A Selective Quantification of Cardiac Sympathetic and Parasympathetic Control and Its Validation through Pharmacological Blockade

X Xiao[1], R Mukkamala[2], RJ Cohen[1]

[1]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, USA
[2]Dept. of Electrical and Computer Engineering, Michigan State University, East Lansing, MI, USA

Abstract

A quantitative evaluation of parasympathetic and sympathetic function is often desirable in clinical practice. We previously proposed a noninvasive method to selectively quantify cardiac sympathetic and parasympathetic control. This method involves system identification analysis of the coupling mechanism between the instantaneous lung volume and heart rate signals. In the present study, we validated this method in conjunction with a newly developed Weighted Principal Component Regression-based system identification technique. We utilized data collected from 14 subjects in the control and autonomic blockade conditions in the standing posture. The results showed that a statistically significant reduction in parasympathetic function and sympathetic function was identified when atropine or propranolol was administered, respectively, and with autonomic double blockade, consistent with the well-accepted physiologic knowledge.

1. Introduction

The autonomic nervous system plays an important role in regulating cardiovascular hemodynamics. A quantitative study of the autonomic function can provide insights in understanding mechanisms of various pathophysiological processes, such as orthostatic hypotension, microgravity- or bed rest-induced cardiovascular deconditioning, *et al*. It can also help monitor disease development and guide therapies for, *e.g.*, diabetes, heart failure and other illnesses related to autonomic abnormality. Many noninvasive techniques have been proposed to quantitatively evaluate autonomic function. Heart rate (HR) response to provocative maneuvers such as deep respiration, postural change, and a Valsalva maneuver are often used to measure parasympathetic function [1]. Sympathetic function is typically evaluated by measuring the blood pressure (BP) response to postural change, a cold pressor stimulus, and isometric exercise [1]. These tests require patient participation and they are usually poorly standardized due to varying patient effort. In the past two decades, signal processing techniques have been developed to determine changes in autonomic activity with minimal active patient participation. HR spectral analysis [1,2] is one of the most widely used techniques for this purpose. However, with this method, an accurate quantification of the sympathetic control is usually difficult to obtain due to the overlapping of the parasympathetically and sympathetically regulated HR components in the low frequency range. To enable a selective quantification, other techniques have been developed assuming independence or orthogonality of the two autonomic pathways [3-5]. However, such assumptions are limited in that it is well-known that the parasympathetic and sympathetic branches interact with each other in their normal operation [6].

We previously proposed a noninvasive method to selectively quantify cardiac sympathetic and parasympathetic control and validated it using data associated with postural change [7]. This method extracts indices to represent sympathetic and parasympathetic function from the coupling mechanism between instantaneous lung volume (ILV) and HR. In this paper, we employ a newly developed system identification technique to identify this coupling mechanism and, subsequently, we validate the resulted autonomic indices by employing data collected in pharmacological blockade experiments. It should be noted that we model the ILV to HR coupling as a linear time-invariant (LTI) system. The LTI assumption is applicable when only stationary signals with small fluctuations are involved.

2. Methods

2.1. Indices of cardiac autonomic function

It is generally accepted that the ILV to HR coupling is mainly regulated by the autonomic system. This notion was demonstrated, for example, in [8], by showing that the ILV to HR impulse response was nearly obliterated in autonomic double blockade experiments. To interpret the components in this impulse response as representatives of

parasympathetic and sympathetic function, respectively, we first review some experimental results in studying the response of the sinoatrial (SA) node discharge rate to parasympathetic and sympathetic neural stimulation.

Berger and coworkers [9] studied the dynamical behavior of the canine cardiac pacemaker – the SA node. The excitation of this system was achieved with a broad-band input signal whose frequency varied about some mean value in proportion to a band-limited Gaussian white-noise signal. The impulse responses of the sinoatrial node discharge rate under pure vagal stimulation and pure sympathetic stimulation at a mean rate of 4 Hz and 1 Hz, respectively, are shown in Figure 1, as adapted from [9]. The parasympathetic response reflects the lack of delay and the broad-band nature of the atrial response to vagal excitation, whereas the sympathetic response reveals a delay of roughly 2 s and a slow-changing feature [9]. Comparing Figure 1 to a representative ILV to HR impulse response illustrated in Figure 2, it can be appreciated that the parasympathetic and sympathetic impulse responses mimic, respectively, the initial upright wave and the delayed negative wave (with a reverse in polarity) in the ILV→HR impulse response.

Assuming linearity of the system, we can interpret and model it into two components as follows (see Figure 2). The initial upright wave represents the brief increase in HR mediated by parasympathetic withdrawal as a result of an impulse ILV input (very rapid inspiration and expiration). The upstroke begins at time < 0, indicating that HR rises in anticipation of the corresponding inspiration which reflects the time delay between central initiation of cardio-respiratory activity and the physical onset of inspiration [9,10]. The delayed negative deflection is the consequence of sympathetic withdrawal which is slower than the parasympathetic response. Therefore, the ILV→HR impulse response consists of two main separable components each reflecting the modulation of the SA node by autonomic efferent signals. If we divide the impulse response into two components at the point where it first crosses zero after reaching the peak (Figure 2), the areas covered by the two components quantify parasympathetic and β-sympathetic efferent activity responsiveness, respectively. Note that from Figure 2, there is little significant overlap in time between the parasympathetic response and the sympathetic response. Our separation approach assumes that such overlap can be neglected.

2.2. Identification of the ILV to HR coupling

To identify the coupling mechanism between ILV and HR, another signal, arterial blood pressure (ABP), must also be considered because of its significant contribution to HR variation. Thus, the system under study is a dual-input, single-output one. In addition, ABP and HR are involved in closed-loop which encompasses both the baroreflex pathway and the circulatory mechanics. Moreover, the ILV→HR coupling is noncausal due to the interaction between central control of respiration and HR [10]. To identify this relatively complicated system, we employ a newly developed system identification method to analyze the ILV to HR coupling. This method is based on a weighted principal component regression (WPCR) approach [11].

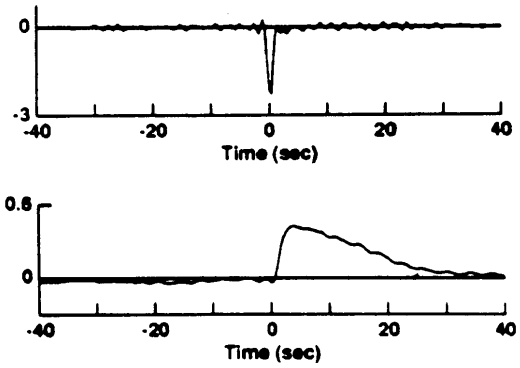

Figure 1. Impulse responses of the canine SA node discharge rate with vagal stimulation (upper) and sympathetic stimulation (lower) [9].

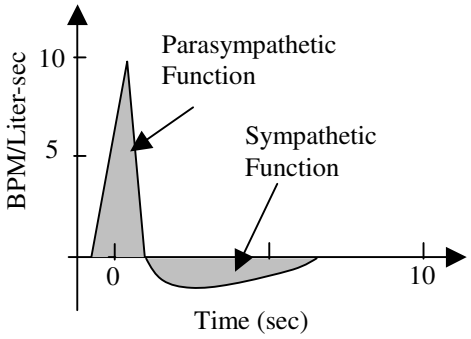

Figure 2. Model of a representative ILV to HR impulse response (note that the axes are labeled only to provide an example of the scale.)

Briefly, in the WPCR approach, the current output is modeled as a linear combination of the current and past inputs (i.e., the so called moving average model). Therefore, the impulse response of the system which is assumed to be finite approximately is essentially the unknown linear coefficients in this structure. To solve for the impulse response, the input data matrix (consisting of

delayed vectors of the input signal) is first weighted by a diagonal weighting matrix. We define the diagonal elements of this weighting matrix as samples of an exponentially decaying function. The weighting constant of this function can be optimized through an iterative search with the aim of minimizing the model selection criterion to be described below. Then, the weighted data matrix is represented with its singular value decomposition (SVD). SVD generates a left singular vector matrix and a right singular vector matrix, in addition to a diagonal matrix of singular values. Subsequently, the principal components (PCs, also left eigenvectors) of the input data resulted from SVD are added into the model structure, one at a time, in an order of descending singular values. In this way, the candidate models are represented with nesting structures differing by the number of PCs involved. The input data play a significant role in determining candidate models, because the PCs are data-specific. The "best" model can then be selected using one of the model order selection criteria, such as the minimum description length (MDL) criterion [12]. Finally, the impulse response of the system can be identified once the coefficients of the PCs were calculated with least squares estimation.

A most important feature of the WPCR method is its frequency-selective property in solving a time domain parametric system identification problem. Based on the properties of Toeplitz matrices [13], it can be shown that the left singular vectors resulted from the SVD are sinusoidal asymptotically, while each right singular vector is a sinusoid modulated by the weighting function. The singular values correspond to the "amplitudes" of these sinusoids. Therefore, candidate models in the WPCR method are essentially constructed in consideration of different frequency components specific to the data being analyzed. In this way, the WPCR method attempts to fit the output signal using the dominant (in energy) frequency components inherent in the input data. Since the insignificant frequency components (with relatively small singular values) are excluded, this method reduces the error variance in the estimated coefficients. Thus, the frequency selective property of the WPCR-based method should be advantageous when colored signals (e.g. physiologic signals) are involved in system identification.

Note that with the frequency domain interpretation, the building blocks of the estimated impulse response are sinusoids modulated by the weighting function (decaying exponential function) which are more appropriate than pure sinusoids (in the non-preweighting case) in modeling finite impulse responses. Moreover, our weighting scheme incorporates the well-known *a priori* knowledge that the current output correlates more with recent inputs than with the remote ones.

The WPCR method can be extended to handle closed-loop systems by incorporating a scheme similar to that in the generalized-least-squares (GLS) method [14]. The major difficulty in closed-loop identification comes from the correlation of the noise processes with the input/output signals. To circumvent this problem, the GLS scheme models the residual noise explicitly with an autoregressive structure iteratively until convergence is achieved.

2.3. Experimental data

To evaluate the effectiveness of the proposed method for quantitating parasympathetic and sympathetic function, we employed previously published data collected from 14 healthy male subjects [8,15]. The experimental protocol has been described in detail in [15]. Briefly, ILV, ABP and ECG signals were obtained with the subjects following a random breathing protocol [8]. This protocol broadens the frequency content of the ILV signal and enables an identification of the ILV to HR coupling in a wide frequency spectrum. After collection of control data in the standing posture, seven subjects received atropine (0.03 mg/kg iv, a competitive antagonist of the parasympathetic receptors) followed by propranolol (0.2 mg/kg iv, a non-selective beta-sympathetic receptor blocking agent). Data recordings were obtained after each medication was given. The remaining seven subjects received the same dosages of drugs but in the reverse order. We employed approximately 6 minutes of data in the analyses hereafter which were downsampled to 1.5 Hz from 360 Hz.

3. Results

In the data analysis, zero-mean ABP and HR signals were normalized with respect to their corresponding time-averaged values and zero-mean ILV with respect to its standard deviation. Univariate comparisons between the autonomic indices of the control condition and the autonomic blockade conditions for each subject were conducted using Wilcoxon's signrank tests. Table 1 shows the averaged autonomic indices identified under each experimental intervention. Both the parasympathetic index (P_I) and the sympathetic index (S_I) decreased significantly after autonomic double blockade. In addition, they were each reduced after atropine (A) and propranolol (P) injection, respectively, consistent with the expected physiology. The decrease of S_I with atropine may be due to a compensatory mechanism attempting to counteract the resulted increase in HR.

4. Discussion and conclusions

In this paper, we presented and validated a non-invasive method to selectively estimate cardiac parasympathetic and sympathetic function. This method analyzes the impulse response between second-to-second ILV and HR signals. It is based on the experimental findings that the parasympathetic control of HR is rapid and brief and the sympathetic control of HR usually induces a delayed response. This method does not impose the assumption that the parasympathetic and sympathetic pathways act independently or orthogonally, as necessitated by other methods in the literature.

Table 1 Parasympathetic and sympathetic indices

	Control	Atropine	Propranolol	Double
P_I	1.11±0.16	0.11±0.05*	0.72±0.12	0.27±0.06§
S_I	1.96±0.60	0.17±0.09*	0.91±0.67*	0.23±0.08†

Values are (mean±SE)*100 (unitless); P_I: parasympathetic index; S_I: sympathetic index; Wilcoxon's signrank tests: *p<0.05; †p<0.01; §p<0.001;

The system identification of the ILV to HR impulse response was carried out utilizing a newly-developed WPCR based method. In contrast to the conventional methods, the strength of the WPCR method lies in its frequency selective property. As a result, it allows the data to play a significant role in determining candidate models. By excluding frequency components weakly represented in the input, this approach may reduce the variance of the estimated transfer function when the input signal is colored. In principle, this may allow an optimal reduction in mean squared error in the estimation of model parameters.

Through experimental data, we demonstrated that the proposed method was able to identify all expected changes in the parasympathetic and sympathetic function when each or both branches were blocked pharmacologically. These results confirmed the effectiveness of our method for the quantification of autonomic function.

Acknowledgements

The NASA supported this work through the NASA Cooperative Agreement NCC 9-58 with the NSBRI.

References

[1] Freeman R, Saul JP, Roberts MS, Berger RD, Broadbridge C, Cohen RJ. Spectral analysis of heart rate in diabetic autonomic neuropathy. A comparison with standard tests of autonomic function. Arch Neurol 1991;48(2):185-90.

[2] Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213(4504):220-2.

[3] Vetter R, Vesin JM, Celka P, Scherrer U. Observer of the human cardiac sympathetic nerve activity using noncausal blind source separation. IEEE Trans Biomed Eng 1999;46(3):322-30.

[4] Vetter R, Virag N, Vesin JM, Celka P, Scherrer U. Observer of autonomic cardiac outflow based on blind source separation of ECG parameters. IEEE Trans Biomed Eng 2000;47(5):578-82.

[5] Zhong Y, Wang H, Ju K, Jan KM, Chon KH. Nonlinear analysis of the separate contributions of autonomic nervous systems to heart rate variability using principal dynamic modes. IEEE Trans Biomed Eng 2004;51(2):255-62.

[6] Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. J Auton Nerv Syst 1979;1(1):33-52.

[7] Xiao X, Mukkamala R, Sheynberg N, et al. Effects of Simulated Microgravity on Closed-loop Cardiovascular Regulation and Orthostatic Intolerance: Analysis by Means of System Identification. J Appl Physiol 2003;96:489-97.

[8] Mullen TJ, Appel ML, Mukkamala R, Mathias JM, Cohen RJ. System identification of closed-loop cardiovascular control: effects of posture and autonomic blockade. Am J Physiol 1997;272(1 Pt 2):H448-61.

[9] Berger RD, Saul JP, Cohen RJ. Transfer function analysis of autonomic regulation. I. Canine atrial rate response. Am J Physiol 1989;256(1 Pt 2):H142-52.

[10] Triedman JK, Perrott MH, Cohen RJ, Saul JP. Respiratory sinus arrhythmia: time domain characterization using autoregressive moving average analysis. Am J Physiol 1995;268(6 Pt 2):H2232-8.

[11] Xiao X, Mukkamala R, Cohen RJ. A Weighted Principal Component Regression Approach for System Identification. In: IEEE Workshop on Statistical Signal Processing; 2003; St. Louis, Missouri: IEEE; 2003.

[12] Rissanen J. Modelling by shortest data description. Automatica 1978;14:465-71.

[13] Brillinger D. Time series, data analysis and theory: Holden-Day, Inc; 1981.

[14] Clarke DW. Generalized-least-squares estimation of the parameters of a dynamic model. In: 1st IFAC Symp Identification Automat Contr Syst; 1967: Prague; 1967. p. 1-10.

[15] Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;261(4):H1231-45.

Address for correspondence

Richard J. Cohen
Room E25-335a
Massachusetts Institute of Technology
45 Carleton Street
Cambridge, Massachusetts 02142
rjcohen@mit.edu