Probability Trends in the Assessment of Cardiovascular Autonomic Fluctuations during Cold Pressor Tests

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Abstract

Eighteen healthy volunteers between 23 and 53 years of age (mean age 34.9 ± 9.8 years) were exposed to CPT while continuous ECG recordings were collected. HRV parameters, including root mean square of successive differences (RMSSD) and low frequency (LF) and high frequency (HF) components, were obtained during baseline and each stage of CPT using an autoregressive (AR) model with Burg's method to evaluate short windows of observation while preserving adequate frequency resolution. HRV parameters obtained during immersion of the hand in cold water, after withdrawal, and every 3 minutes after withdrawal were compared to baseline parameters. A probability trend was updated every 10 seconds for each parameter and $p < 0.05$ was considered significant. Preliminary results show that probability trends from RMSSD and HF provide consistent and prompt information about the sympathetic activation. These results could be applied in the setting of anesthesia and intraoperative monitoring, where sympathovagal imbalances can provide an early warning of physiological stress and thus facilitate timely interventions,

1. Introduction

The Cold Pressor Test (CPT) is used to activate pain by the inmmersion of one hand on ice-cold water. This well known instrument is capable of inducing a reproducible sympathetic activation by way of nociceptive and temperature receptors. Heart Rate Variability (HRV) analysis has been widely used to interpret autonomic activity but its clinical utility is limited when acute and transient phenomena are assessed. To overcome this limitation we propose a probabilistic method to analyze brief changes in the sympathovagal balance during autonomic provocative tests.

The normal response to exposure of a limb to cold water involves reflex arteriolar vasoconstriction producing an increase in blood pressure and cardiac output triggered by cutaneous pain receptors. Increased blood pressure is a response to enhanced sympathetic activity expressed as an increase in vascular resistance. The initial increase in heart rate is blunted by beta adrenoreceptor blockers suggesting that sympathetic rather than parasympathetic outflow mediates this response [1].

When patients are under acute stress, such as surgical or procedural noxious stimulation, the parasympathetic tone tends to be depressed expressing a decrease in HF activity. In the setting of anesthesia and intraoperative monitoring, the development of an instrument able to provide real time information about the Autonomic Nervous System (ANS) state at different stages of any procedure would result in improved monitoring and safety for patients undergoing diagnostic or therapeutic interventions. However, real-time analysis of HRV can be particularly challenging. Retrieving temporal and frequency domain parameters as described by classical methods involves exhaustive conditioning of the HRV signal, limiting its use to research purposes [2].

This study explores a probabilistic approach that analyzes changes of HRV parameters obtained by an autoregressive model technique using Burg´s methods to evaluate very short windows of observations while preserving sufficient frequency resolution [3,4]. These HRV parameters are constantly compared to a baseline state, and a probability trend is updated during provocative maneuvers.

2. Methods

Parametric modeling analysis such as the AR model using the Burg method or maximum entropy method provides high-resolution spectral estimation of short-term signals as the RR windowed segments analyzed in this work [3]. The maximum entropy method (MEM) implicitly extends the correlation function of the signal, extrapolating it beyond the observation interval in order to maximize the entropy of the windowed signal characterized by the extrapolated autocorrelation sequence [4,5]. Burg's AR estimation method is equivalent to MEM and estimates the parameter of an AR model by minimizing the forward and backward prediction errors using the least squares method, to satisfy the Levinson recursion [5,6].

2.1. Study population

Eighteen healthy volunteers were exposed to CPT while continuous ECG recordings were collected. After approval by the hospital Research Ethics Board, all participants provided informed consent to participate in the study after discussing potential risks with the study coordinator before undergoing a battery of provocative tests. No remuneration was provided to participants in this trial. Participants' age ranged from 23 to 53 years old (mean age 34.9 ± 9.8 years) and weight ranged from 47 to 105 Kilograms (mean weight 71 ± 15.1 Kilograms). Patients on regular prescribed medications or with a documented history of cardiovascular or neurological diseases were excluded from this study.

2.2. Signal acquisition and provocative tests

All signals were acquired in an operating room at British Columbia Children's Hospital using a Datex-Ohmeda S/5® monitor system from GE®. ECG, capnographic, and flow signals were collected simultaneously in all patients. For the purposes of this study, only ECG signals were analyzed. Patients underwent a standardized sequence of provocative tests such as the Head up Tilt Table Test (TTT) and the Cold Pressor Test. Only Cold Pressor Tests procedure were analyzed in this work.

Patients were asked to perform a CPT that ended after 180 seconds or when the subject was no longer able to tolerate the discomfort while keeping their non dominant hand in water kept at 4°C. The water used for the CPT as well as the environment temperatures were controlled in each test. All tests followed a period of baseline acquisition. Once subjects withdrew their hands from the cold water, a Pain Rating Scoring was reported every 3 minutes until the completion of the test (Table 1). Pain decreases significantly three minutes after CPT ($p<0.001$); however, these values show substantial variability.

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Table 1. Pain rating following the completion of the test (1 least -10 most).

Subject	0 min	3 min
1	9.0	9.8
2	4.2	1.4
3	7.0	1.5
4	6.0	3.1
5	7.3	2.5
6	7.5	0.0
7	3.8	0.0
8	6.3	4.3
9	6.3	1.0
10	9.0	3.2
11	7.0	1.4
12	1.8	0.0
13	0.6	0.0
14	4.8	0.0
15	6.0	2.5
16	7.7	2.5
17	5.0	1.5
18	6.5	0.9
mean± sd	6.0±2.0	2.0±2.3

2.3. Spectral HRV analysis

RR signals were obtained using a noise-robust wavelet-based algorithm for R-wave detection and QRS wave delineation [7]. In order to optimize the detection of normal sinus beats, artifacts and ectopic beats were removed from the RR signal using a 5-beat sliding window algorithm that rejected any beat with an interval difference more than 15% of the window mean beats. Processing RR signals included the removal of its mean value and regular spaced resampling at 2 Hz after interpolating the signal with cubic splines. The AR model order was chosen using the Broersen's combined information criterion (CIC) [8], selecting a model order of 16 for all signals. This model's order and resampling frequency follow recommendations from previous studies for short term RR trends analyses [9, 11]. Short term HRV analyses were performed using a sliding window 60 seconds of length and continuously shifting one sample each time in all cases. The spectral HRV indices computed from the Power Spectral Density (PSD) were the average power in the low frequency band (LF: 0.04 to 0.15 Hz), in the high frequency band (HF: 0.15 to 0.4 Hz), and the LF/HF ratio. For LF and HF, absolute values (ms2) and normalized units were used. The LF in normalized units (LFn= LF/(LF+HF)) and LF/HF ratio (LFr) were calculated from their original absolute power values. Additionally, the following time domain variables were computed for each RR interval signal: average heart rate (HR), standard deviation of RR interval signal (SD), and square root of the mean square differences of successive RR intervals (RMSSD). Four 1-minute stages were considered under the following conditions: Stage 1, supine position (basal); stage 2, hand in; stage 3, hand out ; stage 4, three (3) minutes after hand out.

2.4. p-trend analysis

ANS changes are traditionally evaluated by averaging parameters over 2-3 minutes; by means of this proposed analysis, temporal trends of HRV parameters can be updated as often as every second. Our study explores a probabilistic approach that analyzes changes in HRV parameters obtained. These HRV parameters are continuously compared to a baseline state, and a probability trend is updated during in the observations window. In p-trend analysis, values are compared every 1 seconds to baseline values during the CPT .

3. Results

Data were considered as means ± standard deviation for each parameter at each stage (Table 2). . Wilcoxon rank sum test was used to determine the significance of the differences between stages.

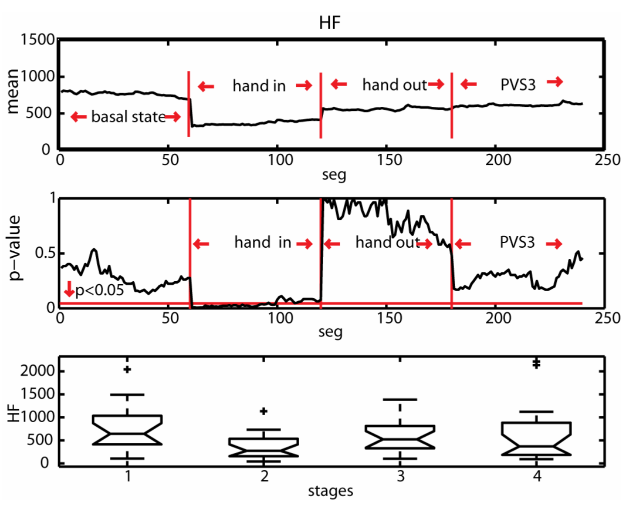

Figure 1. Mean, p-value and boxplots for HF This parameter decrease during CPT (stages 2, 3, and 4).

Mean Values, p-trends and boxplots trends for HF, rmssd and LFn are presented respectively in figures 1,2 and 3. Differences between each stage and baseline were particularly significant for HF and RMSSD. These values decrease significantly during stages 2 ($p<0.05$). LFn increases during CPT but without statistical significance.

Table 2. Mean values for stages 1, 2 and 3.

Variable	Basal	Hand in	Hand out
RR	803±127	802±121	803±126
LFn	0.65±0.21	0.78±0.11	0.77±0.11
HF	767±505	371±288	563±334
LF	2485±3065	1495±1576	2685±2493
rmssd	36.0±17.2	20.8±9.2	29.7±13.8

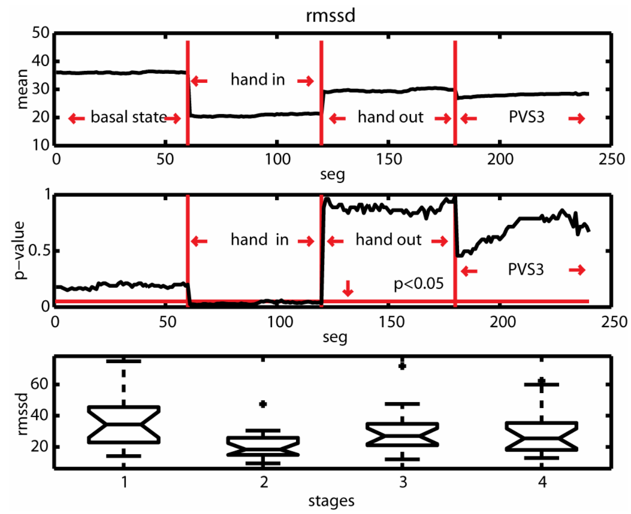

Figure 2. Mean, p-value and boxplots for rmssd. This parameter decrease during CPT (stages 2, 3, and 4).

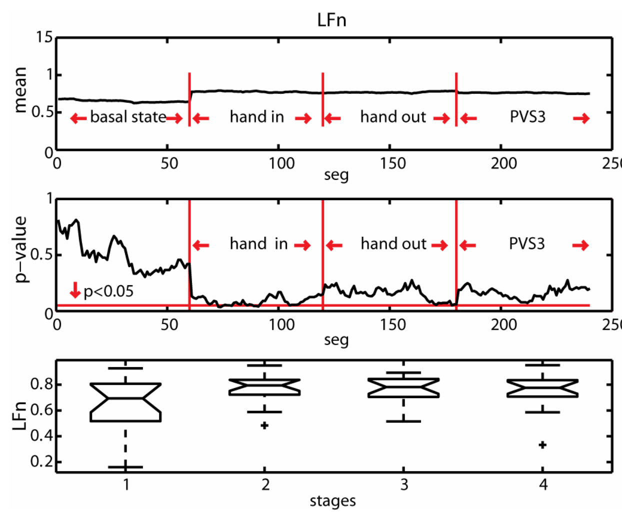

Figure 3. Mean, p-value and boxplots for LFn. This parameter increases during CPT (stages 2, 3, and 4).

4. Discussion

Our preliminary analysis was performed with 18 volunteers. It showed that pain sensation after the initial three minutes of recovery decrease in CPT. This finding is consistent with the evolution of HRV parameters (HF, rmssd and LF). parasympathetic withdrawal (HF and rmssd) and the sympathetic reactivation (LFn) after the CPT . The high variability of HRV parameters is a big defy for this technique in clinical monitoring purposes, also the complex interaction between, both sympathetic and parasympathetic drives, might need not necessarily HRV parameters to improve the identification of autonomic changes. Nonetheless, it is always useful to define the least amount of parameters that could help the clinician identify this condition in his everyday practice.

The main outcomes of this study is the use of a probabilistic trend to validate the ANS changes during CPT. Preliminary results show that trends from RMSSD and HF are consistent and reliable instruments capable of providing information about ANS fluctuations close to real time. These results are promising for pain perception and its relationship with ANS changes. A larger database is needed to define parameters that could be applied in the setting of anesthesia and intraoperative monitoring, for a real time instrument that alerts the physician during intraoperative intervention.

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