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On heart rate variability and autonomic activity in homeostasis and in systemic inflammation

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ABSTRACT

Analysis of heart rate variability (HRV) is a promising diagnostic technique due to the noninvasive nature of the measurements involved and established correlations with disease severity, particularly in inflammation-linked disorders. However, the complexities underlying the interpretation of HRV complicate understanding the mechanisms that cause variability. Despite this, such interpretations are often found in literature. In this paper we explored mathematical modeling of the relationship between the autonomic nervous system and the heart, incorporating basic mechanisms such as perturbing mean values of oscillating autonomic activities and saturating signal transduction pathways to explore their impacts on HRV. We focused our analysis on human endotoxemia, a well-established, controlled experimental model of systemic inflammation that provokes changes in HRV representative of acute stress. By contrasting modeling results with published experimental data and analyses, we found that even a simple model linking the autonomic nervous system and the heart confound the interpretation of HRV changes in human endotoxemia. Multiple plausible alternative hypotheses, encoded in a model-based framework, equally reconciled experimental results. In total, our work illustrates how conventional assumptions about the relationships between autonomic activity and frequency-domain HRV metrics break down, even in a simple model. This underscores the need for further experimental work towards unraveling the underlying mechanisms of autonomic dysfunction and HRV changes in systemic inflammation. Understanding the extent of information encoded in HRV signals is critical in appropriately analyzing prior and future studies.

1. Introduction

A marker of a healthy functioning autonomic nervous system (ANS) is variability in the time intervals between successive heart beats, known as heart rate variability (HRV). There are a wide range of analytical techniques to quantify HRV from heart rate (HR) measurements [6]. Power spectral analysis has traditionally been viewed as a way to quantify the states of the sympathetic and parasympathetic branches of the ANS since both branches converge at the sinoatrial (SA) node and convey oscillatory signals to the heart [30]. This type of mechanistic interpretation of HRV data, where physiological meaning is derived directly from HRV analysis, has long been a contentious issue [12]; however, broad inferences about autonomic activity are still commonly made from HRV data, due in large part to the difficulty of more directly measuring autonomic activity [46]. Analysis of HRV data aimed at diagnostic and prognostic applications is appealing because of the noninvasive nature of HRV assessment and the apparent correlation between HRV depression, i.e., loss of HR variability, with disease severity [4,5,14,25,34,52]. In particular, dysregulation of autonomic signaling is seen as a critical component in the progression of inflammation-linked disorders like sepsis [4,48], which has motivated research on inflammation and HRV. However, there is still a limited understanding of the precise mechanistic links between inflammation and HRV, which limits the clinical uses of HRV metrics and the potential knowledge gained from HRV analysis [11,43].

Due to the significant challenges remaining in understanding the underlying mechanistic basis of the inflammatory response in general, there has been extensive work on experimental models of systemic inflammation such as the human endotoxemia model [28]. While a number of studies have explored the effect of

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endotoxemia on HR and HRV as well as other metrics of autonomic function [2,17,23,24,26,27,39,40,42,44], careful experimental design and analysis is required to interpret results and coherently build a conceptual framework linking inflammation with autonomic dysfunction [43,45]. It is important to extract the maximal amount of information from experiments while understanding their limitations and the scope of remaining unknowns. For instance, while changes in HRV metrics are often cited as evidence for changes in autonomic function, the underlying physiological complexity makes such conclusions difficult [12,19,20]. If alternative hypotheses can equally plausibly explain experimental observations, then further investigations are required for a more complete understanding; but if this is not appreciated, then scientific progress will be impeded. In this respect, a mathematical model can serve as a framework allowing for the rationalization of experimental results and the elucidation of deeper meaning [32].

In this manuscript, we study two models describing the relationship between the autonomic nervous system and patterns of heart beats. These models incorporate mechanisms that govern the relationship between autonomic activity and both HR and HRV, such as high frequency autonomic oscillations, binding kinetics of neurotransmitters to receptors at the SA node, changes in mean levels of autonomic activity, and inflammation-induced uncoupling between the heart and the autonomic nervous system. Frequency-domain metrics are used to quantify HRV, as these metrics are commonly used in literature and are most directly related to the autonomic oscillations included upstream in the model. We analyzed these models first to illustrate the challenges inherent in inferring autonomic function from HR and HRV data alone. We then investigated the human endotoxemia response in particular by leveraging our models to explain and rationalize experimental observations. The unintuitive relationships between autonomic signaling and HRV play a role in explaining the effect of the cholinergic anti-inflammatory pathway on the inflammatory response. Furthermore, by combining experimental data with model analysis, we concluded that significant uncertainty remains in the general function of the autonomic nervous system, even in a very controlled experimental model like human endotoxemia. Multiple plausible patterns of autonomic changes could be leading to the observed responses (increased HR, decreased HRV, uncoupling between the autonomic nervous system and the heart) and it is important to properly interpret what is learned from experiments measuring HRV.

2. Methods

HRV arises largely due to oscillations in autonomic activity which are apparent in the power spectrum of RR intervals primarily in two frequency bands termed low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) [51]. A model to evaluate the relationship between the autonomic nervous system and the beating of the heart requires, at a minimum, four components, as shown in Fig. 1: (1) a representation of sympathetic activity; (2) a representation of parasympathetic activity; (3) a combination of sympathetic and parasympathetic activities, representing autonomic modulation of the SA node; (4) a method to convert this autonomic modulation into heart beats, which can then be analyzed through the application of HRV metrics, as we have previously demonstrated [44]. Each of these four components is, in reality, made up of a multitude of complex interactions and feedback loops, such as autonomic oscillations which arise due to the baroreflex and the respiratory sinus arrhythmia. However, high-level properties of the system can be studied without exhaustively detailing these components. A simple model including these

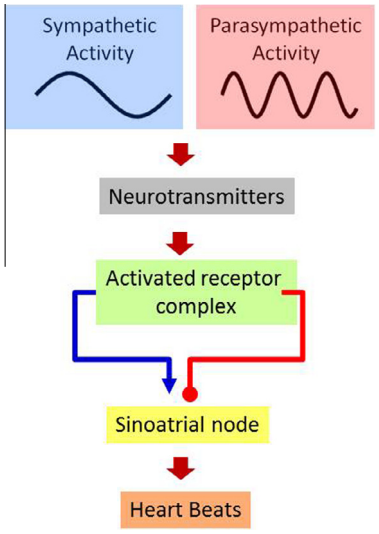

Fig. 1. Components of the models linking autonomic activity with heart beats shown in Eqs. (1) and (2). Sympathetic and parasympathetic nerves impose oscillatory activation of the sinoatrial (SA) node, leading to variability in discrete heart beats. The frequencies of oscillations in sympathetic and parasympathetic activities are derived from the observed frequencies present in the HR power spectrum, the LF and HF bands, 0.095 Hz and 0.275 Hz, respectively.

four components was earlier investigated by Brennan et al. in an attempt to gain insight into the relationship between autonomic signaling and Poincaré plots of RR intervals [7]. Chiu et al. analyzed a slightly more complex model that accounts for some of the signal transduction steps between the release of autonomic neurotransmitters and the regulation of SA node activity [8,9]. The goal was to investigate the relationship between autonomic inputs, such as oscillating frequency and mean levels of autonomic outputs, and the beating of the heart. Eq. (1) shows a general example of this type of model structure.

$$nor = m_{nor} + a_{nor} \cdot \sin(\omega_{nor} \cdot t) \tag{1a}$$

$$ach = m_{ach} + a_{ach} \cdot \sin(\omega_{ach} \cdot t) \tag{1b}$$

$$m(t) = k_{icpm} + k_{nor} \cdot nor - k_{ach} \cdot ach \tag{1c}$$

$$I = \int_{t_k}^{t_{k+1}} m(t)\,dt \tag{1d}$$

The variables *nor* and *ach* represent norepinephrine and acetylcholine, neurotransmitters released by the sympathetic and parasympathetic nerves, respectively which modulate the beating of the heart. Each of these variables has a mean level m_k as well as an oscillatory component with amplitude a_k and frequency ω_k. These sinusoids are the source of variability in the model and represent the underlying LF and HF signals apparent in HRV data. In reality, oscillations at other time scales are also present, such as circadian rhythms, but the analysis presented here focuses only on a short time scale so these much higher frequency rhythms are not included. The two autonomic variables are linearly combined to produce $m(t)$, the autonomic modulation of the SA node. This equation also includes the parameter k_{icpm} to account for the intrinsic cardiac pacemaker function in the absence of autonomic signaling. Sympathetic activity increases $m(t)$ and parasympathetic activity decreases $m(t)$. Then, Eq. (1d) defines an integral pulse frequency modulation (IPFM) model, which consists of the repeated integration of $m(t)$ up to a threshold I. Whenever this threshold is reached, it represents a heartbeat. Thus, the differences between successive firings of the IPFM model constitute RR intervals. It is