Mathematical Biosciences 255 (2014) 71–82

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Central regulation of heart rate and the appearance of respiratory sinus arrhythmia: New insights from mathematical modeling

Alona Ben-Tal [a,*,1], Sophie S. Shamailov [a], Julian F.R. Paton [b]

[a] Institute of Natural and Mathematical Sciences, Massey University, Albany, Private Bag 102-904, North Shore Mail Centre, Auckland, New Zealand
[b] The School of Physiology and Pharmacology, Bristol CardioVascular, Medical Sciences Building, University of Bristol, Bristol BS8 1TD, UK

ARTICLE INFO

Article history:
Received 19 April 2013
Received in revised form 9 June 2014
Accepted 26 June 2014
Available online 6 July 2014

Keywords:
Mathematical model
Respiratory sinus arrhythmia
Heart rate
Autonomic control

ABSTRACT

A minimal model for the neural control of heart rate (HR) has been developed with the aim of better understanding respiratory sinus arrhythmia (RSA) – a modulation of HR at the frequency of breathing. This model consists of two differential equations and is integrated into a previously-published model of gas exchange. The heart period is assumed to be affected primarily by the parasympathetic signal, with the sympathetic signal taken as a parameter in the model. We include the baroreflex, mechanical stretch-receptor feedback from the lungs, and central modulation of the cardiac vagal tone by the respiratory drive. Our model mimics a range of experimental observations and provides several new insights. Most notably, the model mimics the growth in the amplitude of RSA with decreasing respiratory frequency up to 7 breaths per minute (for humans). Our model then mimics the decrease in the amplitude of RSA at frequencies below 7 breaths per minute and predicts that this decrease is due to the baroreflex (we show this both numerically and analytically with a linear baroreflex). Another new prediction of the model is that the gating of the baroreflex leads to the dependency of RSA on mean vagal tone. The new model was also used to test two previously-suggested hypotheses regarding the physiological function of RSA and supports the hypothesis that RSA minimizes the work done by the heart while maintaining physiological levels of arterial CO_2. These and other new insights the model provides extend our understanding of the integrative nature of vagal control of the heart.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

An optimally-functioning heart is of primary importance to the well-being of the entire organism, so perhaps it is not surprising that heart rate (HR) is tightly controlled by several mechanisms [1]. Factors influencing HR are generally well understood [2] but many questions still remain unanswered. In particular, we are interested in the mechanisms that give rise to respiratory sinus arrhythmia (RSA) – a heart rate variability at the frequency of breathing [3,4] (see Fig. 6). It is widely accepted that the loss of RSA is a prognostic indicator for cardiovascular disease and that the prominent presence of RSA indicates a healthy cardiac system [5], yet the reasons for this are still being debated [6–10].

One controversy is over the main mechanism that gives rise to RSA. Most investigators (for example [6,8]) agree that RSA is mainly due to direct central respiratory modulation of the parasympathetic cardiac signal. Recordings from cardiac vagal motoneurones in the nucleus ambiguus, located in the ventrolateral medulla oblongata, demonstrated waves of excitatory post-synaptic potentials occurring during early expiration [11]. This evidence supports the idea that these neurones are synaptically driven by post-inspiratory respiratory neurones residing within the ventral respiratory column, which is located adjacent to the nucleus ambiguus and thus forming part of a centrally integrated cardio-respiratory network [12]. However, others (for example [7,9]) argue that RSA is mediated by the baroreflex responding to blood pressure oscillations triggered by the abdominal thoracic pump.

Another controversy is over the physiological function of RSA. Hayano et al. [13] hypothesized that the physiological function of RSA is to match ventilation and perfusion in the lungs and thus optimize oxygen (O_2) uptake and carbon dioxide (CO_2) removal. Recently, using mathematical models, we showed that RSA may serve to minimize the energy expenditure of the heart while keeping arterial CO_2 levels at physiological tensions [14]; our theoretical study did not support Hayano's hypothesis.

The models we used in [14] did not include feedback mechanisms of the cardio-respiratory system and numerical simulations were performed by pre-setting the heart rate variations. In this paper we present a model that takes the main features of autonomic heart rate control into account, resulting in the natural

* Corresponding author.
E-mail address: a.ben-tal@massey.ac.nz (A. Ben-Tal).
[1] Equal first place with Sophie Shamailov.

http://dx.doi.org/10.1016/j.mbs.2014.06.015
0025-5564/© 2014 Elsevier Inc. All rights reserved.

appearance of RSA. Our model takes direct central respiratory modulation of the parasympathetic cardiac signal as the main mechanism for RSA but includes blood pressure control via the baroreflex, which allows us to study its effect on RSA.

Many mathematical models that include at least some of the factors that influence the HR have been developed at varying degrees of complexity and emphasis. Some models focus on the calculation of HR given certain parasympathetic and sympathetic signals, but do not include the mechanisms that control the autonomic signals themselves [15–21]. Other models include the baroreflex [22–26] as well as respiratory modulation of the HR either via the central nervous system mechanisms [23,25,26] or via blood pressure which affects the baroreflex [24]. More detailed models take into account several feedback signals that affect cardiac vagal tone such as the baroreflex and pulmonary stretch receptor feedback [27–29] as well as the chemoreflex [28,29] and central respiratory modulation [29]. These more detailed models were used to study a range of phenomena such as HR variability [27], the Valsalva maneuver [29,30], whole-body gas exchange [28] and sleep apnea [29] but did not investigate the controversies surrounding RSA described above.

Several studies aiming at modeling RSA specifically have been published. Barbi et al. [31] developed an integrate-and-fire model with an oscillating threshold that mimics RSA. Other models described the relationship between respiration and heart rate using transfer functions [32,33] or treated the lungs and the heart as two coupled oscillators (see, e.g., [34,35]). These models were used to mimic RSA [32], study the heart rate transient during inspiration or expiration [33] and show that the respiratory system can affect heart rate [34]. A Hodgkin–Huxley type model of the sinus node was developed in [36] and used to study the time-course of RSA when the vagal activity oscillated at the frequency of breathing. Negoescu and Csiki [37] developed a model partly based on [16] that takes into account respiratory effects on HR via the parasympathetic system, but also includes the sympathetic influence on the heart. They compared the output of their model to several experiments related to RSA, most notably the dependence of RSA on breathing frequency and on vagal tone.

The model we present in this paper is different from all previously-published models described above. It includes physiological features not previously included in RSA-specific models (such as respiratory gating of the baroreflex [38,39]) and omits other features that have been taken into account in other, more detailed models (such as the chemoreflex, which we think is less important for the purpose of studying RSA). The model is relatively simple compared to some of the previously-published models but we show that it can still reproduce a wide range of physiological observations and that it can be used to study the causes and benefits of RSA, as well as making novel predictions.

2. Methods

Our study consists of three sections: model development (Section 3), parameter fitting (Section 4.1) and model testing (Section 4.2). Throughout the paper we compare our model simulations with a range of published experimental data, summarized in Table 1. One set of experiments is used to set parameters (this is indicated by a star in Table 1) and another to test the model. The ENGAUGE software available from [40] was used to extract experimental data from published figures. In addition we used mathematical analysis and time simulations to explain the model output, produce new predictions and re-examine the two hypotheses regarding the physiological function of RSA. RSA can be observed in both the heart rate (HR) and the heart-beat period (T_L) and both quantities are used in the experimental literature.

Table 1
Main experiments used for comparison with model output. T_L stands for heart beat period, MAP for mean arterial pressure, RSA for respiratory sinus arrhythmia, SA for sinoatrial and f_R for respiratory frequency. The star indicates experiments that were used to set parameters.

Experiments	References	Species
Dependence of T_L on MAP*	[41–45]	humans
Dependence of RSA on vagal tone*	[46,47] [48]	Dogs Humans
Dependence of RSA on lung volume*	[49–53]	Humans
Dependence of RSA on breathing frequency*	[54] [32,55–57]	Cats Humans
Time response of the SA node	[17,58]	Dogs
Dependence of phase between RSA and lung volume on f_R	[54] [32,57,59]	Cats Humans

Note that some experimental studies derive these quantities directly from recorded time series of HR or T_L while some first perform a Fourier transform. Often in the latter case RSA amplitude refers to the spectral power of the peak in the Fourier transform at breathing frequency. However, whenever possible, we compare our model output to the same exact quantity in the experiments. In the rest of the paper, as in the experimental literature, RSA amplitude, magnitude and strength are used interchangeably and refer to the amplitude of oscillations in T_L and in HR (note however that $HR = 1/T_L$).

3. Model assumptions and description

For convenience, we list all the variables and parameters that are introduced in this section and their physiological meaning in Table 2.

The heart, if denervated, will beat at its intrinsic rate (set by the pacemaker cells in the sinoatrial node) of about 100 beats per minute (bpm). However, the two limbs of the autonomic nervous system constantly innervate the heart: the sympathetic system acts to accelerate the HR while the parasympathetic (acting through the cardiac vagal nerve) decelerates it [60]. The rate of change of the heart-beat period can thus be modeled by:

$$\frac{d\,T_L}{d\,t} = -S_1(T_L - T_{L0}) + c_0 C_{VN} - S_M, \tag{1}$$

where T_L is the heart-beat period (R–R interval), T_{L0} is the intrinsic period of the heart, C_{VN} is the integrated cardiac vagal signal (also referred to as *vagal tone*), S_M represents the sympathetic drive to the heart and S_1 and c_0 are constants. It is well-known that the sympathetic system acts on a much slower time-scale than the parasympathetic [17]. Therefore, we take S_M as being constant in time while C_{VN} is a dynamic variable. We take into account three main factors that affect the vagal tone:

- The baroreflex strives to keep blood pressure constant [61], and since mean arterial pressure (MAP) is proportional to HR, if MAP changes, the arterial baroreceptors send a signal to the heart (via the autonomic nerves) to change HR accordingly. In addition, experiments show that the baroreflex signal is only effective during expiration although the exact location of this gating by respiration is unknown [62–66].

Download English Version:

https://daneshyari.com/en/article/4500062

Download Persian Version:

https://daneshyari.com/article/4500062

Daneshyari.com