Estimation of Respiratory Rate using Pulse Transit Time under the Modulation of Cardiac Autonomic Nervous Activity

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***Abstract*—Respiratory rate (RR) is an important indicator of respiratory dysfunction, but its unobtrusive and accurate measurement can be challenging in many clinical situations. Pulse transit time (PTT) derived from routinely measured electrocardiogram (ECG) and photoplethysmogram (PPG), may provide a means for not only indirect monitoring blood pressure (BP), but also RR. This study explores the estimation of RR using PTT under the modulation of cardiac autonomic nervous activity and establishes a model to evaluate the regulation of respiration on BP using PTT. Spontaneous breathing patterns were recorded from 30 subjects undergoing various maneuvers influencing the autonomous nervous system regulation such as Valsalva maneuver, deep breathing, and sustained handgrip test. The number of breath ($RR_{\#}$), instantaneous RR (RR_{inst}) and RR obtained from the power spectral density (PSD) (RR_{PSD}) estimated from PTT were compared with those of the reference respiratory signal obtained from an inductive chest belt. The breathing pattern extracted from PTT correlated with the reference during all the maneuvers. The root mean square error of the $RR_{\#}$, RR_{inst}, and RR_{PSD} estimations were 1.58, 1.95, and 3.33 breaths/min, respectively. These findings demonstrate the potential use of PTT for continuous noninvasive and unobtrusive estimation of RR and suggest that the monitoring of primary cardiopulmonary vital signs (BP, heart rate, RR) is achievable with only two sensing modalities, i.e., ECG and PPG.**

***Index Terms*— Respiratory rate, pulse transit time, cardiac autonomic nervous activity.**

I. Introduction

RESPIRATORY rate (RR), defined as the number of breaths a person takes during one minute (breaths/min), is one of the four main vital signs including heart rate (HR), blood pressure (BP) and body temperature. RR varies in response to metabolic demand and the normal range of RR for an adult at rest is from 12 to 20 breaths/min. Elevated or reduced RR is an indicator of respiratory dysfunction [1, 2]. Real-time measurement of RR is an important instrument for assessing the severity of cardiopulmonary and other diseases. The most common and basic methods for RR assessment are through observation of chest wall movements or auscultation with a stethoscope. These methods provide only a snapshot of current situation rather than continuous measurement. They have been reported to be unreliable because of poor reproducibility in clinical settings [3]. Instrumental RR measurement methods, such as detection of respiratory gas variations (i.e. through flow, temperature, humidity, O_2 or CO_2) or mechanical effort measured with strain gauges or impedance, provide continuous and more reliable RR measurements. However, these methods can be obtrusive and cumbersome to apply, particularly for non-ventilated patients, hence their routine application is limited [4].

Noninvasive, continuous and reliable RR estimation techniques are thus highly desirable. Estimation of RR from noninvasively obtained physiological signals, such as electrocardiogram (ECG), photoplethysmogram (PPG), or arterial BP has been extensively studied [5, 6]. A common method for noninvasive RR measurement is to analyze HR variability (HRV) obtained from ECG/PPG signal.

Pulse transit time (PTT) refers to the propagation time of a pulse wave between two places in the cardiovascular system, and is a popular alternative marker for BP [7]. PTT is often derived from ECG and PPG, and also contains the respiratory components [8]. Hence, PTT has been applied to detect the respiratory events, as exemplified by Pitson *et al.* [9]. The authors find that as an indirect estimate of beat-to-beat BP, PTT can provide a noninvasive estimate of inspiratory effort as well as a measure of arousals that may benefit the management of obstructive sleep apnea. In addition, studies show the potential of PTT to evaluate respiratory effort associated with intrathoracic pressure changes [10, 11]. Johansson *et al.* has found correlations between PTT and RR under different BP levels [12], but only the relative variation of PTT with respiration was reported and RR accuracy was not quantitatively estimated. It remains unclear whether PTT can accurately estimate RR in clinical situations and provide a

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continuous and reliable RR. Our recent study utilized PTT as a measure of RR, and combined the estimation from PTT with estimations from HR interval and pulse rate interval [13]. This approach was validated on the CapnoBase dataset [14] and we demonstrated that PTT is promising for RR estimation in ventilated patients. However, the ability of PTT to estimate RR for spontaneous breathing remains unclear. In addition, the underlying mechanisms of PTT that root in respiration have not clarified in previous studies.

This study aims to explore the utilization of PTT for monitoring different breathing patterns and quantifying RR measurement with the modulation of cardiac autonomic nervous activity under spontaneous breathing. We propose a simplified closed-loop model to characterize the interrelationship among PTT, respiration and BP based on previous study, and experimentally validate the usage of PTT for RR measurement under different situations.

II. Closed-loop Modeling of the Regulation of Respiration on BP via PTT

In our recent study on PTT for RR estimation on ventilated subjects we demonstrated that PTT is able to track respiratory variation and estimate RR [13]. Therefore, we assumed that PTT is a function of respiration in term of the tidal volume change ΔV as given in (1), where the tidal volume is a measure of the amount of air breathed in and out in one breath cycle.

$$PTT \propto f(\Delta V) \tag{1}$$

Furthermore, the effect of respiration on BP, particularly systolic BP (SBP), depends on two aspects. The first is direct effect of respiration (DER) through the mechanical transmission of intrathoracic pressure to arterial BP. The other one is the change of stroke volume via respiratory-cardiac coupling in the form of respiratory sinus arrhythmia (RSA), and the circulation dynamics. These two factors as well as other intermediate factors on arterial BP are illustrated in Fig. 2.

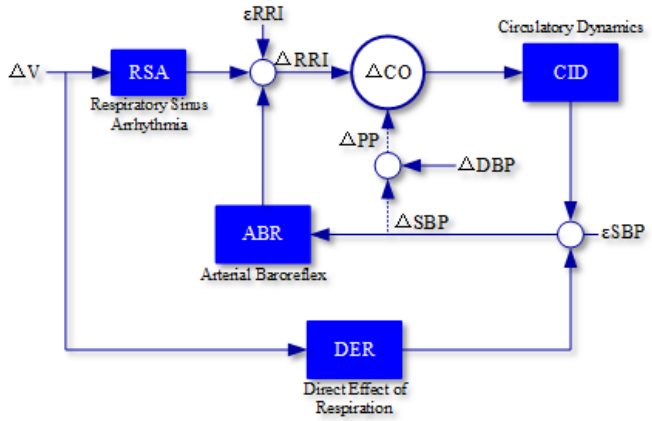

Fig. 2. Diagram of the interrelationships between respiration and blood pressure (BP). The respiration (represent by tidal volume change △V) impacts on BP on the one hand through the direct effect of respiration (DER), and on the other hand via the effect of circulatory dynamics (CID) underlying the interaction of respiratory sinus arrhythmia (RSA) and the feedback BP changes (adapted from the study [15]).

To characterize the interrelationships among respiration, PTT and BP, a simplified closed-loop model is presumed. The differential equations are derived based on the abovementioned two factors. That is, the fluctuations of SBP are attributable on the one hand to the direct effect of respiration (DER), and on the other hand to the indirect effect of circulatory dynamics (CID) that are caused by the HR variability (ΔRRI). The central and peripheral changes were interrelated and evidence is presented that the latter are due to the effects of intrathoracic pressure upon cardiac filling [16]. Based on these facts, the changes in SBP are modeled by the following equation.

$$\begin{aligned}\Delta SBP(n) = &\sum_{i=0}^{M} H_{DER}(i,n)\cdot PTT(n-i) \\ &+ \sum_{i=0}^{M} H_{CID}(i,n)\cdot \Delta CO(n-i-\tau_{CID})\end{aligned} \tag{2}$$

Here, H_{DER} and H_{CID} are the transfer function of the direct effect of the respiration and the circulatory dynamics, respectively; △CO is the change of cardiac output caused by the heart rate variability (△RRI) and changes in PP, and they are interconnected with the equation: △CO=△PP/△RRI; τ_{CID} is the time delay in the peripheral circulatory system.

On the other hand, RRI is under the modulation of respiration due to RSA mechanism caused by the coupling of the respiratory system and the cardiac system, and the influence of the arterial baroreflex (ABR) mechanism subjected to the arterial BP. As a result, the change of RRI can be modeled by :.

$$\begin{aligned}\Delta RRI(n) = &\sum_{i=0}^{M} H_{RSA}(i,n)\cdot PTT(n-i-\tau_{RSA}) \\ &+ \sum_{i=0}^{M} H_{ABR}(i,n)\cdot \Delta SBP(n-i-\tau_{ABR})\end{aligned} \tag{3}$$

In (3), the H_{RSA} and H_{ABR} represent the transfer function of the RSA system and the ABR system, and τ_{RSA} and τ_{ABR} are the time delay in the RSA and ABR system.

III. Experiment

A. Subject and Experimental Procedure

The cardiac autonomic nervous experiment was conducted on 30 subjects, including 18 healthy subjects without history of cardiac and respiratory diseases (10 male, 24.8±2.3 years) and 12 patients with different stages of hypertension (10 male, 67.8±8.8 years). All the subjects volunteered to participate and gave their informed consent before taking part in this study. The study was approved by the Institutional Review Board of the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee, Hong Kong, China.

One-lead ECG electrodes were placed on the chest of the subjects and the PPG signal was obtained from the left index finger. Continuous BP was recorded by Finometer (FMS, Amsterdam, Netherlands) with the finger cuff placed on the left

middle finger and the calibration cuff on the left upper arm. Respiratory effort was measured using a respiration monitoring belt (Vernier Software & Technology). All signals were recorded simultaneously at a sampling rate of 1000 Hz.

The experimental protocol involved the acquisition of the signals at different body positions and during different maneuvers regulating the respiratory and cardiac system through the autonomous nervous system. For each subject, data was collected in order: 1) supine, 2) from supine to active standing (AS), 3) sitting at rest, the maneuvers while sitting 4) deep breathing (DB), 5) Valsalva maneuver (VM), and 6) sustained handgrip (HG) test, 7) supine after maneuvers (Fig. 1). The maneuvers included are commonly used in clinics to assess cardiovascular autonomic function [17]. AS was performed 5 min after rest at supine, when the subject was asked to stand up from the supine position and to remain in the standing posture for 3 min. The cyclic DB was performed for 2 min with controlled breathing rate of six breaths/min, with 30s inspiration and 30s expiration in each breath cycle; VM performed with moderately forceful attempted exhalation against a closed airway for 20s; and HG was conducted with continual handgrip at one third of the subject's maximal strength for 90s.

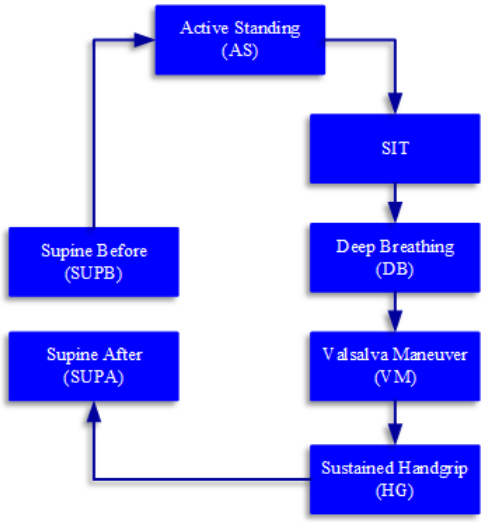

Fig. 1. Diagram of the experiment protocol.

B. Respiratory Rate Measurement

PTT was calculated as the time interval between R peak of ECG signal and maximal upslope of PPG signal for every cardiac cycle [18]. Since PTT is an intermittent variable, it was interpolated with a spline function to 1000 Hz. The interpolated PTT was segmented into 60 s windows with a sliding window of 30s (50% overlap). For each window we derived the number of breaths in one minute ($RR_{\#}$), the instantaneous RR (RR_{inst}) and the RR that derived from the maximum peak of the power spectral density (PSD) (RR_{PSD}), where the PSD was calculated using Welch's method. $RR_{\#}$ was calculated by automatically counting the number of peaks in a window using adaptive threshold method. RR_{inst} was measured as the average instantaneous rate for each window, where the instantaneous rate was calculated as the time interval between two peaks divided by 60. The corresponding reference RRs were calculated from recorded respiratory signal using the same method.

C. Data Analysis

The performance of the RR estimation was evaluated against the RR measured from the reference respiratory signal. The root mean squared error (RMSE) and mean absolute error (MAE) were calculated. A Bland-Altman plot was used to analyze the agreement between the estimated and the reference RR. A paired-Sample Wilcoxon Signed Rank Test was used to test the significance level when comparing the performance for different maneuvers. Boxplot was plotted to check the estimation errors of different maneuvers. The significance level was tested with the Kruskal-Wallis ANOVA test, with p values less than 0.05 being considered as statistically significant.

IV. Results

A. Variations of BP, PTT and Respiration

Continuous BP varied during each cardiac cycle and oscillated with respiration from inspiration to expiration in each breath cycle (Fig. 3). The oscillation pattern, as depicted by the envelope of SBP, varied depending on different positions and maneuvers. It can be observed that the fluctuations in arterial BP were relatively stable for different postures while at steady state, i.e., supine and sitting (Fig. 3 (a, e)). In contrast, the oscillations during hemodynamic transients induced by various maneuvers were more dramatic. During DB (Fig. 3b), the amplitude of BP increased about 20 mmHg during inspiration. The opposite changes occurred during expiration. The variation pattern of SBP was similar to the respiratory signal. For AS, during the transition from supine to standing as shown in Fig. 3c, SBP abruptly increased due to increase of cardiac output, whereas the pressure in the respiratory belt increased because of the position transition. At steady state while standing, BP recovered to a stable level that was slightly higher than that at supine state, and varied moderately with respiration. For VM, there were four stages of variations in SBP (Fig. 3d), i.e., increased at stage I then diminished at stage II, with another dip at stage III and finally increased and recovered to normal state. Respiration halted at this stage because VM was performed against a closed airway. Compared with VM, there were no obvious changes in SBP during sustained HG (Fig. 3f).

Variations of PTT and SBP with respiration were further delineated in time and frequency domain. The interpolated PTT, interpolated SBP as well as the respiratory signal with their corresponding PSD are shown in Figs. 4-9 for different positions and different maneuvers. For variations of PTT, SBP and respiration in time domain (left panel of Fig. 4-9), the interpolated PTT altered during each breath cycle for all different postures and maneuvers, and varied in phase with the respiration, increasing during inspiration and decreasing during expiration. All these changes were reversed for SBP. At rest while supine and sitting (Fig. 4 and Fig. 6), PTT varied relatively slowly compared with that under dynamic conditions. Particularly for AS and VM (Fig. 5 and Fig. 8),

there were steep variations due to transient changes in position and in the airway. For DB (Fig. 7), it may be observed that the variation pattern of PTT was similar to respiratory variation, with increased amplitude during expiration and decreased during inspiration. Whereas, variation pattern of SBP was opposite to that of respiratory variation. Aside from the variation with respiration cycle, there was slight baseline shift in PTT.

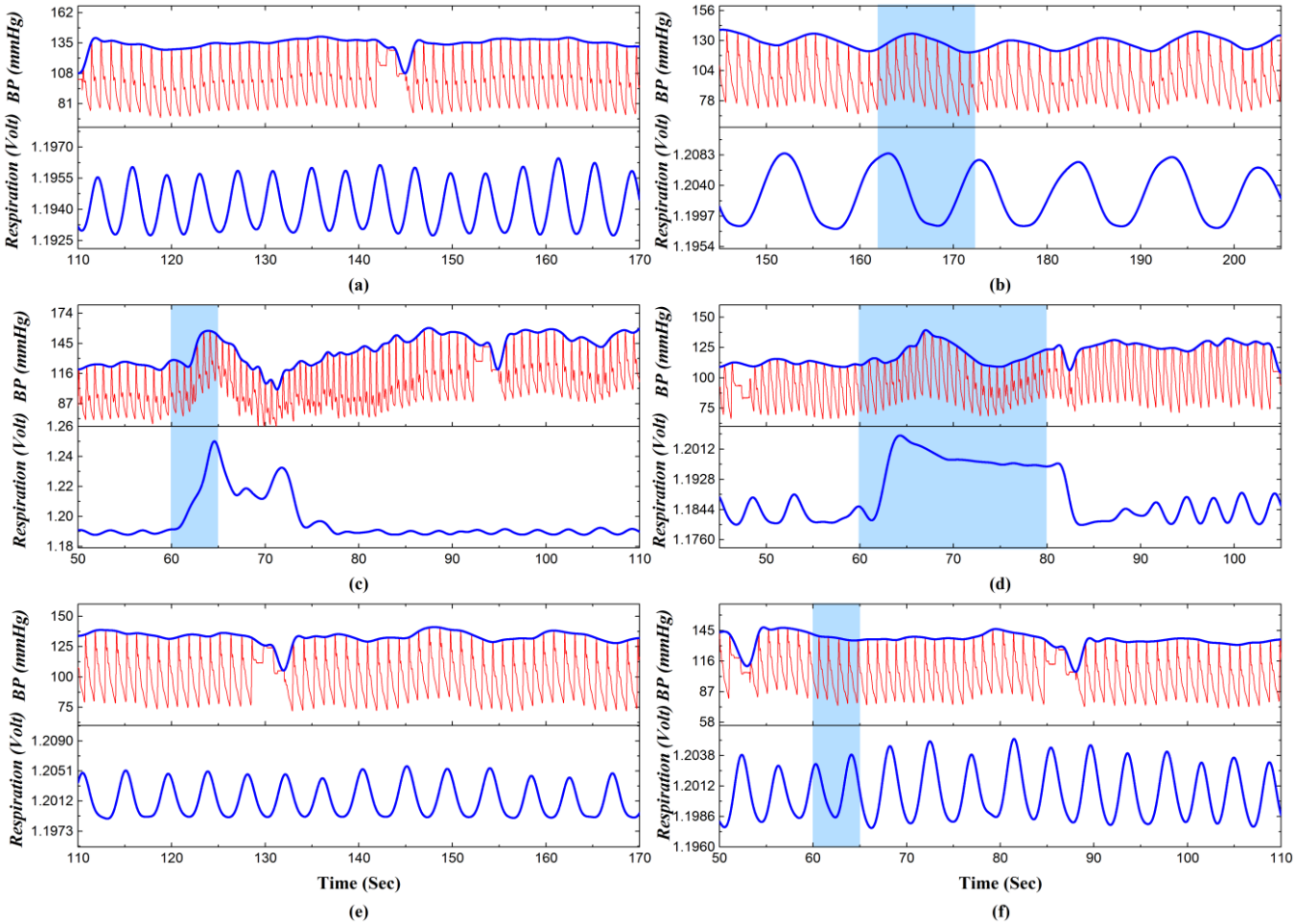

Fig. 3. One representative continuous blood pressure (BP) and respiration signal at different positions (left panel, a: supine, c: active standing, e: sitting) and different maneuvers (right panel, b: deep breathing (DB), d: Valsalva maneuver (VM), f: sustained handgrip (HG)).

In the spectral domain (right panel of Fig. 4-9), the reconciled variations can be observed in PTT and SBP around 0.4 Hz – the respiratory frequency for supine at rest (Fig. 4).

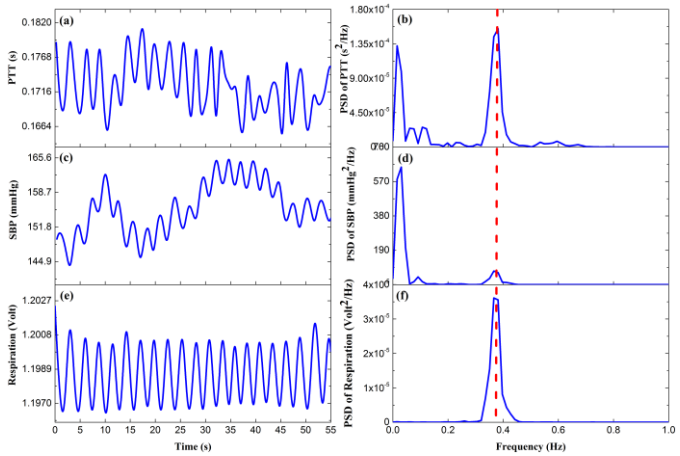

Fig. 4. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiration signal (e), and their corresponding spectrum (b, d, f) at supine.

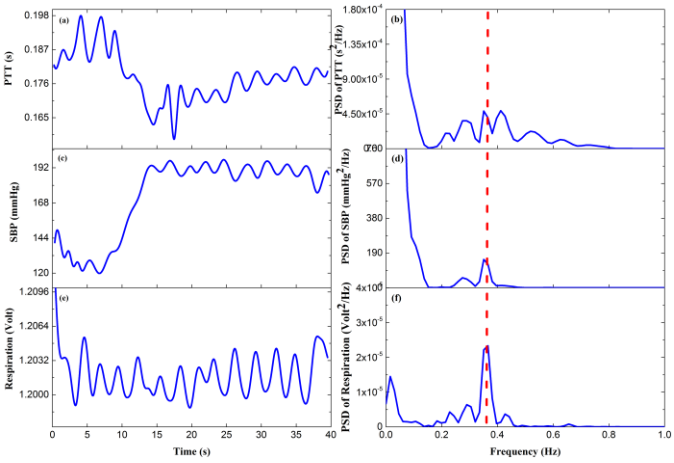

Fig. 5. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiration signal (e), and their corresponding spectrum (b, d, f) at active standing (AS).

Furthermore, slower variations are present in PTT and SBP. In particular, substantial spectral power was present in low

frequency bands of SBP. For AS shown in Fig. 5, there was transient elevation in SBP immediately after the transition from being supine to standing; meanwhile PTT tended to drop. During steady state in standing position, PTT and SBP varied with respiration.

For sitting at rest (Fig. 6), variations were akin to those observed during supine, where PTT oscillated at respiratory frequency, whereas SBP oscillated at a low frequency range. For DB (Fig. 7), PTT varied in line with SBP, with their spectra predominant at the controlled breathing rate at 1 Hz.

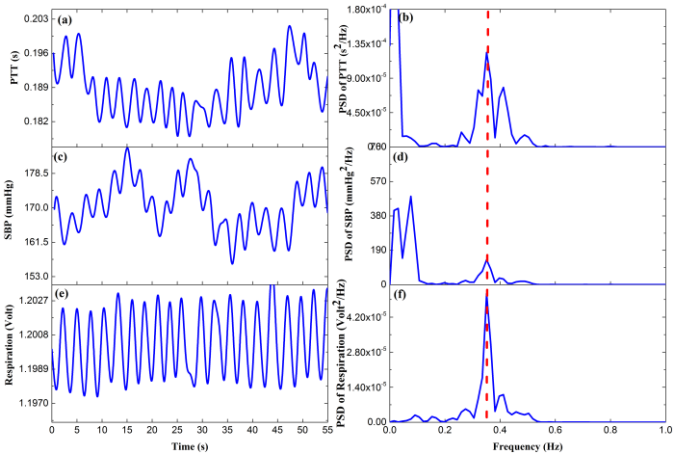

Fig. 6. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiratory signal (e), and their corresponding spectrum (b, d, f) while sitting at rest.

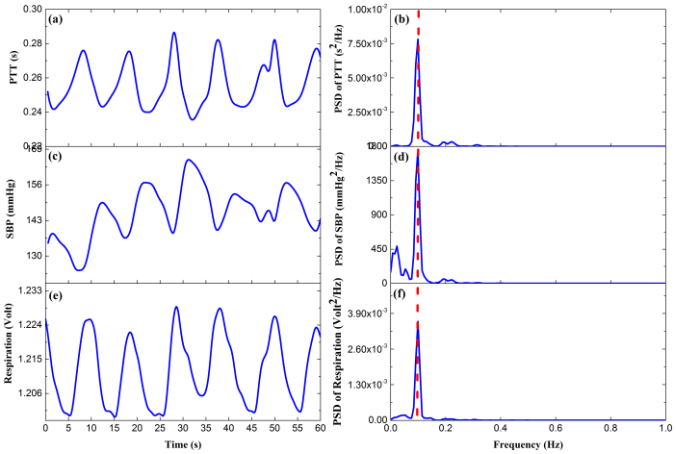

Fig. 7. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiration signal (e), and their corresponding spectrum (b, d, f) during deep breathing (DB).

While for VM (Fig. 8), as expected, there was no respiration during this process, as shown in Fig. 8c. At different stages during VM, SBP slightly increased then abruptly decreased, increased again and finally returned to normal range, meanwhile PTT demonstrated almost the opposite change compared to SBP. This may be why they revealed less power at the respiratory frequency.

As shown in Fig. 9, sustained HG seems to have little influence on respiration, though there were slow variations on SBP. According to the PSD of SBP, low frequency variation was more remarkable than the respiratory frequency with PTT dominant at respiratory frequency.

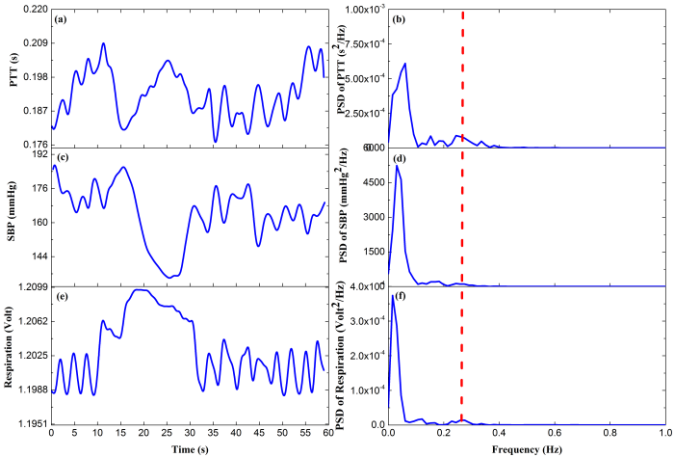

Fig. 8. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiration signal (e), and their corresponding spectrum (b, d, f) during Valsalva maneuver (VM).

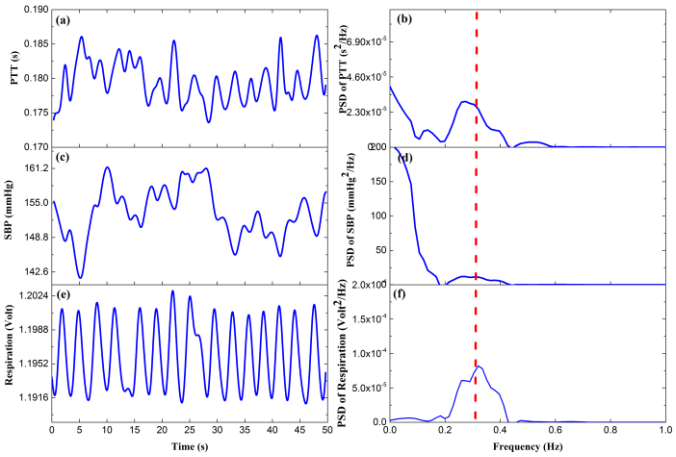

Fig. 9. Time series of interpolated PTT (a), interpolated SBP (c), continuous respiration signal (e), and their corresponding spectrum (b, d, f) during sustained handgrip (HG).

B. RR Estimation with PTT

There were a total of 763 PTT data windows for RR estimation. The estimated RR from PTT agreed closely with the reference RR measured from respiratory signal acquired with the respiratory belt. For $RR_{\#}$ and RR_{inst}, the 95% limit of agreements fell within the range -3.38 to 2.70 breaths/min and from -4.27 to 2.91 breaths/min, respectively (Fig. 10). For RR_{PSD}, the performance was lower with ranged limit of agreement from -6.72 to 6.34 breaths/min. The mean error (estimation bias) for these three parameters were -0.34, -0.68, and -0.19 breaths/min, respectively (Fig. 10).

The estimation of $RR_{\#}$ achieved the lowest RMSE and MAE (Table 1), confirming the observation from the Bland-Altman plots the error from the PSD estimation was higher than the two other estimations.

TABLE I
ESTIMATION ERROR OF RESPIRATORY RATE (RR) USING PULSE TRANSIT TIME (PTT)

	RR parameters (breaths/min)		
	$RR_{\#}$	RR_{inst}	RR_{PSD}
RMSE	1.58	1.95	3.33
MAE	1.06	1.26	1.64

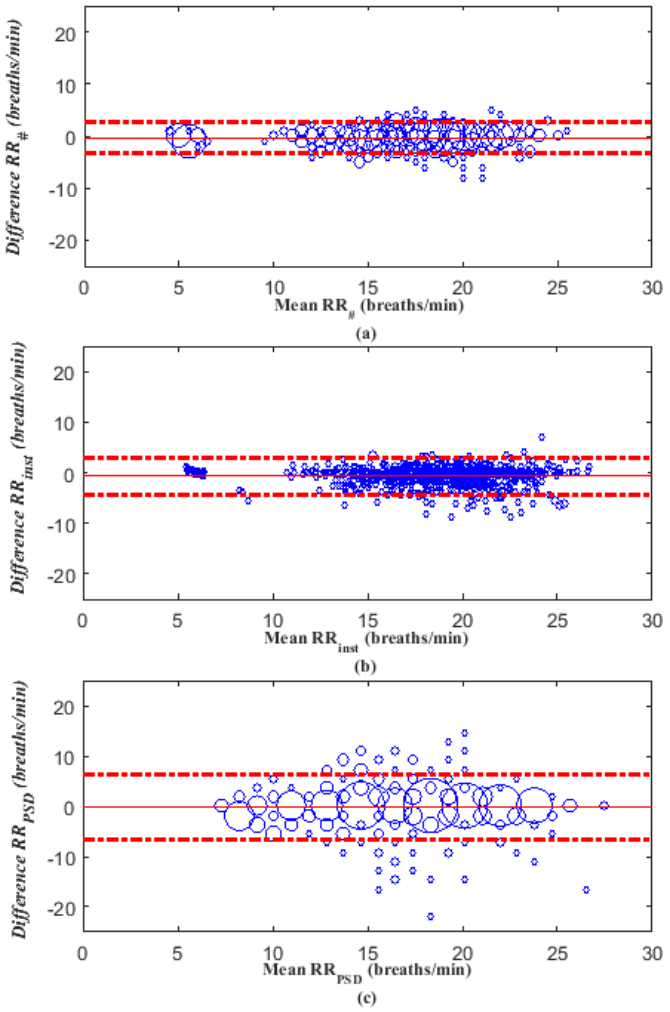

Fig. 10. Bland-Altman plot of differences between RR estimation with PTT method and reference method vs. the mean of these two measurements, with the representation of the limits of agreement (dashdot line) for (a) $RR_{\#}$, (b) RR_{inst}, and (c) RR_{PSD}.

C. Performance of RR Estimation with PTT for Different Positions and Maneuvers

The performance of RR estimation with PTT varied significantly between maneuvers, but showed only minor differences between posture transitions (Fig. 11). There was significant higher error of RR_{PSD} for DB and VM compared with sitting state. Estimation error was significantly reduced during DB for $RR_{\#}$. Error for VM and HG for RR_{inst} was significantly higher (Fig. 11b).

The estimations of $RR_{\#}$ and RR_{inst} were most accurate for DB, and least accurate for VM compared with other states (Table II). However, for RR_{PSD}, estimation error was lowest while supine compared to the highest for VM.

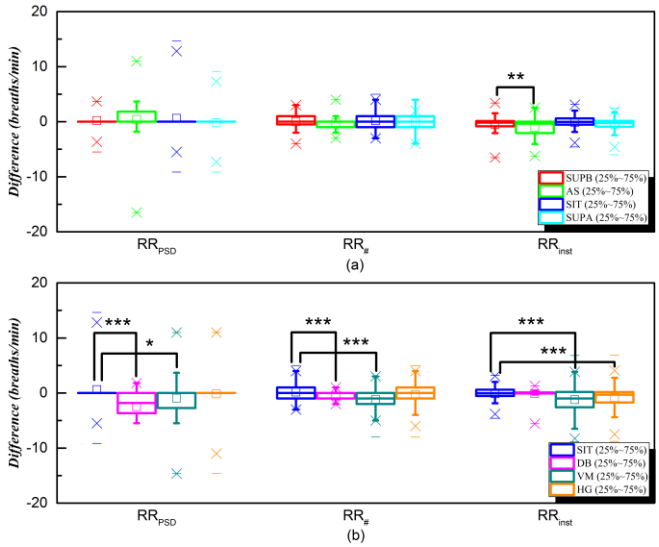

Fig. 11. Boxplots of the estimations for (a) different positions and (b) maneuvers. *, **, and *** represent significant level at $p<0.05$, $p<0.01$ and $p<0.001$.

TABLE II
ESTIMATION ERRORS OF RESPIRATORY RATE (RR) BY PULSE TRANSIT TIME (PTT) FOR DIFFERENT POSITIONS AND MANEUVERS

		SUPB	AS	SIT	DB	VM	HG	SUPA
$RR_{\#}$	RMSE	1.35	1.41	1.27	0.81‡	2.27‡	1.66	1.24
	MAE	0.88	0.98	0.85	0.63	1.79	1.02	0.88
RR_{inst}	RMSE	1.83	2.10	1.28	0.99‡	2.73†	2.19*	1.36
	MAE	1.11	1.46	0.88	0.37	2.10	1.46	0.88
RR_{PSD}	RMSE	1.46	3.86	3.15	4.29‡	5.10*	3.25	2.16
	MAE	0.74	1.87	1.42	2.69	3.14	1.55	0.90

With SIT as control: *$p<0.05$, †$p<0.01$, ‡$p<0.001$

V. DISCUSSION

In this study we investigated the effect of changes in the autonomous nervous system on the estimation of RR from PTT. We demonstrated high accuracy of continuous RR measurements using PTT at rest and under the modulation of different cardiac autonomic nervous activities.

Estimating PTT for estimating $RR_{\#}$ and RR_{inst} was less prone to errors than RR_{PSD}. They had lower limits of agreement and were more robust during the performed different maneuvers. This could be because PSD monitors a full 60 s window and can accommodate less well large changes in RR frequency which is common in spontaneous breathing. The PTT method had particularly low RMSE when the DB maneuver was conducted. This may be due to a stronger modulation of RSA under controlled breathing. This was consistent with findings reported by other studies, where a strong relationship between PTT changes were observed under paced respiration [8].

Validation of RR changes induced by cardiac autonomic nervous activities further demonstrated that PTT has potential to track various breathing patterns and estimate RR with acceptable accuracy. Because these activities work to induce

the nervous regulation of cardiac system and further to affect the interaction between the respiratory and cardiac system. As indicated by equation (1) and (2), BP changes in response to different activities through direct effect of respiration and the circulatory dynamics. Therefore, its respiratory component represented by PTT also changes. The observed RR changes monitors by PTT confirms that during different situations this is the case.

Irrespective of the differences in subjects compared with our prior study [13], the RMSE for the estimated $RR_{\#}$ (1.58 breaths/min) and RR_{inst} (1.95 breaths/min) using PTT alone were better than estimations by combining PTT, HR interval and pulse rate interval. However, the estimation of RR_{PSD} was not accurate enough. One possible reason could be the introduction of different maneuvers, especially AS and VM, which caused the slow variation with frequency range lower than the respiratory frequency, and further affected the detection of the spectrum peak.

RR estimations by PTT was minimally affected by different postures. This suggests that the regulation of respiration on BP is quite stable at different positions although BP varied during the posture transitions. Marked estimation error for RR_{inst} during AS and VM was partly due to the immediate change of PTT during the posture change thereby affecting the accuracy of peak detection of the interpolated PTT signal. Compared with the influence of different positions, the maneuvers had a more marked influence on the estimation performance, notably in VM and DB. This can be explained by the sympathetic and parasympathetic nervous regulations induced by VM and DB, which caused the frequency diversion of PTT thereby the energy of the respiratory frequency band was reduced. This further leads to the inaccurate detection of the dominant spectrum and the peak of the signal in time domain.

There were several limitations of this study. First, this study highlighted the relationship of PTT and respiration in frequency domain. However, the possible relationship between the amplitude of PTT with that of the respiration has not been studied. Further studies are warranted to investigate the relationship between PTT amplitude and tidal volume. In addition, the reference respiratory signal was recorded by the respiratory belt wrapped around the belly that might not exactly represent the thoracic respiration. Another limitation concerns the physiological model which is proposed to explain the role of respiration on regulation of arterial BP by means of PTT, whereas the verification of the model would be of interest for future study.

VI. Conclusion

We investigated the usage of PTT for RR estimation under the modulation of cardiac autonomic nervous activity. We demonstrated that PTT varied with respiration in each breath cycle, and it achieved promising accuracy for estimating RR. In particular, PTT can accurately track RR under controlled breathing rate. Potential application of PTT included continuous and unobtrusive measurement of RR for diagnosing and monitoring respiratory dysfunction. The proposed simple closed-loop model describing the regulation of respiration on BP via PTT has important implications for understanding the regulation of respiration on BP, and offer insight into the indirect measurement of BP.

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