. Manual inspection was also performed to confirm the correctness of the identification. Figure 2 shows the original signals of RRI, respiration and PTT, and the corresponding respiration-induced oscillations extracted from each signal.

2.2.4 *Phase coupling*

To quantify instantaneous phase interactions between cardiovascular and respiratory system, Hilbert transform was applied to provide instantaneous phase of each series [7]. With this approach, a real-valued signal is transformed into a complex-valued one, from which we obtain a value of the phase for each sample. For a time series $s(t)$, its Hilbert transform is defined as:

$$\tilde{s}(t) = \frac{1}{\pi} \cdot p.v. \int \frac{x(\tau)}{t-\tau} d\tau, \tag{1}$$

where $p.v.$ denotes Cauchy principal value. The instantaneous phase is expressed as

$$\varphi(t) = \arctan \frac{\tilde{s}(t)}{s(t)} \tag{2}$$

With the instantaneous phase information, point-by-point phase differences between paired signals of RRI and respiration were calculated.

In our study, we defined the phase coupling between paired signals on the degree of phase synchronization index (PSI) as proposed by Cysarz et al. [6]. For RRI and respiration time series, if the phase difference $\phi_i = \phi_{\mathrm{Resp}} - \phi_{\mathrm{RRI}}$ (ϕ_{Resp} for respiration and φ_{RRI} for RRI) is constant, then both time series are synchronized. We quantified the PSI as

$$\mathrm{PSI} = (\overline{\cos \varphi_i})^2 + (\overline{\sin \varphi_i})^2, \tag{3}$$

where φ_i is the point-by-point phase difference of the paired time series, and $(\overline{\cos \varphi_i})$ and $(\overline{\sin \varphi_i})$ represent the average value during a certain time interval.

When cardiorespiratory variables are highly synchronized, the distribution of phase difference φ_i should be within a narrow range. Otherwise, for non-synchronized signals, the distribution should be wide. Consequently, the normalized index PSI will increase as the strength of synchronization increases. The phase coupling strength was quantified by this normalized index ranging from 0 to 1, with larger values indicating higher coupling between respiration and cardiovascular systems.

2.2.5 *RRI amplitude oscillation*

With the extracted respiratory oscillations from RRI series, we calculated the amplitude oscillations of RRI within breathing cycles at each PB section. Peak and valley onsets were identified within each breathing cycle by extreme point searching algorithm, and oscillatory amplitude was calculated by the amplitude difference between peak and valley points. For each PB section, we got one mean value of the amplitude oscillation.

The baseline of PTT and RRI was also computed at each PB section. The baseline of PTT and RRI was defined as the mean value of the trend component, i.e., the sum of IMFs 8–14 in our dataset, in PTT and RRI series in each PB section. For BP, we calculated the mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at each PB section, respectively.

2.2.6 *Breathing regularity*

As regularity of breathing is also a key factor to practice slow breathing exercise [35], we further investigate the effect of breathing regularity on phase and amplitude dynamics, testing whether breathing regularity has impacts on CPC. In our study, the breathing regularity was measured by the coefficient of variation (CV), which is defined as the ratio of the standard deviation σ to the mean μ,

$$\mathrm{CV} = 100 * \frac{\sigma}{\mu} \tag{4}$$

Accordingly, a smaller value of CV corresponds to a higher regularity. With this parameter, we assessed the amplitude regularity (breathing amplitude) and periodic regularity (breathing rate) at each PB section, respectively.

For ease of understanding of the work developed in this study, a global scheme of the measurements and the algorithms used for each measurement is presented in Fig. 3.

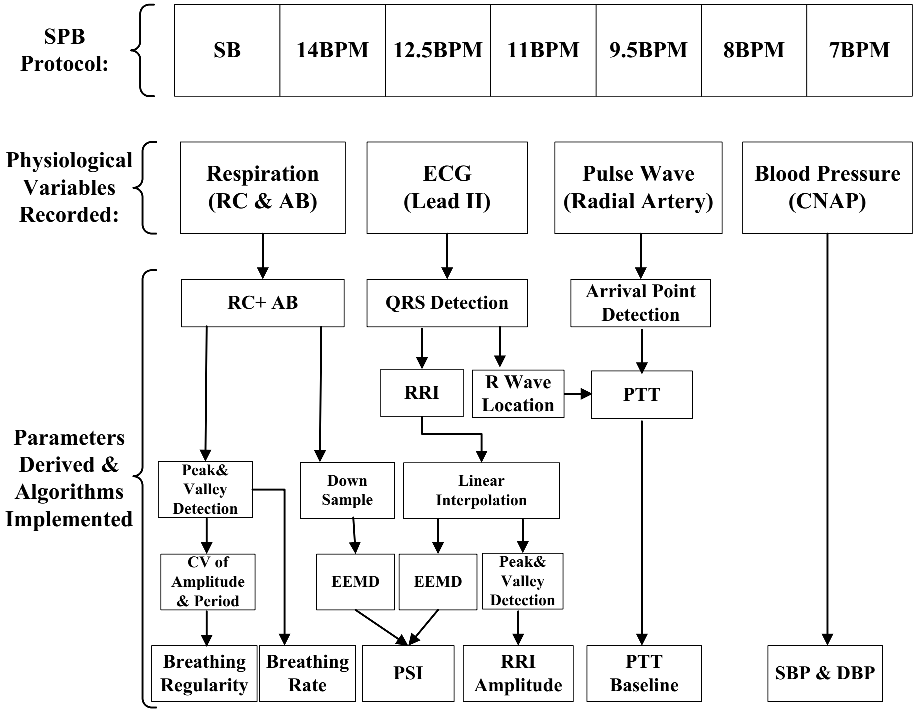
2.3 Statistical analysis

In our study, results are reported as mean ± standard deviation. To explore the cumulative effects of slow breathing on cardiovascular system, paired t test was performed to assess the significance of the difference in BP, RRI amplitude and PTT baseline between the SB and the last section of the SPB procedure. All statistical analyses were performed using MATLAB version R2010b (MathWorks, Natick, MA, USA).

3 Results

Most subjects were able to accurately and comfortably follow the paced breathing protocol. There were four subjects who did not follow the protocol either during the whole procedure or in certain sections of the SPB procedure (by screening the respiratory signals summed by rib cage and abdomen). There were another 3 subjects with low signal quality of pulse wave and thus unreliable PTT estimations. Therefore, physiological data from the other 48 subjects (21 female and 27 male, with age ranging from 20 to 43, 27 ± 6 years), were used for analysis in this study. The actual breathing rate of the 48 subjects in each breathing section during the SPB procedure are shown in Table 1. It can be seen that the mean breathing rate at each PB section is very close to the pre-defined PB rate, indicating that the volunteers could follow the SPB protocol to perform the stepwise slow breathing exercise. Slow breathing was

Fig. 3 Global scheme of the measurements and the algorithms used for each measurement



associated with an increase in tidal volume (judged from the respiratory signals summed by rib cage and abdomen) but no other complaints.

3.1 Phase and amplitude dynamics show different patterns during the SPB procedure

The variations of phase dynamics (quantified by PSI) and amplitude dynamics (quantified by RRI amplitude) of CPC are shown in Table 1. It can be seen from Table 1 that both the phase and amplitude dynamics were improved by the SPB procedure. RRI amplitude changed from 47.4 ± 27.6 ms (the SB section) to 113.5 ± 48.0 ms gradually (the 7 BPM section, $p < 0.01$). The change of amplitude oscillation is consistent with other's study, i.e., amplitude-modulation effect of PB gets more evident when the breathing rate gets lower [37]. PSI, however, did not increase monotonically along with the RRI amplitude when the PB rate got much lower. Based on our SBP protocol, PSI increased gradually when the breathing rate changed from SB to 11 BPM ($p < 0.001$ between the SB section and the 11 BPM section) and then decreased after 11 BPM. When the PB rate lowered to 7 BPM, the value of PSI dropped almost back to that of the SB state. The variation of PSI indicates that there is an optimal range of PB rate for slow breathing exercise to induce a best coherent state between respiration and heart rate.

Figure 4 shows the details of the distributions about phase difference between paired RRI and respiratory signals, and RRI oscillations from one subject (numbered 29) at each breathing condition during the SPB procedure. It can be seen from Fig. 4 that the PB procedure can produce narrowed distribution of phase difference between respiration and RRI, leading to higher synchronization between cardiorespiratory variables than the SB procedure. Meanwhile, RRI amplitude increases with the reduced breathing rate. The values of PSI, RRI amplitude, PTT baseline, SPB and DBP at each breathing stage are also presented in Fig. 4. Along with the increase in phase coupling and RRI oscillation, PTT baseline increased and BP decreased. For this subject, the change of PTT baseline is more coincided with the change of the PSI than RRI amplitude. Both PSI and PTT baseline reached their maximum at 11 BPM and then decreased with the lowered breathing rate, while RRI amplitude increased monotonously along with the decreased breathing rate.

Fig. 4 Distribution of phase difference between RRI and respiration, and RRI oscillation from one subject at each breathing condition during the SPB procedure. **a** spontaneous breathing, **b** PB at 14 BPM, **c** PB at 12.5 BPM, **d** PB at 11 BPM, **e** PB at 9 BPM, **f** PB at 8 BPM and **g** PB at 7 BPM. Values of PSI, RRI amplitude, PTT baseline, SPB and DBP at each breathing stage are also presented

▶

The SPB procedure performed in this study could generate different levels of CPC for each individual, and the relationship between the phase coupling and amplitude oscillation during slow breathing exercise was further investigated. Figure 5 shows the relationship between PSI and RRI amplitude from the 48 subjects during the SPB procedure. Figure 5 roughly indicates that high PSI may be associated with different levels of RRI amplitude and there is no direct linear relationship between PSI and RRI amplitude. The results from both Table 1 and Fig. 5 demonstrated that phase coupling and amplitude modulation are two different aspects for CPC analysis. Phase dynamics can provide another inspection to the change of CPC for slow breathing exercise.

3.2 BP was lowered by the SPB procedure

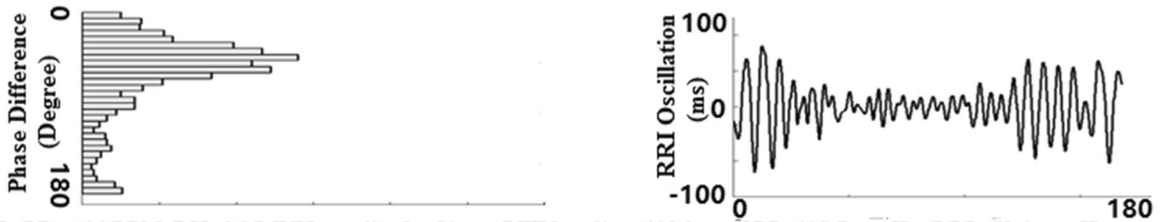
From Table 1, it can also be seen that the BP was reduced by the SPB procedure. The mean values of both the SBP and DBP decreased gradually with the reduction in breathing rate. There are statistically significant difference in SBP

Table 1 Variations of PSI, RRI amplitude, PTT baseline, SBP, DBP and the actual breathing rate during the SPB procedure ($n = 48$, and the results are presented as mean ± SD)

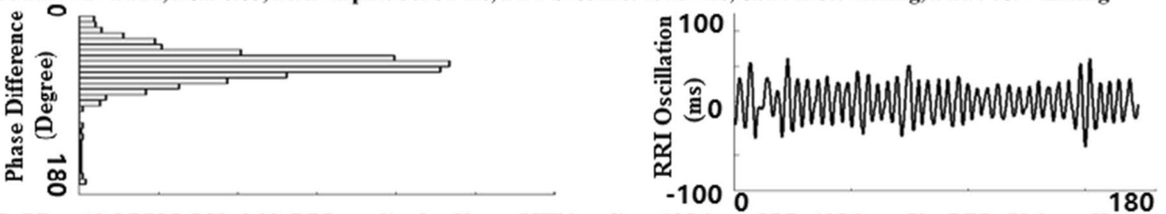
Variables	SPB procedure ($n = 48$)						
	SB	14 BPM	12.5 BPM	11 BPM	9.5 BPM	8 BPM	7 BPM
PSI	0.76 ± 0.12	0.81 ± 0.10	0.85 ± 0.09	0.87 ± 0.10	0.85 ± 0.12	0.81 ± 0.12	0.78 ± 0.18
RRI amplitude (ms)	47.4 ± 27.6	61.8 ± 31.2	64.9 ± 35.6	77.2 ± 37.4	89.1 ± 39.4	103.6 ± 41.8	113.5 ± 48.0*
PTT baseline (ms)	172.8 ± 20.1	170.8 ± 20.4	173.7 ± 20.5	175.4 ± 20.4	176.7 ± 20.3	177.2 ± 19.7	176.8 ± 19.2#
SBP (mmHg)	122.0 ± 13.4	121.5 ± 13.7	118.5 ± 14.2	116.5 ± 14.6	115.3 ± 14.9	114.6 ± 15.0	114.2 ± 14.9+
DBP (mmHg)	82.2 ± 8.6	80.7 ± 9.1	79.6 ± 9.2	78.6 ± 9.4	78.1 ± 9.5	77.5 ± 9.6	77.0 ± 9.8^
Breathing Rate (BPM)	16.2 ± 3.7	14.1 ± 0.2	12.2 ± 0.2	10.8 ± 0.1	9.1 ± 0.3	8.2 ± 0.4	7.5 ± 0.6

‘*’,’#’,’+’,’^’ Represent that there is a significant difference between the SB and PB at 7 BPM by paired t test, $p < 0.001$

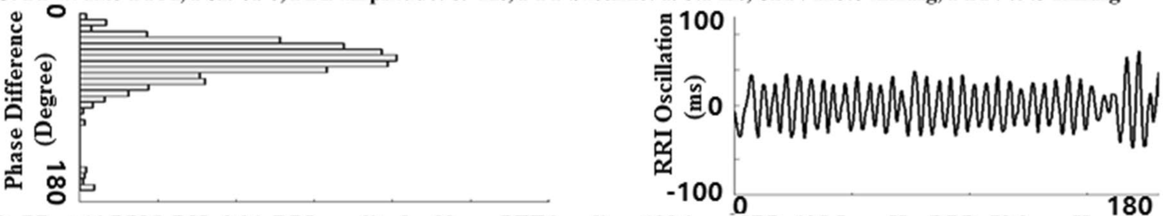
A: Spontaneous Breathing, PSI: 0.67, RRI amplitude: 44 ms, PTT baseline: 191.5 ms, SBP: 127.1 mmHg, DBP: 80.2 mmHg



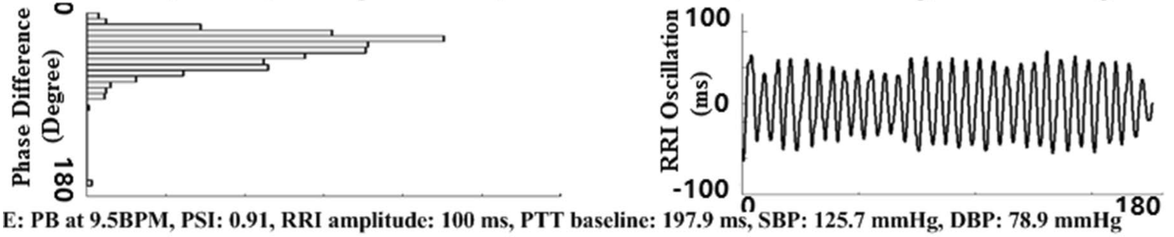
B: PB at 14 BPM, PSI: 0.85, RRI amplitude: 51 ms, PTT baseline: 192.2 ms, SBP: 125.7 mmHg, DBP: 78.4 mmHg



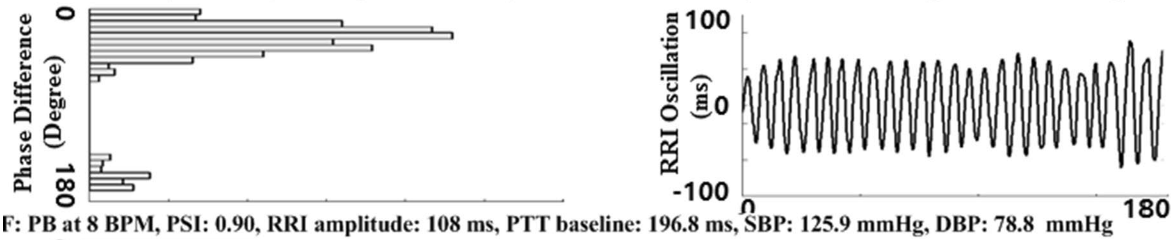
C: PB at 12.5 BPM, PSI: 0.90, RRI amplitude: 59 ms, PTT baseline: 195.1 ms, SBP: 125.8 mmHg, DBP: 79.3 mmHg



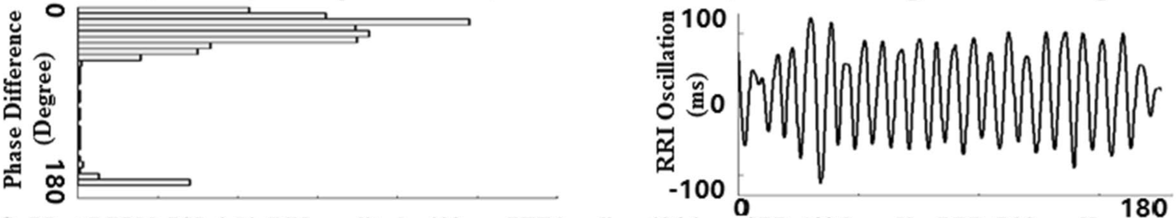
D: PB at 11 BPM, PSI: 0.94, RRI amplitude: 89 ms, PTT baseline: 198.1 ms, SBP: 125.5 mmHg, DBP: 79.3 mmHg



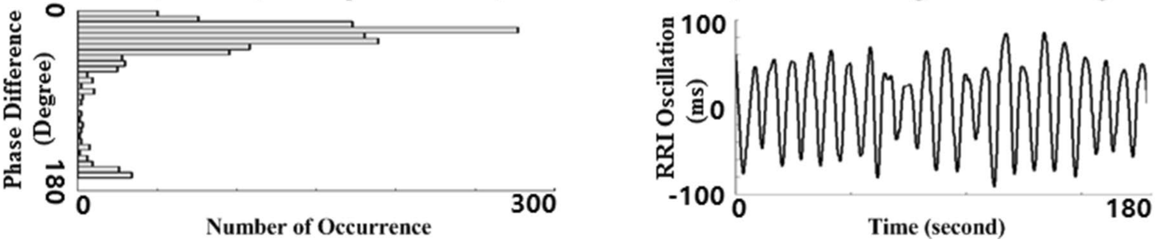
E: PB at 9.5BPM, PSI: 0.91, RRI amplitude: 100 ms, PTT baseline: 197.9 ms, SBP: 125.7 mmHg, DBP: 78.9 mmHg



F: PB at 8 BPM, PSI: 0.90, RRI amplitude: 108 ms, PTT baseline: 196.8 ms, SBP: 125.9 mmHg, DBP: 78.8 mmHg



G: PB at 7 BPM, PSI: 0.81, RRI amplitude: 122 ms, PTT baseline: 194.1 ms, SBP: 122.8 mmHg, DBP: 76.3 mmHg



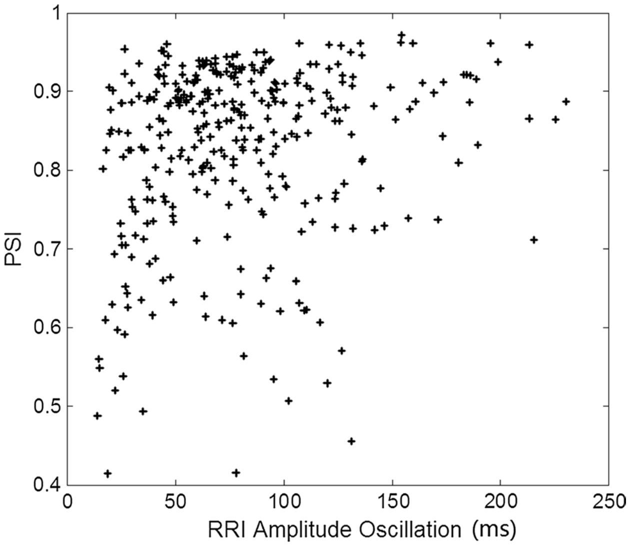


Fig. 5 Relationship between the PSI and RRI amplitude oscillation during the SPB procedure

(from 122.0 ± 13.4 to 114.2 ± 14.9 mmHg, $p < 0.001$) and DBP (from 82.2 ± 8.6 to 77.0 ± 9.8 mmHg, $p < 0.001$) between the SB and the PB section at 7 BPM.

An interesting phenomenon of PTT baseline lengthening was observed during the SPB procedure. There is a significant difference in PTT baseline between the SB section and the PB section at 7 BPM (from 172.8 ± 20.1 to 176.8 ± 19.2 ms, $p < 0.001$). As PTT is inversely proportional to BP [10, 41], the increase in the PTT baseline also suggests the beneficial effect of the SPB procedure to cardiovascular system.

Figure 6 shows an illustration of the variations of PTT, SBP and DBP during the SPB procedure (from the same subject with Fig. 4). The SBP procedure not only produced rhythmical oscillations in both PTT, SBP and DBP, but also exaggerated amplitude in oscillations. Furthermore, the baselines of PTT, SBP and DBP were also changed by the SPB procedure. Compared with the SB section, PB sections lengthened PTT baseline and decreased SBP and DBP.

3.3 The optimal frequency for slow breathing exercise to lower BP

The SPB procedure performed in this study provided a close insight into the changes of CPC, PTT and BP during slow breathing exercise. Some knowledge about the optimal frequency for slow breathing exercise can be derived from this procedure. The changes of SBP, PTT baseline, PSI and breathing regularity from the 48 subjects during the SPB procedure are shown in Fig. 7. It can be seen that both cardiorespiratory coherence (indicated by PSI) and breathing regularity were greatly improved and reached their maximums at 11 BPM section and then decreased gradually. In terms of cardiorespiratory coherence, 11 BPM is the optimal frequency for our paced breathing exercise to enhance the CPC and induce BP reduction. As CPC was improved by the SPB procedure, even though the cardiorespiratory coherence progressively deteriorated after 11 BPM, the cumulative effects of lowering BP and lengthening PTT were still sustained. Therefore, there were still slight changes in SBP and PTT baseline after 11 BPM.

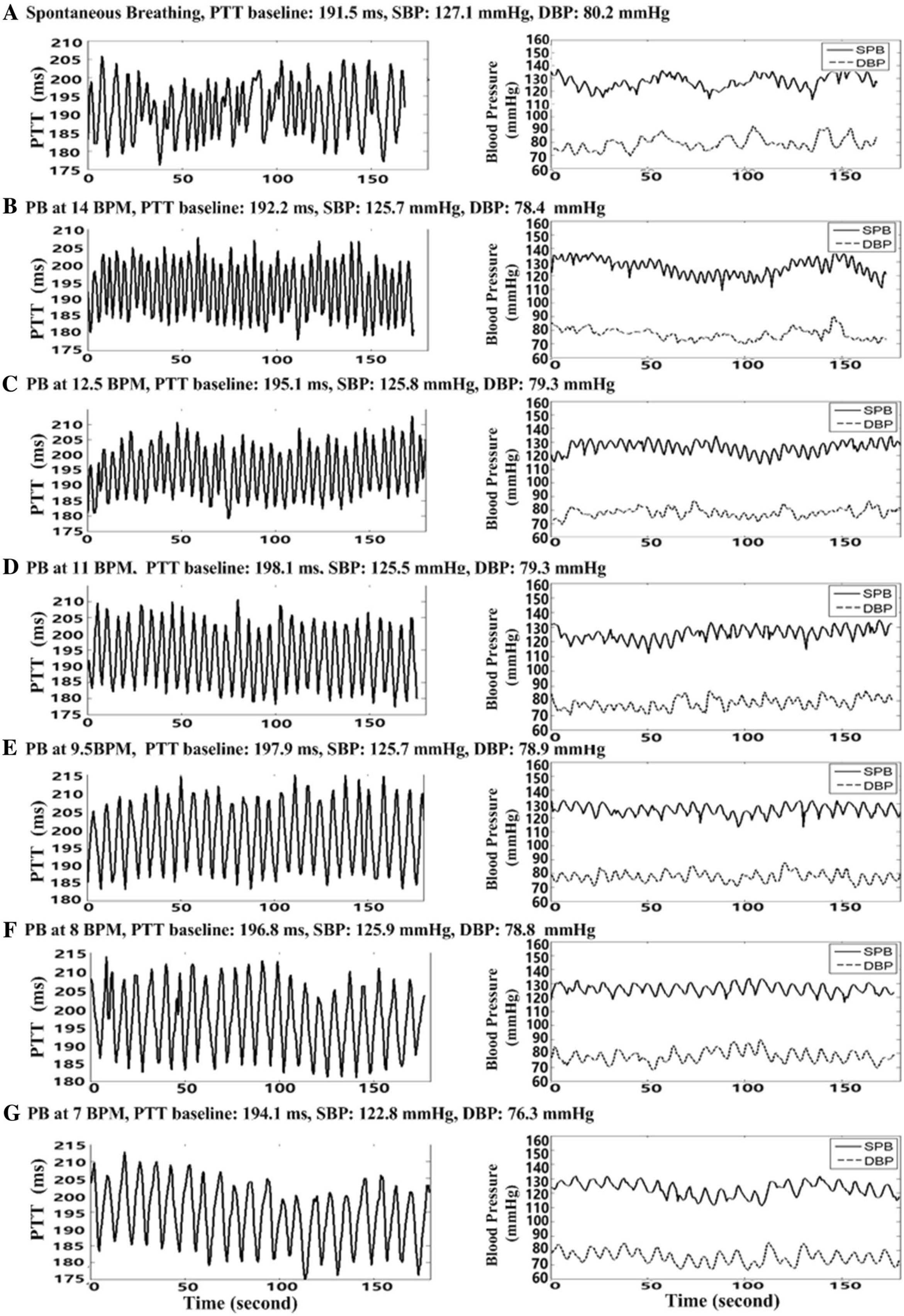
Generally, the changes of PTT baseline and BP during the SPB procedure show two distinctive phases: steady ascending and plateau. The PTT baseline gradually increased as the PB rate got lower and reached a plateau around 9.5 BPM. In terms of PTT baseline increasing, 9.5 BPM can be deemed as the optimal frequency for our paced breathing exercise. Considering the potential time delay between CPC augment and PTT baseline change, breathing rate around 10 BPM can be considered as the target breathing frequency for slow breathing exercise to generate beneficial effects on cardiovascular system.

4 Discussion

Prior work has documented the effects of slow and deep breathing on cardiovascular system, such as increasing the oscillatory amplitude of HR and BP [37] and reducing BP by cardiovascular reflex [15]. However, the change of phase coupling between cardiovascular and respiratory system during the SPB procedure has rarely been reported. The results presented in this study clearly indicate that the changes of phase coupling and amplitude oscillation show different patterns. In our protocol, the strength of phase coupling achieves the maximum at the PB rate of 11 BPM and then decreases gradually when breathing rate gets lower. Moreover, phenomena of PTT baseline increasing and BP decreasing were observed during the SPB procedure. There is a significant difference in both BP and PTT baseline between the SB section and the PB section at 7 BPM. Through our SPB procedure, several basic issues in practicing slow breathing exercises to benefit cardiovascular system were also investigated. To the best of our knowledge, this is the first study to investigate the changes of CPC, BP and PTT baseline, and the relationship between phase coupling and breathing regularity during a SPB procedure. Our findings provide evidence of how to practice slow breathing exercise to benefit cardiovascular system.

4.1 EEMD versus band-pass filter

This paper introduces a novel approach to investigate the CPC during the SPB procedure. Instead of using band-pass filtering approach [6], EEMD was applied to each



A Spontaneous Breathing, PTT baseline: 191.5 ms, SBP: 127.1 mmHg, DBP: 80.2 mmHg

B PB at 14 BPM, PTT baseline: 192.2 ms, SBP: 125.7 mmHg, DBP: 78.4 mmHg

C PB at 12.5 BPM, PTT baseline: 195.1 ms, SBP: 125.8 mmHg, DBP: 79.3 mmHg

D PB at 11 BPM, PTT baseline: 198.1 ms, SBP: 125.5 mmHg, DBP: 79.3 mmHg

E PB at 9.5BPM, PTT baseline: 197.9 ms, SBP: 125.7 mmHg, DBP: 78.9 mmHg

F PB at 8 BPM, PTT baseline: 196.8 ms, SBP: 125.9 mmHg, DBP: 78.8 mmHg

G PB at 7 BPM, PTT baseline: 194.1 ms, SBP: 122.8 mmHg, DBP: 76.3 mmHg

Fig. 6 Variations of PTT, SBP and DBP during the SPB procedure. **a** Spontaneous breathing, **b** PB at 14 BPM, **c** PB at 12.5 BPM, **d** PB at 11 BPM, **e** PB at 9 BPM, **f** PB at 8 BPM and **g** PB at 7 BPM

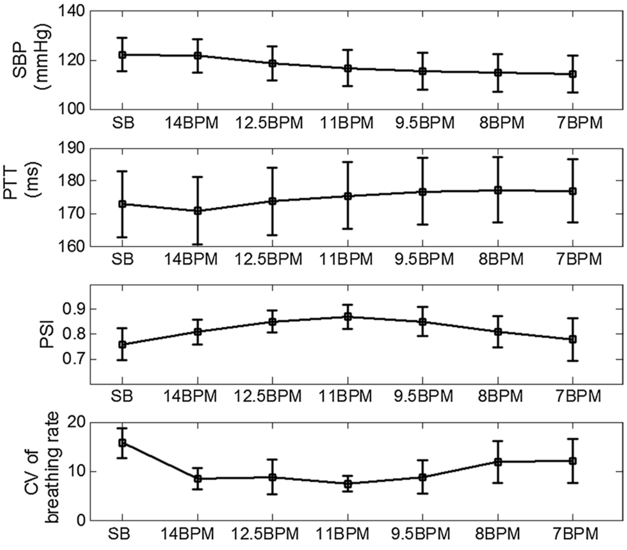


Fig. 7 Each *plot* represents the mean values with *error bars* representing the standard deviation

cardiorespiratory variable, decomposing the signal into a number of IMFs at different timescales. Compared with band-pass filter approach, EEMD approach offers an adaptive method to extract the information of interest. In our case, EEMD approach essentially functions as a band-pass filter with variable center frequency and bandwidth, selecting the respiratory IMF from the decomposed time series adaptively. Because lung ventilation is the driving force to the respiratory component residing in all cardiorespiratory variables, in each subsection, the IMF within the respiratory band was identified as the respiration-induced oscillation in each time series. Therefore, with this approach, respiratory component is fully determined by the data. This approach is especially important for phase coupling estimation, as band-pass filter tends to either overestimate or underestimate the phase dynamics if the filter bandwidth is too narrow or too broad, leading to spurious phase coupling [42, 43]. The approach of quantifying the amplitude and phase dynamics of CPC proposed in this paper can be used in other breathing conditions to investigate the CPC status, such as sleep, hypoxia, and on patients with certain cardiorespiratory diseases.

4.2 Phase coupling versus amplitude oscillation

Currently, the nature of cardiorespiratory interaction and its relation to mechanisms of neural control is not well understood. The relationship between phase coupling of respiratory and cardiac rhythms and respiratory modulation of heart rate has been studied in spontaneous breathing at rest and sleep, and it has been demonstrated that phase synchronization and respiration-induced RRI oscillation represent different aspects of the cardiorespiratory interaction [4, 32]. Our results show that the changes of phase and amplitude dynamics also exhibit different patterns during slow breathing exercise. In recent years, heart rate variability biofeedback, respiratory sinus arrhythmia (RSA) biofeedback or resonance frequency feedback has got substantial supports for a variety of disorders and for performance enhancement [18]. This form of cardiorespiratory feedback training tries to maximize RSA through beat-by-beat heart rate feeding back, without tracking the change of cardiorespiratory coherence. The results from our experiment indicate that there is another optimal breathing frequency within cardiovascular system in terms of cardiorespiratory coherence, rather than resonance frequency around 6 BPM. Phase dynamics can be used as another marker for cardiorespiratory feedback training. Compared with breathing exercise around 6 BPM, PB at cardiorespiratory coherent state around 11 BPM is easy to perform. Future work for this study is to conduct experiments to investigate which breathing frequency (resonance frequency around 6 BPM and coherence frequency around 11 BPM) can achieve better performance for biofeedback training.

4.3 PTT baseline change versus continuous BP monitoring

In our study, besides continuous BP measurement, PTT was also measured and employed as an outcome of the SPB procedure. As mentioned above, PTT used in this study is actually PAT, which consists of two components: the pre-ejection period (PEP) and PTT [23]. The PTT baseline changes (should be PAT_baseline in the strict sense) observed in this study actually reflect the changes in both PEP and PTT. A recent comprehensive review on PTT shows that PAT correlated well with SBP while showing some relationship to DBP [23]. Since ECG can be easily and robustly measured in practice, this method of approximating PTT is widely used. In short-term cardiovascular control, change of PEP and PTT is both reflections of sympathetic nervous activity [5, 31]. Therefore, PTT baseline can be used as a marker to represent the effects of slow breathing exercise on cardiovascular system, suggesting the suppression of the sympathetic nervous system activity and the reduction in BP. Compared with continuous BP measurement by CNAP Monitor 500, PTT is a cost-effective approach to reflect the change of BP for slow breathing exercise.

4.4 Implications to slow breathing exercise

The SPB procedure performed in our study is actually a simulation of slow breathing exercise with breathing rate changing from high to low. Therefore, the findings through this study provide insight into adopting slow breathing exercises to benefit the cardiovascular system.

4.4.1 The effectiveness of slow breathing exercise

In 2002, Resperate was approved by FDA (USA) as an over-the-counter device for non-pharmacological treatment of hypertension [22]. Many studies have been published in this area demonstrating the effectiveness of slow breathing on reducing BP [15, 35]. However, several recent studies suspected the effectiveness of this device to lower BP [1, 20, 22]. In our study, most of the subjects showed the phenomenon of BP reduction and PTT baseline increasing during the SPB procedure (87.7 % detected by PTT and 85.4 % detected by CNAP), which suggests that slow breathing exercise can generate the beneficial effect of reducing BP to cardiovascular system.

There might be certain confounding effect from the sedation of the volunteers on the decrease in blood pressure during the SPB procedure, which is not easy to be excluded. In our experiment, we have tried to reduce this confounding factor by requiring each subject to have 10 min of quiet rest and familiarization with the laboratory and instruments before each experiment.

Meanwhile, it is observed that both BP and PTT baseline changed to a certain level and remained almost constant in the SPB procedure, which means sympathetic tone or BP can only be reduced to a certain level with the PB technology.

4.4.2 The setting of target breathing rate

The change of phase coupling and breathing regularity, along with the pattern of PTT baseline and BP during our SPB protocol, provides evidence of the setting of the target breathing rate for slow breathing exercises. This result suggests that target breathing rate around 10 BPM is generally reasonable for PB technology to generate beneficial effects on cardiovascular system. As only healthy and young subjects were recruited in this experiment, whether this target breathing rate is applicable for elderly subjects and patients with cardiopulmonary diseases need to be investigated further. Moreover, our study provided indications of the setting of target breathing rate on average level; to achieve the best effects during the PB exercise, individualized target breathing rate should be used. If both cardiovascular and respiratory signals are recorded during slow breathing exercise, PSI can be used to induce individualized biofeedback effects. More work need to be done to test its effectiveness.

In this study, an SPB procedure with 6 PB rates in a sequence of [14, 12.5, 11, 9.5, 8 and 7] BPM was performed for each subject. The initial PB rate was set at 14 BPM based on our finding in a preliminary experiment that the average breathing rate for the enrolled subjects was around 14 BPM. Other study also took 14 BPM as a usual breathing rate for PB study [38]. The protocol of changing PB rate gradually is to make the subjects feel less stressed to follow the guided breathing rates during the whole experiment. The lowest PB rate in our study was set at 7 BPM. It could be preferred to decrease the breathing rate to the resonance frequency (6 BPM or less) [18] during the SPB procedure. However, the protocol with that low breathing rate would make the whole procedure rather long and would make it difficult to accurately follow the target breathing rhythm for a long time, especially at low breathing rates. It is worth pointing out that our study scheme is generic and can also adopt some other suitable PB protocols. In this work, our major research concerns about adopting slow breathing exercises to benefit the cardiovascular system, such as the setting of target breathing rate, change of CPC and the importance of regular breathing, can be effectively addressed by the adopted SPB protocol.

4.4.3 The change of cardiorespiratory coherence

Phase coupling between RRI and respiration provides information about cardiorespiratory coherence. From our study, it can be observed that the cardiorespiratory coherence increased to a higher level in the PB section than that in the SB section, but dropped when the PB rate was slower than 11 BPM. As all the subjects in our experiment had no experience of practicing slow breathing exercises, it is likely that for some subjects when the respiration slows down too much, it becomes challenging for cardiovascular system and respiration system to keep paced. Hence, PB becomes a stress to their cardiovascular system. That might help explain why some subjects even showed PTT baseline decreasing during the SPB procedure. This subtle change of cardiorespiratory coherence was detected by phase dynamics, but not by amplitude dynamics. Different from the amplitude oscillation, the cardiorespiratory coherence does not increase monotonically when the PB rate becomes lower. In terms of cardiorespiratory coherence, 11 BPM is the optimal frequency for our PB exercise to induce a maximum coherent state within cardiorespiratory system. Meanwhile, the BP was reduced and the PTT baseline was lengthened when the breathing rate changes from 14 to 11 BPM.

The findings in this study suggest that the cardiorespiratory coherence can be used as another marker for slow breathing exercise. When respiration and RRI are both monitored during biofeedback training, phase coupling can be used as an index to induce the beneficial effects on cardiovascular system, such as cardiorespiratory coherence, lowering BP and lengthening PTT baseline. When only heart rate is available, breathing around 10 BPM can be set as a target breathing rate for slow breathing exercise. It will be interesting to test the long-term effects of slow breathing on cardiorespiratory coherence in the future study.

4.4.4 The importance of regular breathing

Our study also provided evidence of the importance of regular breathing for slow breathing exercises. The relationship between the phase coupling and breathing regularity shows that cardiorespiratory coherence is largely associated with breathing regularity (shown in Fig. 7). This result is consistent with a prior report [42]. In our SPB procedure, all subjects were guided by a melody with two distinct tones to practice the slow and regular breathing, but breathing rhythm may still be disrupted by sudden change of mind or stress, or lose of concentration, leading to irregular breathing. The irregular breathing produced low cardiorespiratory coherence, which attenuated the effects of slow breathing on cardiovascular system. Figure 8 shows the relationship between the breathing regularity (assessed by CV on both breathing period and amplitude) and phase synchronization. It can be observed that breathing regularity has significant effect on phase coupling, a lower regularity (larger values of CV) largely corresponding to a lower PSI. In addition, from Fig. 8, it can also be seen that the periodic regularity is better than the amplitude regularity during the SPB procedure. This means the PB protocol used for slow breathing exercise is more effective in controlling the breathing rate rather than in dealing with the breathing amplitude. It should be noted that in this study respiration signal is the sum of rib cage and abdominal movement measured by RIP. It is necessary to include both rib cage and abdominal movement for breathing regularity and phase dynamics analysis, since different breathing patterns in rib cage and abdominal movement were observed from our subjects.

4.5 Limitations

Some limitations are worth noting. In our study, only healthy subjects were recruited for experiment. The changes of CPC, BP and PTT baseline for aging people and some patients with cardiorespiratory diseases during the SPB procedure need to be tested further. In addition, our study only shows the short-term effect of the SPB procedure on cardiovascular system. Long-term effects should be studied in the future, i.e., whether frequent practice of slow breathing can improve the cardiorespiratory coherence, and change the patterns of both PTT baseline increasing and phase coupling variations during the SPB procedure. Another aspect worth noting is the SPB procedure performed in our study. The SPB procedure is a simulation for slow breathing exercise to answer some questions on PB exercise, such as the PB technology to lower BP. Therefore, there was no short rest after each PB section and the protocol of PB rate was not randomized during the procedure. The duration of whole PB exercise is also relative long. For patients with cardiorespiratory diseases, a different SPB protocol with shorter duration might be used, or different protocol, such as using ramped-frequency breathing, can be used for different research purposes.

5 Conclusion

The results presented in this work clearly indicate that the SPB procedure leads to a high level of CPC for both phase and amplitude dynamics and that BP was lowered during the SPB procedure. The SPB protocol used in this study is a simulation of slow and regular breathing exercise. For healthy subjects, the SPB protocol performed in this study can be used to enhance CPC, generating larger RRI amplitude oscillations and stronger phase synchronization within a cardiorespiratory system. Meanwhile, BP can be lowered by this slow and regular breathing exercise.

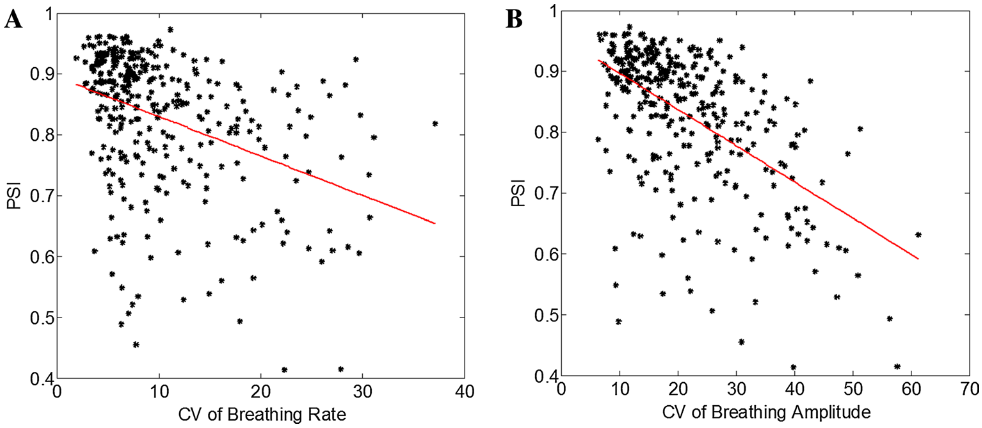


Fig. 8 Relationship between breathing regularity (assessed by on breathing rate and amplitude) and phase coupling. **a** PSI and breathing rate regularity (Pearson correlation coefficient = -0.62, $p < 0.01$); **b** PSI and breathing amplitude regularity (Pearson correlation coefficient = -0.58, $p < 0.01$)

Compared with RRI amplitude dynamics, phase dynamics can be deemed as another marker for CPC analysis in reflecting cardiorespiratory coherence during the slow breathing exercise. In our SPB procedure, breathing rate at 11 BPM produced the largest PSI, indicating the maximum coherent state in cardiorespiratory system. PSI can be used as a new marker for cardiorespiratory biofeedback training. Compared with breathing rate at resonance frequency around 6 BPM, PB at cardiorespiratory coherent state around 11 BPM is easy to perform. More work needs to be done to test the effectiveness of cardiorespiratory coherent biofeedback on cardiovascular system, as well as the usability of this technique on patients with cardiopulmonary diseases.

The findings in our study also provide a methodology to develop slow breathing techniques. Generally, breathing rate around 10 BPM is reasonable as the target breathing rate for slow breathing exercise. Cardiorespiratory coherence does not increase monotonically along with the RRI amplitude oscillation during slow breathing exercise. The relationship between breathing regularity and phase coupling also provides evidence about the importance of regular breathing for slow breathing exercise. Moreover, the PB protocol used for slow breathing exercise is more effective in controlling the breathing rate than in dealing with the breathing amplitude.

Acknowledgments This project was supported in part by the Natural Science Foundation of China (Grant Number: 61471398), Beijing Natural Science Foundation (Grant Number: 3122034), General Logistics Science Foundation (Grant Number: CWS11C108) and National Key Technology Research and Development Program (Grant Numbers: 2013BAI03B04, 2013BAI03B05).

Compliance with ethical standards

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

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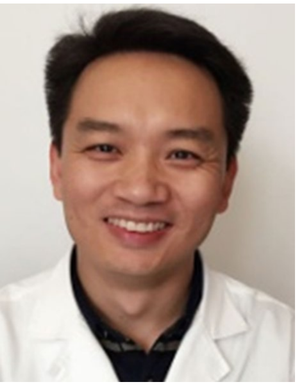

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