Selective Quantification of Cardiac Sympathetic and Parasympathetic Nervous Function Based on the Heart Rate Baroreflex Impulse Response

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Abstract

We introduce an improved technique for selectively quantifying cardiac sympathetic and parasympathetic nervous function based on the identification of the heart rate (HR) baroreflex impulse response from non-invasive cardio-respiratory measurements. We have tested the technique with respect to 24 humans breathing randomly or spontaneously under selective pharmacological autonomic blockade. Our results show that the technique performs much better than traditional HR power spectral indices in terms of predicting the known drug effects and is effective during spontaneous breathing.

1. Introduction

Over two decades ago, Cohen and co-workers popularized power spectral analysis of resting heart rate (HR) variability by showing that it could provide specific measures of the cardiac autonomic nervous system (ANS) [1,2]. Using selective pharmacological autonomic blockade, these investigators specifically demonstrated that the high frequency (HF, 0.15-0.4 Hz) power of HR variability is mediated by the parasympathetic nervous system (PNS), whereas the low frequency (LF, 0.04-0.15 Hz) power is jointly mediated by the β-sympathetic nervous system (SNS) and PNS. Today, the HF power of HR variability is widely accepted as a useful index of the PNS, while the LF power, expressed in normalized units, and the ratio of the LF power to HF power are considered by some to be indices of the SNS [3].

Despite their popularity, the HR power spectral indices suffer from two limitations. The first limitation is that neither the normalized LF power nor the LF/HF power provides an effective index of the SNS, because the LF power reflects the complex functioning of both branches of the ANS. As a result, the LF/HF power is considered by others to be an index of sympatho-vagal balance [3]. The second limitation is that none of the HR power spectral indices is truly specific to the ANS, since HR is just one of its outputs. For example, it is well known that the ultimate source of the HF power is respiration [2]. Thus, changes in the HF power may reflect changes in respiratory effort as well as ANS functioning.

Consequently, investigators have recently sought improved ANS indices based on more sophisticated signal processing analyses of beat-to-beat cardiovascular variability. Vetter et al. proposed to selectively quantify the SNS and PNS using blind source separation [4,5]. However, this approach assumes that the two branches of the ANS operate independently of each other, even though they are known to be reciprocally related [6]. Chon and co-workers proposed to determine the separate contributions of the SNS and PNS in modulating HR based on a nonlinear expansion [7]. Remarkably, these investigators were able to show that the first two principal dynamics modes of the first- and second-order Volterra kernels derived from HR variability just happened to correspond to PNS and SNS functioning in their datasets.

These recent studies have sparked our own interest in pursuing specific indices of SNS and PNS function. We have recently proposed a non-invasive technique for selectively quantifying the SNS and PNS based on the HR baroreflex impulse response, which relates variability in arterial blood pressure (ABP) to HR [8]. More specifically, first, the impulse response is estimated by applying system identification to measured beat-to-beat fluctuations in HR, ABP, as well as respiratory activity in terms of instantaneous lung volume (ILV). Then, the estimated impulse response is decomposed into SNS and PNS components based on known physiology. Finally, scalar indices of each ANS branch are computed from the respective impulse response components. We have previously demonstrated the promise of this technique in humans following a random-interval breathing protocol [8]. The purpose of this protocol was to broaden the spectral content of the measurements for more reliable system identification [9].

In this study, we improve the system identification analysis by employing a recently developed, weighted principal component regression method [10] and propose more specific indices of ANS function. We then conduct more thorough testing of the refined technique, while comparing it to traditional HR power spectral indices, based on two previously collected datasets comprising

cardio-respiratory measurements from 14 healthy humans breathing randomly and 10 healthy humans breathing spontaneously under selective pharmacological autonomic blockade [11,12].

2. The technique

Our basic idea for developing specific indices of SNS and PNS function is to exploit the information reflected in the dynamic couplings between beat-to-beat fluctuations in multiple cardio-respiratory signals. This idea stems from the experimental findings of three previous studies [13,14,15]. These studies have generally shown that 1) the couplings responsible for modulating *resting* HR fluctuations are governed, to first order, by linear and time-invariant relationships [14]; 2) the impulse response coupling fluctuations in ABP to HR (ABP→HR), which characterizes the HR baroreflex, and the impulse response coupling fluctuations in ILV to HR (ILV→HR), which is responsible for mediating the respiratory sinus arrhythmia phenomenon, are exclusively mediated by both branches of the ANS [13]; and 3) the initial, fast dynamics in the ABP→HR and ILV→HR impulse responses are specifically reflective of the PNS [13,15].

According to the above studies, a technique for selectively quantifying the SNS and PNS may be based on the ILV→HR impulse response and/or the ABP→HR impulse response. Indeed, we have previously proposed techniques using each of these impulse responses [8,16]. However, accurate estimation of the ILV→HR impulse response may be more reliant on the random-interval breathing protocol, which may not always be viable in practice (*e.g.*, intensive care unit). We therefore describe here an improved technique based on the ABP→HR impulse response. This technique is specifically implemented in three steps (Figures 1 and 2).

In the first step, the ABP→HR impulse response is estimated by applying parametric system identification to beat-to-beat fluctuations in HR, ABP, and ILV according to the block diagram of Figure 1. In this way, the technique is able to 1) account for the known correlation between the ABP and ILV inputs to HR by including ILV as a second input (*i.e.*, the ILV→HR impulse response is simultaneously identified) and 2) disentangle the feedback baroreflex effects of fluctuations in ABP on HR from the feedforward mechanical effects of fluctuations in HR on ABP through the imposition of causality [17]. The block diagram of Figure 1 also includes a perturbing noise source N_{HR}, which is also estimated and represents the residual HR variability not accounted for by the two impulse responses. The block diagram is mathematically represented here by the following dual-input equation:

$$HR(t) = \sum_{i=1}^{m} h(i)ABP(t-i) + \sum_{i=n'}^{n} g(i)ILV(t-i) + N_{HR}(t)$$

$$N_{HR}(t) = \sum_{i=1}^{p} d(i)N_{HR}(t-i) + W_{HR}(t),$$

where t is discrete time, the terms m, n', n, and p limit the number of parameters in the equation, and W_{HR} is the unmeasured residual error. The sets of parameters $\{h(i), g(i)\}$ specify finite impulse response (FIR) approximations respectively characterizing ABP→HR and ILV→HR, while the residual error W_{HR} and the set of parameters $\{d(i)\}$ fully define N_{HR}. (Note that causality is imposed here by virtue of forcing the $h(i)$ parameters to zero for non-positive values of i.) The parameters are estimated from ~6-min intervals of beat-to-beat fluctuations in normalized HR, ABP, and ILV signals sampled at 1.25-1.5 Hz based on a weighted principal component regression method [10]. This method succinctly represents the FIR approximations, asymptotically, with exponentially varying sinusoidal basis functions that reflect the dominant frequency content of the inputs. Thus, the number of unknown parameters for estimation is dramatically reduced and reliable system identification may potentially be achieved even without the random-interval breathing protocol.

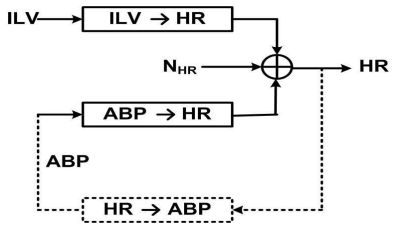

Figure 1. Block diagram illustrating how the technique identifies the ABP→HR impulse response.

In the second step, the estimated ABP→HR impulse response is separated into SNS and PNS components based on the prior studies described above. More specifically, the initial downstroke of the ABP→HR impulse response is regarded as the first part of the PNS component (Figure 2). The time interval of the initial downstroke is precisely defined to be from time zero to the time of the minimum impulse response value, which has been shown to be a specific index of the PNS [13]. The remaining part of the PNS component (*i.e.*, the return of this stable component to zero), which is usually obscured by the subsequent SNS component, is assumed to be symmetric to the visible first part (Figure 2). This assumption is based on a previous canine study showing that the impulse response characterizing the HR response to pure external vagal stimulation may be approximated as an isosceles triangle whose first leg is similar in timing to the initial downstroke of the ABP→HR impulse

response [15]. The SNS component is then established by subtracting the total PNS component from the entire ABP→HR impulse response (Figure 2).

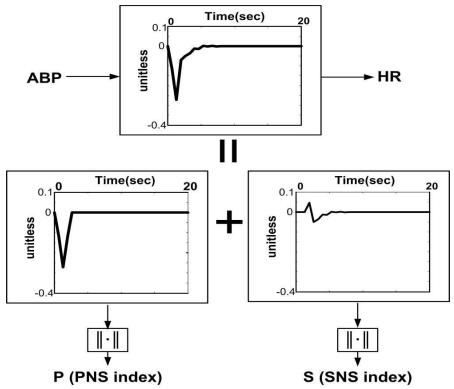

Figure 2. Diagram illustrating how the technique derives PNS (P) and SNS (S) indices from the identified ABP→HR impulse response.

In the third step, scalar indices representing SNS and PNS function are established by computing the two-norm of the SNS (S) and PNS (P) impulse response components (Figure 2). In this way, in contrast to the HR power spectral indices and the indices of our original HR baroreflex technique [8], the S and P indices reflect only the ANS and not their inputs.

3. Experimental evaluation

3.1. Human cardio-respiratory data

We evaluated the improved technique with respect to two existing human cardio-respiratory datasets collected under various postures and selective pharmacological autonomic blockade. The datasets are described in detail elsewhere [11,12]. Here, we briefly present those aspects of the two datasets that are relevant to the present study.

The first dataset comprises surface ECG, ABP (radial artery catheter), and ILV (chest-abdomen inductance-plethysmography) recordings from 14 young and healthy humans. Throughout the recordings, the subjects initiated each respiratory cycle based on a sequence of randomly spaced audible tones. The recordings for half the subjects were obtained under the following conditions: 1) supine, control; 2) standing, control; 3) supine, atropine; 4) standing, atropine; 5) supine, double blockade (propranolol+atropine); and 6) standing, double blockade. The recordings for the remaining subjects were obtained similarly with the two drugs given in reverse order.

The second dataset includes surface ECG, ABP (finger-cuff photoplethysmography), and ILV (chest-abdomen inductance-plethysmography) recordings from ten young and healthy humans. The recordings were obtained on two separate days while the subjects were breathing spontaneously. On one day, the recordings were obtained under the following conditions: 1) 4° head-down tilt, control; 2) supine, control; 3) supine, propranolol; 4) supine, double blockade; and 5) 4° head-down tilt, double blockade. On the other day, the recordings were obtained under the following conditions: 1) supine, control; 2) 30° upright tilt, control; 3) 30° upright tilt, atropine; 4) 30° upright tilt, double blockade; and 5) supine, double blockade.

3.2. Data analysis

A HR tachogram was constructed from each surface ECG as described in [18]. The technique was then applied to each set of HR, ABP, and ILV signals as described above to arrive at the S and P indices. For comparison, power spectral analysis was applied to each HR tachogram as described in [18], and the HF, LF/HF, and normalized LF (LF/(LF+HF)) powers were computed. Finally, paired t-tests were performed to determine if the ANS indices were altered from the control condition to each drug condition. A $p<0.05$ was considered statistically significant.

4. Results

Tables 1 and 2 summarize the group average results of the P and S indices and the HF and LF/HF powers from the first and second datasets, respectively. These tables show that the P index was able to correctly predict the expected effects of the drugs on the PNS for all 12 of the performed statistical comparisons, while the HF power was in error as an index of the PNS for three of the 12 comparisons. The tables also indicate that the S index was able to correctly predict the expected effects of the drugs on the SNS for nine out of the 12 comparisons. In contrast, the LF/HF power was in error as an index of the SNS for seven out of the 12 comparisons and may actually be a somewhat better marker of sympatho-vagal balance. Moreover, though not shown here, the normalized LF power was likewise an ineffective index of the SNS. Note that the S index twice predicted a reduction in SNS functioning following the administration of atropine. It is possible that these changes are real (*i.e.,* not in error) as a result of a compensatory mechanism aiming to counteract the increase in HR. Overall, *regardless of the chosen level of statistical significance*, the tables indicate that the P and S indices are substantially better markers of the SNS and PNS than traditional HR power spectral indices.

5. Summary and conclusion

In summary, we have refined a non-invasive technique for selectively quantifying SNS and PNS

function based on the identification of the HR baroreflex impulse response and known physiology. We have tested the technique in 24 human subjects breathing randomly or spontaneously under selective pharmacological autonomic blockade. Our results show that the technique is much better than HR power spectral analysis in terms of correctly predicting the known drug effects and is effective even during spontaneous breathing. With further successful testing, the technique may ultimately be employed to help guide therapy in various diseases such as diabetic autonomic neuropathy and heart failure.

Table 1. First dataset (random-interval breathing) results.

	Supine					
	C	A	C	Pr	C	DB
P	7.2±1.1	$2.0\pm0.5^{0.028}$	8.7±2.1	$10.6\pm1.7^{0.410}$	8.1±1.3	$1.7\pm0.4^{0.001}$
HF	8.7±2.0	$0.2\pm0.1^{0.024}$	5.6±1.4	$4.9\pm1.3^{0.040}$	6.7±1.3	$0.1\pm0.02^{0.001}$
S	4.9±1.0	$2.4\pm0.7^{0.136}$	4.0±0.5	$5.2\pm0.7^{0.100}$	4.7±0.6	$1.2\pm0.2^{0.0004}$
LF/HF	2.8±0.2	$9.3\pm5.0^{0.248}$	3.3±0.4	$2.6\pm0.3^{0.025}$	3.1±0.3	$2.1\pm0.6^{0.121}$
	Standing					
	C	A	C	Pr	C	DB
P	4.7±0.3	$2.7\pm0.5^{0.0401}$	4.6±0.7	$3.8\pm0.5^{0.432}$	4.6±0.4	$1.7\pm0.2^{0.0000}$
HF	7.7±1.5	$1.4\pm0.5^{0.020}$	5.4±1.1	$2.3\pm0.3^{0.010}$	6.4±0.9	$1.2\pm0.3^{0.0001}$
S	4.7±0.6	$1.6\pm0.2^{0.003}$	4.1±0.4	$2.2\pm0.5^{0.018}$	4.1±0.3	$1.8\pm0.2^{0.0003}$
LF/HF	5.7±0.4	$13.1\pm5.7^{0.273}$	5.7±0.8	$4.5\pm0.6^{0.088}$	5.9±0.5	$11.3\pm3.3^{0.095}$

Table 2. Second dataset (spontaneous breathing) results.

	Supine		Supine		Head-down tilt	
	C	Pr	C	DB	C	DB
P	9.9±3.5	$2.7\pm0.5^{0.066}$	11.6±3.3	$0.02\pm0.01^{0.012}$	11.1±2.4	$0.4\pm0.1^{0.002}$
HF	2.1±0.4	$2.9\pm1.8^{0.598}$	2.1±0.4	$0.1\pm0.02^{0.004}$	1.8±0.4	$0.1\pm0.01^{0.002}$
S	10.1±2.7	$2.9\pm1.1^{0.034}$	9.0±2.1	$0.4\pm0.2^{0.004}$	9.4±2.2	$0.6\pm0.2^{0.005}$
LF/HF	1.0±0.1	$0.8\pm0.1^{0.113}$	1.2±0.2	$0.8\pm0.1^{0.157}$	1.0±0.3	$0.9\pm0.1^{0.678}$
	Upright tilt		Upright tilt		Supine	
	C	A	C	DB	C	DB
P	10.8±2.1	$2.1\pm0.7^{0.003}$	10.2±2.2	$0.8\pm0.3^{0.003}$	11.1±2.9	$0.5\pm0.2^{0.011}$
HF	2.5±0.7	$0.2\pm0.01^{0.007}$	2.4±0.6	$0.2\pm0.03^{0.004}$	1.9±0.8	$0.2\pm0.03^{0.068}$
S	9.3±1.8	$2.1\pm0.5^{0.007}$	9.1±2.0	$0.7\pm0.3^{0.003}$	11.9±2.3	$0.5\pm0.2^{0.003}$
LF/HF	1.2±0.1	$1.7\pm0.3^{0.134}$	1.2±0.1	$0.9\pm0.1^{0.013}$	1.3±0.3	$0.9\pm0.1^{0.290}$

C is control; A, atropine; Pr, propranolol; and DB, double block. Values are (mean±SE)*10 $^{\text{p-value}}$ (unitless) for P and S, and (mean±SE) $^{\text{p-value}}$ (bpm^2) for HF and LF/HF.

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