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Model-based assessment of cardiopulmonary autonomic regulation in paced deep breathing

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ABSTRACT

Autonomic dysfunction can lead to many physical and psychological diseases. The assessment of autonomic regulation plays an important role in the prevention, diagnosis, and treatment of these diseases. A physiopathological mathematical model for cardiopulmonary autonomic regulation, namely Respiratory-Autonomic-Sinus (RSA) regulation Model, is proposed in this study. A series of differential equations are used to simulate the whole process of RSA phenomenon. Based on this model, with respiration signal and ECG signal simultaneously acquired in paced deep breathing scenario, we manage to obtain the cardiopulmonary autonomic regulation parameters (CARP), including the sensitivity of respiratory-sympathetic nerves and respiratory-parasympathetic nerves, the time delay of sympathetic, the sensitivity of norepinephrine and acetylcholine receptor, as well as cardiac remodeling factor by optimization algorithm. An experimental study has been conducted in healthy subjects, along with subjects with hypertension and coronary heart disease. CARP obtained in the experiment have shown their clinical significance.

1. Introduction

Autonomic nervous system (ANS) is closely related to the body's regulation of urinary, circulatory, and cardio-respiratory activity of human beings. The assessment of ANS regulation has got much attention from researchers [1]. Respiratory sinus arrhythmia (RSA) represents a particular physiological phenomenon of cardiopulmonary interaction under the regulation by ANS, that is, how breathing stimulates the sinoatrial node to regulate the heart rate through neural response [2]. The RSA measurement is regarded as an assessment of circulation system efficiency, as well as a biomarker of cardiac vagal tone and well-being [3].

HF in HRV has been considered as an RSA activity measurement using the heart rate variability in frequency domain from 0.14 Hz to 0.5 Hz [1,4]. However, as the phenomenon of cardiopulmonary interaction, RSA is closely related to the breathing condition of people. To derive a quantitative measure for RSA, researchers began to focus on the interaction of respiration and heart rate. For example, Gisler, Porta, and Fonoberova use the transfer function of heart rate and respiration in the frequency domain [5–7]. Dong F and Lee calculate the RSA assessment by circuit. Inhale and exhale are simulated as the changes in AC power supply, while LC oscillating circuit is used to simulate lungs function. The control gain of the circuit is taken as the measure of RSA in their research [8,9]. Buchner uses resonator as the representative of cardiopulmonary coupling [10]. In this study, the phase difference between respiration and heart rate has been analyzed, yet RSA has not been quantitative assessed. We proposed Cardiopulmonary Resonance Indices (CRI) as a quantitative measure of RSA with Granger causality [11]. CRI has demonstrated great potential in clinical applications [12]. All these studies measured RSA as a cardiopulmonary coupling state. Though circumventing the complexity of the physiological process of RSA, these assessments might be biased and rough due to the lack of comprehensive physiological basis.

Physiological mechanism models express the physiological process of cardiopulmonary regulation. Lung Volume Model describes the effect of respiratory changes on venous return and cardiac output [13]. The arterial baroreceptor and lung stretch receptor are taken into account. The spectral correlation analysis between respiratory signal and heart rate is used for ANS assessment in this study [14]. Peripheral Mechanism Model comprises the central, chemical, and mechanical properties of

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ANS regulation. The model was proposed in 1987 [15], and the equation of respiration was added in 2016 [16]. The neural output is simulated as the near-linear relation with the respiratory wave. The model uses the change of blood pressure as a single index for the evaluation of ANS, overlooked deeper physiological process parameters.

In these studies, the assessments and parameters of cardiopulmonary regulation have not been able to reveal the whole intrinsic characteristics of autonomic nerve because they are not fully linked with individual RSA procedure. More importantly, the sensitivity of the heart's response to neural regulation and the pathological change of heart have not been taken into consideration. Therefore, it's necessary to build a comprehensive physiopathological model for cardiopulmonary autonomic regulation with detailed regulation process parameters.

Under the paced deep breathing scenario at the rate of 6–9 times per minute, heart rate variations can be considered mainly caused by respiration through autonomic regulation [17–19]. Thus, we design a strict breathing control experiment to assess the cardiopulmonary autonomic regulation by observing heart rate and respiratory signals at the same time. Respiratory-Autonomic-Sinus regulation Model (RASM), a mathematical model for cardiopulmonary autonomic regulation, is proposed in our study. A series of differential equations are used to simulate the whole process of RSA. RASM consists of the following cardiopulmonary autonomic regulation parameters (CARP): sensitivity of sympathetic parasympathetic nerves and the time delay of sympathetic nerve, which define the nerves output for a given respiration signal strength; cardiac remodeling factor, a pathological parameter which defines the ill-condition of sinoatrial node caused by chronic diseases, presented as the bias of resting heart rate; and norepinephrine (nor) and acetylcholine (ach) receptor sensitivity. The CARP is calculated by solving RASM via an optimization algorithm, using electrocardiograph (ECG) and respiration signals as the input and output of the RASM. The preliminary experimental results have shown the clinical significance.

In the rest of this article, the second section introduces the physiopathological mathematical model: Respiratory-Autonomic-Sinus regulation Model. The physiological processes of the regulation of the cardiopulmonary system and the mathematical expression are described in this section. The methods of optimizing CARP are described in the third section. The fourth section elaborates the experimental design and the data selection of this study. The assessment results of healthy subjects, patients with hypertension, and coronary heart disease (CHD) patients are presented in the fifth section. In the discussion section, clinical significance of CARP is described. The last section is the conclusion of this study.

2. The physiopathological mathematical model: Respiratory-Autonomic-Sinus regulation Model (RASM)

2.1. Physiological process of cardiopulmonary modulation in paced deep breathing

Regulation of heart rate is the result of the autonomic nerve transmitters acting on the atrial sinus. The transmitters output is driven by numerous inputs, such as respiratory, blood pressure, motor, psychological immunity [20–22], etc. In a deep breathing scenario, respiration accounts for most of the changes in heart rate [17–19].

Under paced deep breathing, the central nervous system, humoral regulation, and mechanical feedback mechanisms work together, producing RSA. During inhalation, the chest cavity expands with the increment of negative pressure in the pleural cavity. The central vein and right atrium dilatation urge the blood backflow. Affected by the increased concentrations of neurotransmitters, the internal flow of the cell calcium in the sinoatrial node pacemaker is accelerated. As a result, the heart rate begins to speed up [23,24]. During exhalation, the airflow increases chest pressure and stimulates parasympathetic nerve via the vocal cords [25]. Then the acetylcholine which is released at the end of the vagus nerve fibers acts on M−type cholinergic receptors on the membrane of the heart muscle, causing the heart rate to slow down. During the whole process of breathing, sympathetic and parasympathetic activities changes with the process of inhalation and exhalation, thus the ANS eventually works together to regulate the heart rate [2]. We conclude the whole process of the cardiopulmonary modulation in paced deep breathing in Fig. 1.

2.2. Mathematical expressions

This section describes the physiopathological mathematical modeling of the cardiopulmonary regulation process. Through simplification of the above physiological process of cardiopulmonary modulation, the flow of RASM is shown in Fig. 2. Breathing stimulates the sinoatrial node to regulate the heart rate through neural response.

The parasympathetic response to the respiration is modeled as below:

$$\frac{dT_{par}}{dt} = \sigma_1 \frac{dresp}{dt} \tag{1}$$

Respiration acts as a direct parasympathetic stimulus. T_{par} represents the parasympathetic response, and σ1 represents the personalized parasympathetic activation sensitivity.

The sympathetic nervous system turns on through the central nervous system reaction [2]. Compared with the transient parasympathetic response, there is a certain delay in the sympathetic response [26]. In addition, the parasympathetic response also has an inhibitory effect on the sympathetic nerve [27–29]. Therefore, the sympathetic response is modeled:

$$\frac{dT_{sym}}{dt} = \frac{-\sigma_2 \frac{dresp(t-\tau_d)}{dt}}{1+\beta T_{par}} \tag{2}$$

In which β is the parasympathetic inhibitory factor, τ_d represents the time delay, and T_{sym} is the sympathetic response, σ2 is the personalized sympathetic sensitivity.

The autonomic nervous system's influence on the heart rate is mainly achieved by controlling the release of transmitters. The parasympathetic transmitter is acetylcholine (ach), and the sympathetic transmitter is norepinephrine (nor). The following two equations are obtained respectively [30,31]:

$$\begin{aligned} \frac{dC_{nor}}{dt} &= \frac{-C_{nor}+T_{sym}}{\tau_{nor}} \\ \frac{dC_{ach}}{dt} &= \frac{-C_{ach}+T_{par}}{\tau_{ach}} \end{aligned} \tag{3}$$

where C_{nor} is the concentration of nor; C_{ach} is the concentration of ach; τ_{ach} and τ_{nor} are time constants.

Afterwards, the transmitters act on the sinus node to change the heart rate. Regulation of the sinus node on heart rate contains three

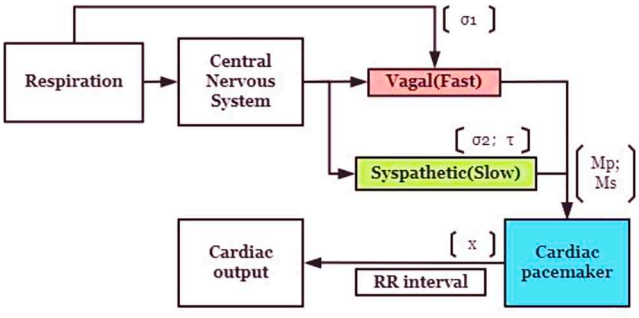

Fig. 1. The process of cardiopulmonary regulation in paced deep breathing. (The definition and physiological significance of the parameters in the figure will be described in next section.)

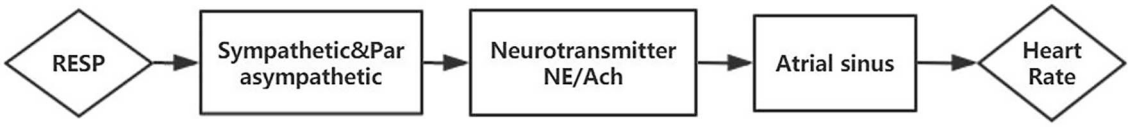

Fig. 2. The basic flow of cardiopulmonary regulation of the model. Breathing stimulates the sinoatrial node to regulate the heart rate through neural response.

parts: intrinsic self-discipline [32,33]; hypothalamus - suprachiasmatic nucleus - autonomic nerve regulation, including sympathetic and parasympathetic transmitter regulation [34,35]; disease caused sinus node remodeling [36–38]. Therefore, the heart rate potential energy Φ can be represented by the following integrate and fire model [39]:

$$\frac{d\Phi}{dt} = H_0(1 + MsC_{nor} - MpC_{ach} + x) \tag{4}$$

here H_0 is the intrinsic heart rate (age-related) parameter [40,41]. *Ms* and *Mp* are receptor properties of nor and ach. x is the cardiomyocyte state properties. It defines the ill-condition of sinoatrial node caused by chronic diseases, including heart geometric variation [36], electrolyte changes[37], and abnormity of angiotensin-converting enzyme[38], etc. Considering two heartbeats occur at consecutive times t_i and t_{i+1}, with potential energy Φ changing from 0 to 1, we can get heart rate as:

$$HR = \frac{1}{t_{\Phi=1} - t_{\Phi=0}} \tag{5}$$

3. Assessment of Cardiopulmonary autonomic regulation parameters (CARP)

Through sensitivity analysis of the parameters in the model RASM, we divide all the parameters (Table 1) into two categories: fixed attribute properties and personalized parameters (CARP). The sensitivity analyses will be detailed in the Results section.

The assessment of cardiopulmonary autonomic regulation (CARP), includes the sensitivity of respiratory-sympathetic nerves *σ1*, respiratory-parasympathetic nerves *σ2*, the time delay of sympathetic τ, nor and ach receptor sensitivity *Ms* and *Mp*, and the cardiac remodeling factor x. In the model, CARP is regarded as the state vector, and state space equations (1) - (5) are established.

With the respiratory signal as the input, the appropriate CARP values are chosen through the optimization algorithm, so that the output of RASM (fitted heart rate) gradually approaches the real heart rate (true value). We consider both the accuracy and efficiency of several algorithms and downhill simplex method is selected finally [42–45]. The iteration mode and objective equation of our model are shown in the Algorithm 1 below.

Table 1
CARP, fixed attribute properties and their physiological significance.

CARP	Physiological significance
$\sigma 1$	parasympathetic activation sensitivity
$\sigma 2$	sympathetic activation sensitivity
τ	the time delay of sympathetic response
M_p	Connection of acetylcholine and heart, acetylcholine receptor sensitivity
M_s	Connection of norepinephrine and heart, norepinephrine receptor sensitivity
x	Cardiac remodeling factor, ill-condition of sinoatrial node caused by chronic diseases
fixed attribute properties	**Physiological significance**
τ_{nor}	time constant of norepinephrine
τ_{ach}	time constant of acetylcholine
β	the parasympathetic inhibitory factor

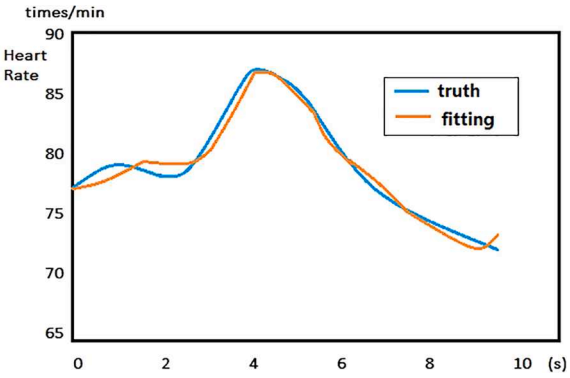

Fig. 3. The real heart rate (truth) and the output (fitting heart rate) of the model.

As shown in Fig. 3, our algorithm has achieved a good fitting effect.

Algorithm1 CARP from RASM

Input: heart rate, respiration signal; age;
$\tau_{nor} = 1.0$, $\tau_{ach} = 1.0$, $\beta = 1.0$
1. $H_0 \leftarrow$ age [40,41]
2. $HR_{output} \leftarrow$ respiration signal, equation (1)-(5) one after another
3. x, $\sigma 1$, $\sigma 2$, *Ms*, $\tau \leftarrow$ heart rate and HR_{output}, *Mp*, down-hill simplex [43]
4. *Mp* ← *Ms,* assuming a linear correlation
5. $\sigma 1$, $\sigma 2$, x, $\tau \leftarrow$ *Mp, Ms,* down-hill simplex
$\min \sum |HR_{input} - HR_{output}| + |\Delta Sampen(HR_{output})|$*
▷Repeat until stable.
Output: $\sigma 1$, $\sigma 2$, τ, *Mp*, *Ms*, x

* $\triangle Sampen$ represents the difference between two successive iterations of the sample entropy. Take average of the forward and reverse calculation as the result.

4. Experiments and data acquisition

4.1. Experimental design

To verify our model RASM and the CARP parameters, we selected different pathological groups in the experiment. Hypertensive patients are the typical observation objects of sympathetic hyperactivity; coronary heart disease is a typical disease of the sinoatrial node and myocardial ischemia. Therefore, we did this study on healthy subjects, as well as patients with hypertension and coronary heart disease. For people with hypertension, we conducted a clinical trial at the China-Japan Friendship Hospital in Beijing. The trial has been approved by the hospital's clinical ethics committee. Similarly, we experimented on patients with coronary heart disease in Qixia Hospital, Qixia District, Nanjing.

Subjects are required to wear the intelligent hardware that can monitor the ECG and respiratory signals synchronously. The subjects sit up straight with their hands flat on their knees and adjust their breathing rate according to guide. The breathing process is divided into four stages one by one with 5 min each, including free-breathing, 0.20 Hz, 0.15 Hz and 0.1 Hz [11]. During the experiment, the medical staff guides the whole process.

4.2. Equipment

The intelligent hardware we designed is about 4 cm*2 cm in size. The hardware is based on ADS1292R developed by TI company, which can collect ECG signal and respiratory signal by chest impedance method. The intelligent hardware and the collected signals are shown in Fig. 4.

4.3. Data

The heart rate and respiratory signals at 0.15 Hz and 0.1 Hz respiration are selected as the research objects for modeling. The respiratory signal and the initial heart rate in a breathing cycle are selected as the excitation of the model, and the heart rate changes in this cycle are the corresponding response.

For ECG signals, the Butterworth filter is used to remove low-frequency interference. After removing the abnormal points, detection of R points and calculation of RR interval are conducted. For the respiratory signal, the noise outside the normal range of respiratory frequency is filtered by wavelet decomposition. Because in the experiment, subjects are required to breathe at a certain breathing frequency, the concentration degree of the respiratory signal in the frequency domain is monitored for further analysis. After the screening of the quality of the signal, the data of 21 healthy people, 7 hypertensive patients, and 9 patients with coronary heart disease are finally chosen for the model. All measurements are calculated and analyzed using MATLAB.

5. Experimental results

In section 5.1, sensitivity analysis is conducted on all the parameters in the model: initial fixed attribute properties and calculated parameters CARP. In section 5.2, the CARP of patients with hypertension, patients with coronary heart disease (CHD), and healthy subjects are calculated. One-way ANOVA and Dunnett's post hoc test for the CARP is performed to verify its significance and stability.

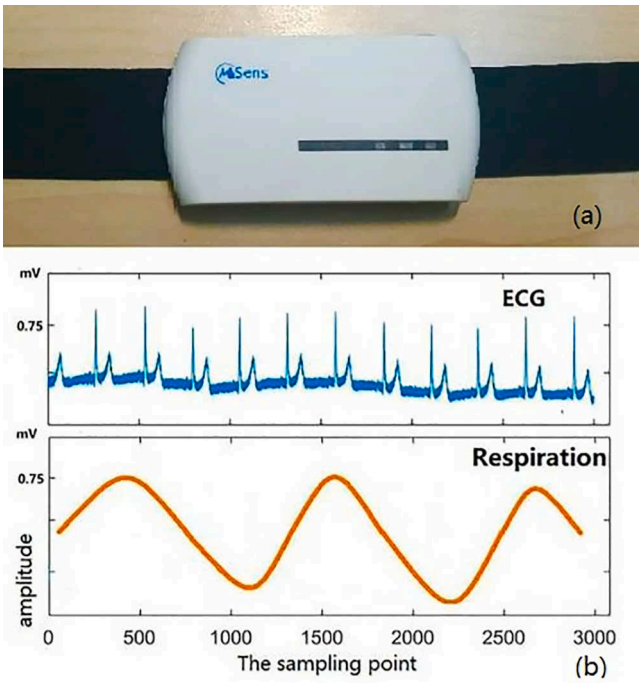

Fig. 4. The intelligent hardware (a); ECG and respiratory signals collected synchronously (b).

5.1. Sensitivity analysis

Sensitivity analysis is to study and analyze the sensitivity of the output when the model changes due to parameter conditions. It can be used to assist in identifying important uncertainties and determining the priority of data collection or research. In addition, sensitivity analysis is an important tool for model validation in the process of model establishment. Sensitivity analysis can also be used to analyze the robustness of model results when making decisions. It has been applied in many fields, such as complex engineering systems, economics, physics, social sciences, medical decision-making, etc [46–48].

In our model, we used the finite difference method for local sensitivity analysis via central difference equation, as shown below:

$$\frac{\partial HR}{\partial \theta} = \frac{HR(\theta + h) - HR(\theta - h)}{2h} \tag{6}$$

In this formula, θ represents the parameter and h represents the minimal disturbance of θ. For each healthy subject, we calculated the sensitivity of the parameters in Table 1.

Then we got the sensitivity ranking of the initial parameters as shown in Table 2: τ_{nor}, τ_{ach}, β, x, Ms, Mp, τ, $\sigma 2$, $\sigma 1$. The bigger the value, the higher the sensitivity of the parameter. According to this, we divide the model parameters into two categories: initial fixed attribute properties (β, τ_{nor}, τ_{ach}) and calculated parameters CARP (x, Ms, Mp, τ, $\sigma 2$, $\sigma 1$) which we focus on. For parameters with very low sensitivity, fixed values are adopted in the model.

5.2. Clinical implication of CARP in hypertension and coronary heart disease

Under the paced deep breathing at the same frequency, changes in the heart rate of healthy subjects and patients are different, and the corresponding physiopathological parameters are also different. To illustrate the validity of our model RASM and the CARP parameters, we compared CARP among patients with hypertension, coronary heart disease, and healthy subjects.

After clinical experiments of paced deep breathing in three groups of people, we obtained the CARP results through our model shown in Table 3. The performance of these parameters varies among the three groups. Values are expressed as mean ± standard deviation. Only in one subject did × show significantly different manifestations shown in the table. This subject is a patient with severe coronary heart disease.

Except for x, one-way ANOVA for CARP is performed between the groups shown in Table 4. We performed Dunnett's post hoc test, shown in Table 5. The sensitivity of sympathetic nerves $\sigma 1$ and parasympathetic nerves $\sigma 2$ and the time delay of sympathetic τ, these three parameters show significantly different between patients with hypertension and healthy subjects. The Ms and Mp express the heart's ability to respond to neurotransmitters. The two parameters are significantly different between patients with CHD and healthy subjects. Compared CHD with hypertension, there are marked differences in these five-parameter-patterns.

6. Discussion

To verify the physiological meaning of CARP further, autonomic nerve measurements of other researchers are considered. Measurements that are also analyzed based on the ECG and respiratory signals are selected. HRV in resting state is adopted in [1,4], while *HRV-LF* measures the performance of the activity of the sympathetic nerve to the heart rate; *HRV-HF* expresses the performance of the parasympathetic nerve. The measurements of three groups of people, including health, Hypertension, and CHD, are compared. Results are shown in Fig. 5 and Table 6. As a representative, CARP at 0.10 Hz is shown. The data are normalized using the results of healthy people as a baseline.

As shown in Fig. 5 and Table 6, for diagnosis and etiology study of

Table 2
Sensitivity of the parameters in the model.

Parameters	τ_{nor}	τ_{ach}	β	x	Ms	Mp	τ	$\sigma 2$	$\sigma 1$
Sensitivity	0.002	0.015	0.028	0.100	0.150	0.150	0.231	0.810	0.900

Table 3
Statistics of CARP of different groups under 0.15 Hz and 0.1 Hz respiration. Values are expressed as mean ± standard deviation. For τ, 250 represents 5 s time in the table.

CARP	$\sigma 1$	$\sigma 2$	τ	M_P	M_S	x
Health(0.15 Hz)	0.131 ± 0.042	0.003 ± 0.001	250 ± 50	0.0036 ± 0.0013	0.0013 ± 0.0011	0.00001 ± 0.00001
Hypertension (0.15 Hz)	0.087 ± 0.042	0.081 ± 0.001	312 ± 53	0.0033 ± 0.0012	0.0014 ± 0.0011	0.00001 ± 0.00001
CHD(0.15 Hz)	0.129 ± 0.044	0.004 ± 0.001	264 ± 48	0.0020 ± 0.0013	0.0017 ± 0.0010	0.00003 (1)
Health(0.10 Hz)	0.151 ± 0.040	0.003 ± 0.001	250 ± 43	0.0036 ± 0.0009	0.0012 ± 0.0010	0.00001 ± 0.00001
Hypertension (0.10 Hz)	0.105 ± 0.040	0.079 ± 0.001	300 ± 45	0.0032 ± 0.0010	0.0011 ± 0.0010	0.00001 ± 0.00001
CHD(0.10 Hz)	0.150 ± 0.043	0.004 ± 0.001	256 ± 46	0.0018 ± 0.0010	0.0016 ± 0.0010	0.00004 (1)

Table 4
The p-values of $\sigma 1$, $\sigma 2$, τ, *Ms*, *Mp* and x among hypertensive patients, CHD and healthy subjects. The p-value represents the result of the repeated measures one-way ANOVA. $P < 0.05$ show that there is a significant difference between the groups.

Comparative group	$\sigma 1$	$\sigma 2$	τ	M_P	M_S	x
Hypertension and The health(0.15 Hz)	0.025	0.003	0.035	0.341	0.528	0.911
Hypertension and The health(0.10 Hz)	0.024	0.002	0.035	0.115	0.210	0.911

Comparative group	$\sigma 1$	$\sigma 2$	τ	M_P	M_S	x
CHD and The health(0.15 Hz)	0.168	0.215	0.520	0.013	0.011	0.495
CHD and The health(0.10 Hz)	0.064	0.191	0.520	0.013	0.008	0.495

Comparative group	$\sigma 1$	$\sigma 2$	τ	M_P	M_S	x
Hypertension and CHD (0.15 Hz)	0.024	0.003	0.035	0.011	0.010	0.495
Hypertension and CHD (0.10 Hz)	0.024	0.003	0.035	0.011	0.004	0.495

hypertension and coronary heart disease, *HRV_HF* and *HRV_LF* in these two kinds of patients are similar. *HRV_HF* is lower and *HRV_LF* is higher than the health in the two groups. For CARP, combined with the results of Table 4 and Table 5, compared to the health, the three metrics of the activation sensitivity about sympathetic and parasympathetic nerve conduction ($\sigma 1$, $\sigma 2$, and τ) in patients with hypertension show significant differences, while there is an obvious difference in the cardiac sensor and myocardial characteristic metrics (*Ms* and *Mp*) between CHD and the health.

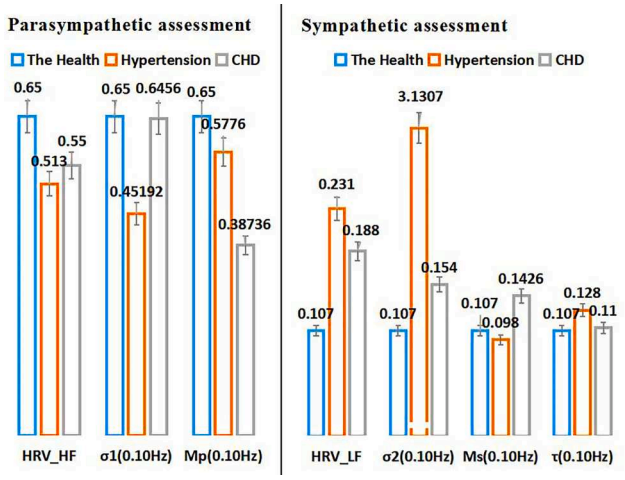

Fig. 5. HRV (HRV_HF, HRV_LF), and CARP (0.1 Hz) in the health, Hypertension and CHD groups.

Table 6
The p-values of CARP and HRV among hypertensive patients, CHD and healthy subjects. The p-value represents the result of the repeated measures one-way ANOVA. $P < 0.05$ means that there is a significant difference between the groups.

Parasympathetic	Hypertension& health	CHD & health
$\sigma 1$	0.024	0.064
Mp	0.115	0.013
HRV_HF	0.040	0.045

Sympathetic	Hypertension& health	CHD & health
$\sigma 2$	0.002	0.191
Ms	0.210	0.008
τ	0.035	0.520
HRV_LF	0.015	0.040

Table 5
Dunnett's post hoc test of CARP for different groups: the health (1), Hypertension (2), and CHD (3). If the value of difference of the mean (DM) > LSR($p = 0.05$), there is a significant difference between the groups being compared ($p < 0.05$).

group	$\sigma 1$		$\sigma 2$		τ		M_P		M_S		x	
	DM	LSR	DM	LSR	DM	LSR	DM	LSR	DM	LSR	DM	LSR
1 and 2(0.15 Hz)	0.0439	0.040	0.0800	0.04	62	9.7	0.0003	0.0010	0.0001	0.0003	0.000001	0.00003
1 and 2(0.10 Hz)	0.0455		0.0800		50		0.0004		0.0001		0.000001	
1 and 3(0.15 Hz)	0.0004		0.0008		14		0.0016		0.0004		0.000008	
1 and 3(0.10 Hz)	0.0004		0.0012		6		0.0018		0.0004		0.000009	
2 and 3(0.15 Hz)	0.0425		0.0773		48		0.0013		0.0003		0.000001	
2 and 3(0.10 Hz)	0.0451		0.0751		44		0.0014		0.0005		0.000001	

Hypertension is characterized by a sustained increase in peripheral resistance leading to an abnormal increase in blood pressure, accompanied by structural changes in the heart and blood vessels. Neuroregulation is an important aspect of blood pressure stabilization [49]. When studying the mechanism of increased total peripheral resistance in hypertension, people came up with the role of the sympathetic nerve first [50]. In our model, $\sigma 2$ represents sympathetic activation sensitivity, and τ represents the time delay of sympathetic response. For the performance of sympathetic nerve on heart rate regulation, *HRV_LF* is bigger in the hypertension group, and both $\sigma 2$ and τ of hypertension group is much greater than that of the health. In other studies, the sympathetic nervous system and the renin-angiotensin system are found significantly activated in hypertension patients too [50,51]. Though it has been considered that the increase of sympathetic nerve activity is the initial factor of hypertension, in the whole process of the circulatory system from the normal state to hypertensive state, the role of parasympathetic nerves and the balance of parasympathetic and sympathetic nerves are also important [51]. For measurement of the performance of parasympathetic nerve on the regulation of heart rate, $\sigma 1$ shows a similar performance with *HRV_HF*, characterized by the measurement of hypertension is lower than that of the health. The low parasympathetic sensitivity, high sensitivity and time delay of sympathetic nerve have been verified in many hypertension patients [52–54]. The performances of assessments we proposed are consistent with the findings of these studies.

The formation process of CHD is that coronary artery blood vessel produces atherosclerosis pathological change and causes vascular lumen narrow or block, leading to myocardial ischemia, hypoxia or necrotic and thus bringing about heart disease. Coronary heart disease includes inflammation, embolism, and other causes of lumen narrowing or occlusion [55]. For parasympathetic nerve, $\sigma 1$ between CHD and health shows a smaller gap than that of *HRV_HF*. Meanwhile, the *Mp* of CHD is the lowest among the three groups. For the performance of sympathetic nerve on heart rate, *HRV_LF* is much bigger in CHD than in the health, while τ do not show obvious differences compared with the health in CHD. This phenomenon is caused by the existence of heart-related parameters, just as we can see that *Ms* of CHD is the biggest. The *Ms* and *Mp* represent norepinephrine and acetylcholine receptor sensitivity of sinoatrial node. These two parameters indicate abnormality in the cardiac responsiveness to the neurotransmitters. Inflammatory reactions and damage to coronary artery lining development in coronary plaques may be related to this phenomena [55,56]. The sympathetic activation sensitivity $\sigma 2$ of CHD is slightly higher than that of the healthy subjects. This shows the sympathetic neural overdrive and it is consistent with some researchers' findings [57]. Only in one subject did x show a significant difference, which presented as the bias of resting heart rate and could tolerate the heart geometric variation. This subject is a patient with severe coronary heart disease. The resting heart rate of this patient is 117, which is significantly higher than that of healthy people. So we think the parameter x may be related to the great cardiac pathological changes of coronary heart disease [36–38].

Because states of cardiovascular regulation of human being can not be observed directly, we use extrinsic measurements, heart rate and respiration signals, to model the state space of these physiological mechanisms through differential equations. Thus the state vector CARP could express the internal states of the cardiovascular regulation. The results show that CARP can analyze the causes of different cardiovascular diseases.

7. Conclusion

The assessment of autonomic nerve has always been the focus of researchers. A physiopathological mathematical model (RASM) for cardiopulmonary autonomic regulation in paced deep breathing is proposed in this study. Detailed physiological process of cardiopulmonary modulation is described via a series of partial differential equations. Through optimization algorithm, the CARP, including the sensitivity of respiratory-sympathetic nerves and respiratory-parasympathetic nerves, the time delay of sympathetic, cardiac remodeling factor, norepinephrine and acetylcholine receptor sensitivity can be obtained.

The experimental study has been conducted in the health, subjects with hypertension and coronary heart disease. The preliminary experimental results have shown the clinical significance of CARP. It is detailed, physiologically explicable, and can not only express differences in the neurological performance between the patients and the health, but also can help doctors delve into the details of the regulatory process.

The experimental scenario of our model is simple and feasible. In the future, on the one hand, more clinical trials need to be conducted to standardize CARP. The metric value and physiological significance of the parameter about the ill-condition of the sinoatrial node still need to be verified further. On the other hand, we would explore the possibility of the model extension with more comprehensive physiological parameters.

8. Data availability

The.txt data used to support the findings of this study were supplied by [Sensor Networks and Application Research Center, School of Electronic, University of Chinese Academy of Sciences] under license and so cannot be made freely available. Requests for access to these data should be made to Jiajia Cui, Cuijiajia17@mails.ucas.ac.cn.

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CRediT authorship contribution statement

Jiajia Cui: Conceptualization, Project administration. **Zhipei Huang:** Methodology, Writing – original draft, Software. **Jiankang Wu:** Data curation, Investigation. **Hong Jiang:** Supervision. **Fei Qin:** Formal analysis. **Zhiqiang Zhang:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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