34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Autonomic-Cardiorespiratory Regulation: A Physiology-Based Mathematical Model

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Abstract— **This paper presents a novel physiology-based mathematical model of autonomic-cardiorespiratory regulation described by a set of three nonlinear, coupled differential equations. We improved our previously proposed autonomic-cardiac regulation model by considering neuromechanical and mechanical coupling of cardiovascular and respiration systems including lung stretch-receptor reflex and venous return variation. We also introduced a differential equation describing respiration rate regulation which mainly originates in the medullary respiratory center. The results of simulation experiments suggest that the venous return variation generates a higher perturbation on heart rate and blood pressure than lung stretch-receptor reflex. The proposed model is also powerful in determining and removing direct respiratory impacts on parasympathetic activation tone to accurately extract parasympathetic activity caused by emotional states and environmental conditions.**

I. INTRODUCTION

Autonomic-cardiorespiratory regulation operates through interactions between the autonomic nervous system (ANS), the cardiovascular system, and the respiration system. The ANS maintains homeostasis in the cardiorespiratory system in order to deliver adequate oxygenated blood-flow to organs against physical (e.g., exercise and orthostatic hypotension) and psychological (e.g., fear and anxiety) stressors [1]–[3]. The ANS consists of two branches, the parasympathetic nervous system which is dominant in "rest and digest" states, and the sympathetic nervous system which is aroused in "fight or flight" states. The ANS regulates respiration rate (RR), instantaneous lung volume (ILV), blood pressure (BP), cardiac output (CO), and heart rate (HR) using different mechanisms, e.g., adjusting sympathetic and parasympathetic activation tones on the sinoatrial node, cardiac contractility, and peripheral resistance [4]–[6].

A variety of mathematical models to describe autonomic-cardiac regulation using black-box and white-box (physiology-based) approaches have been previously proposed [6]–[8]. However, a physiology-based mathematical model for the respiratory system impacts were investigated only to some extent [3]. Further, the respiratory system impacts on HR (i.e., respiratory sinus arrhythmia or RSA) and BP (i.e., venous return variation) have been either neglected [8] or simply modeled by a non-physiology function (e.g., a sine function) [9].

In this paper, we introduce a physiology-based mathematical model of autonomic-cardiorespiratory regulation described by a set of three nonlinear, coupled differential equations each of which describes regulations of HR, BP, and RR. A unique strength of the proposed model is its physiology-based modeling approach to describe most of the internal mechanisms within the in-vivo systems. Recently [10], we proposed a relatively improved model of the autonomic-cardiac regulation based on the work of Fowler et. al. [11]. However, the respiration system dynamics and effects such as venous return variation during respiration phases, lung stretch receptor reflex, and respiratory generator center were not studied in [10].

II. METHODS

We first present a physiological background on the major origins of HR and BP fluctuations. Then, a mathematical model of the autonomic-cardiac regulation (without respiration system effects) described by a set of two coupled nonlinear delay-differential equations is presented, followed by an improvement in the mathematical model to describe autonomic-cardiorespiratory regulation. In this section, we propose a mathematical representation for neuromechanical and mechanical coupling of cardiovascular and respiration systems, i.e, lung stretch-receptor reflex and venous return variations. We also introduce a differential equation to model RR regulation that mainly originates from the medullary respiratory center in the brainstem, which is influenced by voluntary actions and chemoreflex.

A. Physiological Background

Heart rate variability (HRV) or HR fluctuations around the mean HR are genrated by the sympathetic and parasympathetic nervous systems in the cardiorespiratory control system. In healthy individuals, the HRV spectrum shows two predominant peaks: one at low frequency around 0.1Hz (Mayer waves) associated with arterial pressure biofeedback; the other one at higher frequency around 0.25Hz (corresponding to respiration frequency) is called RSA. RSA is mainly generated through two mechanisms: neural-based modulation of cardiac vagal activation by the medullary respiratory center, and neuromechanical-based modulation of cardiac vagal activation by lung stretch-receptor reflex [12]. RSA has been observed at the approximate respiratory frequency even in the absence of respiration due

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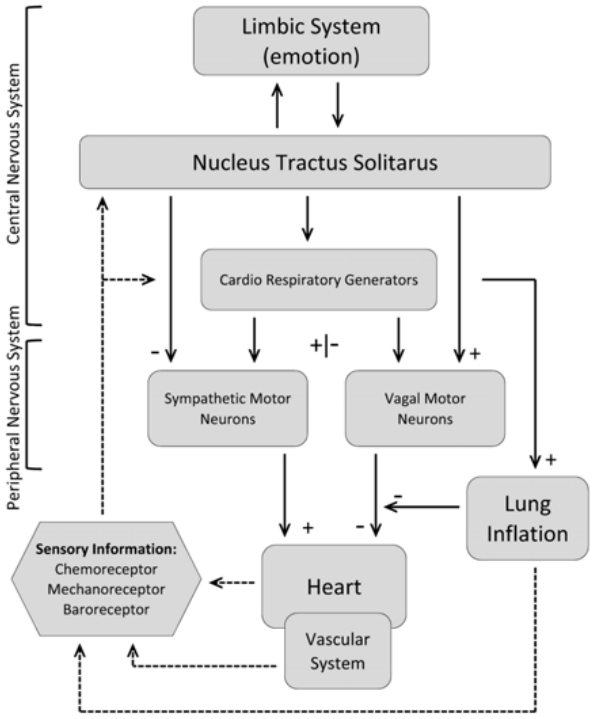

Fig. 1. Schematic diagram of interactions between cardiovascular, respiratory and nervous systems

to the activation of the medullary respiratory center [13]. The lung stretch-receptor reflex inhibits and excites cardiac vagal activation tone during inspiration (lung inflation) and expiration (lung deflation) respectively, causing a decrease and an increase in heart periods during respiratory cycles [12], [13]. The synchrony of heart period fluctuations (i.e., HRV) and respiration cycles due to the lung stretch-receptor reflex potentially increases the efficacy of the pulmonary gas exchange between the capillary blood-flow and the alveolar gas volume by matching perfusion to ventilation within each respiratory cycle [12], [14].

Blood pressure variability (BPV) is mainly caused by HRV as well as direct mechanical effects of respiration (either spontaneous or mechanical) on BP [15]. The HRV influences the BP through the heart period baroreflex mechanism. Further, the direct mechanical effect of respiration results in variation of venous return in each respiratory cycle. During spontaneous inspiration, the chest wall expands and the diaphragm descends resulting in lower intrapleural pressure[1] and therefore expansion of the lungs and cardiac chambers [16]. This expansion causes an increase in cardiac pre-load[2] and stroke volume due to the Frank-Starling mechanism as well as a decrease in right atrial pressure which is important in pressure gradient for the venous return

[1]The pressure within the thoracic space between the organs (lungs, heart, vena cava) and the chest wall is called intrapleural pressure.

[2]Cardiac pre-load is the end-diastolic volume (EDV) of the ventricle at the beginning of systole.

TABLE I

MODEL PARAMETERS OF AUTONOMIC-CARDIAC REGULATION.

Parameter	Definition	Nominal Value
C_a	arterial compliance	1.55 $mlmmHg^{-1}$
R_a^0	minimum arterial resistance	0.6 $mmHgsml^{-1}$
ΔV	stroke volume	50 ml
H_0	intrinsic heart rate	100 min^{-1}
τ	sympathetic delay	3 s
V_H	vagal tone	1.17 s^{-2}
β_H	sympathetic control of HR	0.84 s^{-2}
α	sympathetic effect on R_a	1.3
γ	vagal damping of β_H	0.2
δ_H	relaxation time	1.7 s^{-1}

[16], [17]. Consequently, the venous return increases during spontaneous inspiration and decreases during spontaneous expiration. During mechanical ventilation, the chest wall and diaphragm are not displaced; however, lungs are inflated due to an external air force which causes different consequences such as an increase in intrapleural pressure during mechanical inspiration. Similarly, venous return decreases during mechanical inspiration and increases during mechanical expiration (Table II).

B. Autonomic-Cardiac Regulation

We introduced a physiology-based mathematical model of the autonomic-cardiac regulation in [10] using two coupled differential equations (1)-(2) having nonlinear and delayed dynamic interactions, each of which describe the dynamics of HR and BR regulation:

$$\dot{H}(t) = \frac{\beta_H T_s}{1+\gamma\ T_p} - V_H T_p + \delta_H\big(H_0 - H(t)\big) \qquad (1)$$

$$\dot{P}(t) = -\frac{P(t)}{R_a^0(1+\alpha T_s)C_a} + \frac{H(t)\Delta V}{C_a}. \qquad (2)$$

where H is HR, and P is mean arterial BP. $T_s = 1-\sigma\big(P(t-\tau)\big)$ and $T_p = \sigma\big(P(t)\big)$ are sympathetic modulating function and parasympathetic modulating function respectively, generated by the baroreflex control mechanism. Note that T_s and T_p are both purely BP-dependent while the sympathetic and parasympathetic nervous system are also modulated by other physiological variables (e.g., O_2 and CO_2 concentration in blood) or psychophysiological states (e.g., fear and anger). The time delay associated with the sympathetic pathway is denoted by τ. $\sigma(P)$ is defined as follows:

$$\sigma(P) = T_{min} + \frac{T_{max}-T_{min}}{1+e^{-\alpha_{sp}(P-P_{sp})}} \qquad 50 \le P \le 200. \quad (3)$$

where T_{min} and T_{max} are minimum and maximum values of inter-beat interval (H^{-1}). Further, P_{sp} and α_{sp} are the BP setpoint and the sensitivity of a baroreflex mechanism, respectively.

C. Autonomic-Cardiorespiratory Regulation

In this study, we improve our previous mathematical model of autonomic-cardiac regulation (1)-(2) (see [10]) by modeling two major interactions of cardiovascular and respiration systems, i.e., mechanical and neuromechanical.

Further, we introduce a differential equation representing dynamic of respiration rhythm originated in the medullary respiratory center.

The mechanical coupling of the cardiovascular and respiration systems causes an increase in venous return and consequently an increase in stroke volume, during spontaneous inspiration and mechanical expiration. On the contrary, venous return and therefore stroke volume decreases during spontaneous expiration and mechanical inspiration (Table II). We modeled this pure mechanical effect by adding (during mechanical respiration) or subtracting (during spontaneous respiration) $k_2\dot{V}_L$ with positive coefficient k_2 to the stroke volume (ΔV) as follows:

$$\dot{P}(t) = -\frac{P(t)}{R_a^0(1+\alpha T_s)C_a} + \frac{H(t)(\Delta V \pm k_2\dot{V}_L)}{C_a}. \quad (4)$$

The neuromechanical coupling of the respiration and cardiovascular systems is generated by the lung stretch-receptor reflex. This reflex causes an increase in HR during inspiration while ILV consistently increases (i.e., $\dot{V}_L > 0$), and a decrease in HR during expiration while ILV consistently decreases (i.e., $\dot{V}_L < 0$) (Table II). The lung stretch-receptor reflex inhibits and excites cardiac vagal activation tone during inspiration and expiration, respectively [12]. We model this mechanism by subtracting a respiration-related term consisting of a rate of change in ILV, $\dot{V}_L$, multiplied by a positive coefficient k_1, to cardiac vagal activation tone V_H in the HR equation as follows:

$$\dot{H}(t) = \frac{\beta_H T_s}{1+\gamma\ T_p} - (V_H - k_1\dot{V}_L)T_p + \delta_H\big(H_0 - H(t)\big) \quad (5)$$

During inspiration while $\dot{V}_L > 0$, inhibition effects of the parasympathetic nervous system on HR reduces, and therefore HR increases. Similarly, during expiration while $\dot{V}_L < 0$, HR decreases due to a rise in inhibition effects of the parasympathetic nervous system.

The medullary respiratory center in each individual generates a relatively constant rhythm (R_0) which is modulated in different conditions such as low O_2 or high CO_2 concentration in blood, sleep, and emotions (e.g., fear and anxiety). Specifically, the respiration rhythm R_0 is modulated by the chemoreflex stimulation due to changes in chemoreceptors responses throughout body. The chemoreflex mainly operates based on the CO_2 levels rather than O_2 levels [16]. We model the dynamics of respiration rate, denoted by R, generated in the respiratory center as follows:

$$\dot{R}(t) = k_3\Big[\big(1+\sigma_{co_2}\big)R_0 - R(t)\Big] + u(t) \quad (6)$$

where σ_{co_2} is a sigmoid function representing chemoreflex modulating function on R_0 and $u(.)$ is a voluntary component of RR regulation. Note that the only voluntary term in autonomic-cardiorespiratory regulation is the individual's ability in changing RR. Finally, we propose the mathematical model of autonomic-cardiorespiratory regulation as follows:

$$\dot{H}(t) = \frac{\beta_H T_s}{1+\gamma\ T_p} - (V_H - k_1\dot{V}_L)T_p + \delta_H\big(H_0 - H(t)\big) \quad (7)$$

TABLE II

RESPIRATION SYSTEM IMPACTS ON V_L, HR, VR, AND ΔV

	Spontaneous		Mechanical	
	Inhale	Exhale	Inhale	Exhale
V_L (Instantaneous Lung Volume)	↑	↓	↑	↓
HR (Heart Rate)	↑	↓	↑	↓
VR (Venous Return)	↑	↓	↓	↑
ΔV (Stroke Volume)	↑	↓	↓	↑

$$\dot{P}(t) = -\frac{P(t)}{R_a^0(1+\alpha T_s)C_a} + \frac{H(t)(\Delta V \pm k_2\dot{V}_L)}{C_a} \quad (8)$$

$$\dot{R}(t) = k_3\Big[\big(1+\sigma_{co_2}\big)R_0 - R(t)\Big] + u(t) \quad (9)$$

where nominal values of the non-respiratory related parameters are shown in Table I, and nominal values of k_1 and k_2 are $0.073\ l^{-1}s^{-1}$ and $3.12\ ms$, respectively. Nominal values of k_1 and k_2 are assigned such that the respiration-related terms $k_1\dot{V}_L$ and $k_2\dot{V}_L$ generate 10% perturbation on the amplitude of V_H and ΔV, respectively.

III. RESULTS AND DISCUSSION

To investigate neuromechanical coupling effects of respiration $k_1\dot{V}_L$ on HR and BP, we assigned $k_2 = 0$ and all the non-respiratory related parameters to their nominal values whereas k_1 was changed from 50% to 150% (25% increment) of its nominal value. Further, to compute perturbation of HR and BP merely caused by neuromechanical coupling effects $k_1\dot{V}_L$, the average sum of absolute normalized errors of HR and BP J_1 was used as follows:

$$J_1 = \frac{E_{P,1} + E_{H,1}}{2};\ E_{X,1} = \sum_{t=0}^{30}\left|\frac{X_{k_1\neq 0}(t) - X_{k_1=0}(t)}{X_{k_1=0}(t)}\right| \quad (10)$$

whereas $X_{k_1\neq 0}(t)$ and $X_{k_1=0}(t)$ are HR or BP ($X = H, P$) with and without neuromechanical coupling effects, respectively. To solve the mathematical model (7)-(8) for each given set of parameteres, we first generated an arbitrary ILV signal for a 30s-length segment with constant rate of change in lung volume $\dot{V}_L = 2\ ls^{-1}$ during inhaling and exhaling phases (Fig. 2). Then, we numerically solved the mathematical model (7)-(8) using a DDE (delay-differential equation) solver in MATLAB to obtain perturbed HR and BP for 5 different values of k_1 (Fig. 2). Similarly, J_2 is the average sum of absolute normalized errors of HR and BP while k_2 was changed from 50% to 150% (25% increment) of its nominal value. This study shows that HR and BP perturbation caused by mechanical coupling effects J_2 is higher than perturbation caused by neuromechanical coupling effects J_1 (Table III).

Moreover, researchers in developmental psychophysiology have increasingly acknowledged that physiological responses to stress can be used to monitor and predict a variety of problems such as poor emotion regulation and cognitive impairments in children [18]. Physiological responses have been measured using parameters reflecting autonomic nervous system activation including sympathetic and parasympathetic activation tones. We proposed an identification technique for sympathetic and parasympathetic activation tones in [10]. By

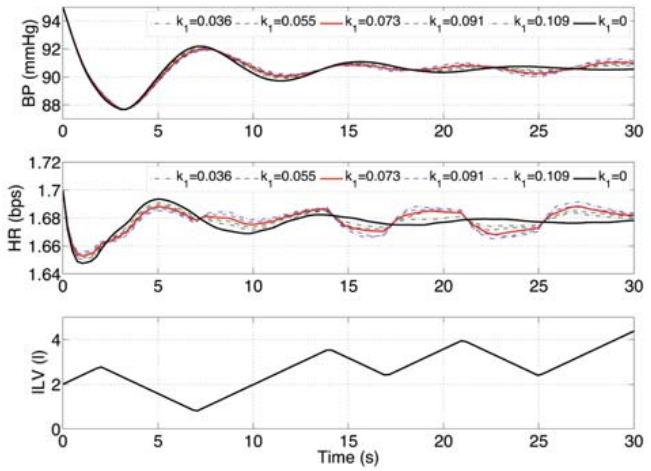

Fig. 2. Neuromechanical coupling effects of respiration on HR and BP.

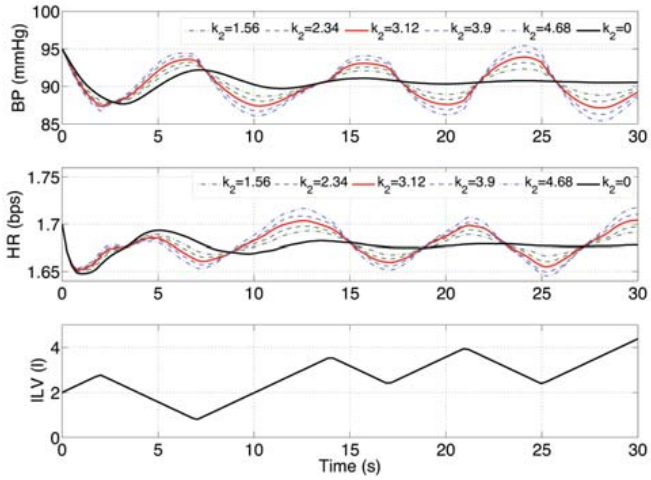

Fig. 3. Mechanical coupling effects of respiration on HR and BP.

using the mathematical model (7)-(8) with the previously proposed identification technique, we will be able to compute effects of respiration system on parasympathetic activity $k_1\dot{V}_L$, and then a pure parasympathetic activation tone caused by different mental states and environmental conditions can be extracted. Similarly, results of the identification technique will be improved for anaesthetized and awake individuals, since we mathematically differentiate spontaneous (during consciousness) and mechanical (during anaesthesia) ventilation effects in HR and BP regulation.

TABLE III

A NUMERICAL MEASURE OF PERTURBATION CAUSED BY MECHANICAL COUPLING EFFECTS J_2 AND NEUROMECHANICAL COUPLING EFFECTS J_1

$k_1/k_{1,Nom}$	J_1	$k_2/k_{2,Nom}$	J_2
50%	0.18	50%	0.76
75%	0.27	75%	1.14
100%	0.36	100%	1.52
125%	0.44	125%	1.89
150%	0.53	150%	2.28

IV. CONCLUSIONS AND FUTURE WORK

In this paper, we resolved the lack of accuracy in the autonomic-cardiac regulation model [10] regarding the respiration system effects by considering the major respiratory impacts including lung stretch-receptor reflex and venous return variation on HR and BP. Future work will include the extension of the mathematical model to increase accuracy of the model as well as revising our previous identification technique to adjust with the proposed autonomic-cardiorespiratory model.

REFERENCES

[1] A. Dudkowska and D. Makowiec. Seidel-Herzel model of human baroreflex in cardiorespiratory system with stochastic delays. *Journal of Mathematical Biology*, 57:111–137, 2008.

[2] R.A.L. Dampney, J. Horiuchi, and L.M. McDowall. Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour. *Autonomic Neuroscience : Basic & Clinical*, 142(1-2):3–10, November 2008.

[3] J.L. Elghozi and C. Julien. Sympathetic control of short-term heart rate variability and its pharmacological modulation. *Fundamental & Clinical Pharmacology*, 21(4):337–47, August 2007.

[4] B.M. Appelhans and L.J. Luecken. Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*, 10:229–240, 2006.

[5] E. Magosso, V. Biavati, and M. Ursino. Role of the baroreflex in cardiovascular instability: a modeling study. *Cardiovascular Engineering*, 1:101–115, 2001.

[6] S. Cavalcanti. Arterial baroreflex influence on heart rate variability: a mathematical model-based analysis. *Medical & Biological Engineering & Computing*, 38:189–197, March 2000.

[7] J.V. Ringwood and S.C. Malpas. Slow oscillations in blood pressure via a nonlinear feedback model. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, 280:R1105–15, April 2001.

[8] H. Van de Vooren, M.G.J. Gademan, C.A. Swenne, B.J. TenVoorde, M.J. Schalij, and E.E. Van der Wall. Baroreflex sensitivity, blood pressure buffering, and resonance: what are the links? Computer simulation of healthy subjects and heart failure patients. *Journal of Applied Physiology*, 102:1348–1356, 2006.

[9] PE McSharry, MJ McGuinness, and AC Fowler. Confronting a cardiovascular system model with heart rate and blood pressure data. *Computers in Cardiology*, 32:587, 2005.

[10] P. Ataee, J.O. Hahn, C. Brouse, G.A. Dumont, and W.T. Boyce. Identification of cardiovascular baroreflex for probing homeostatic stability. *Computing in Cardiology*, (37):141–144, 2010.

[11] A.C. Fowler and M.J. McGuinness. A delay recruitment model of the cardiovascular control system. *Journal of Mathematical Biology*, 51:508–526, 2005.

[12] Fumihiko Yasuma. Respiratory Sinus Arrhythmia: Why Does the Heartbeat Synchronize With Respiratory Rhythm? *Chest*, 125(2):683–690, February 2004.

[13] G G Berntson, J T Cacioppo, and K S Quigley. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology*, 30(2):183–96, March 1993.

[14] J. Hayano, F. Yasuma, A. Okada, S. Mukai, and T. Fujinami. Respiratory sinus arrhythmia: A phenomenon improving pulmonary gas exchange and circulatory efficiency. *Circulation*, 94(4):842–847, 1996.

[15] M.C.K. Khoo. Modeling of autonomic control in sleep-disordered breathing. *Cardiovascular engineering (Dordrecht, Netherlands)*, 8(1):30–41, March 2008.

[16] J.B. West. *Respiratory physiology: the essentials*. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2008.

[17] G.G. Berntson and J.T. Cacioppo. *Integrative physiology: Homeostasis, allostasis and the orchestration of systemic physiology*, pages 433–452. 2007.

[18] J.A. Quas, A. Bauer, and W.T. Boyce. Physiological reactivity, social support, and memory in early childhood. *Child development*, 75(3):797–814, 2004.