

Point Process Heart Rate Variability Assessment during Sleep Deprivation

L Citi^{1,2}, EB Klerman³, EN Brown^{1,2}, R Barbieri^{1,2}

¹Department of Anesthesia, Critical Care and Pain Medicine,
Massachusetts General Hospital – Harvard Medical School, Boston, MA, USA

²Department of Brain and Cognitive Science,
Massachusetts Institute of Technology, Cambridge, MA USA

³Division of Sleep Medicine,
Brigham and Women's Hospital - Harvard Medical School, Boston, MA, USA

Abstract

To investigate the potential relationships between Heart Rate Variability (HRV) and objective performance-subjective alertness measures during sleep deprivation, a novel point process algorithm was applied to ECG data from healthy young subjects in a 52-hour Constant Routine protocol that includes sleep deprivation. Our algorithm is able to estimate the time-varying behavior of the HRV spectral indexes in an on-line instantaneous method. Results demonstrate the ability of our framework to provide high time-resolution sympatho-vagal dynamics as measured by spectral low frequency (LF) and high frequency (HF) power. Correlation analysis on individual subjects reveals a relevant correspondence between LF/HF and subjective alertness during the initial hours of sleep deprivation. At longer times awake, high correlation levels between LF/HF and objective performance indicate an increasing sympathetic drive as performance measures worsen. These results suggest that our point-process based HRV assessment could aid in real-time prediction of performance-alertness.

1. Introduction

The autonomic nervous system and the circadian system are central candidates for the roles of controllers of the choral synchronization of apparently independent vital physiological regulating mechanisms (e.g. blood pressure waves, breathing, hormonal and circadian oscillations). Heart rate variability (HRV) is an important quantitative marker of cardiovascular regulation by the autonomic nervous system [1]. Recently, links between cardiac oscillations and circadian rhythms have been reported in several correlation studies in humans and other animals. Furthermore, changes in autonomic tone are correlated with changes in states of alertness and sleep, during performance tasks, and during sleep deprivations [2-8].

To investigate the potential relationships between HRV and performance-alertness measures, we have studied these measures in healthy subjects during a 52-hour Constant Routine (CR) protocol (an extended period of enforced wakefulness in a semirecumbent position with frequent small meals that is used to assess circadian phase and amplitude with minimal masking from exogenous factors) that includes continuous wake (and therefore sleep deprivation).

In order to study long duration recordings with a high temporal resolution, we have developed a software tool that combines an R-wave detector able to process lengthy and noisy recordings, with a point-process based monitor of HRV able to track short and long term changes in sympatho-vagal balance.

2. Methods

2.1. Experimental protocol

Data reported here are from two healthy young subjects from a larger cohort recorded at the Brigham and Women's Hospital General Clinical Research Center in a study approved by the Partners Healthcare Institutional Review Board [9]. Electrocardiogram (ECG) was continuously acquired and digitized at 256 Hz. Every half hour while they were awake, subjects were asked to rate their subjective alertness ("Alert") using a 100-mm non-numeric linear scale [10] increasing from Sleepy (0mm) to Alert (100mm). Objective performance was reported every two hours by the using the reaction time in milliseconds as a result of a Psychomotor Vigilance Task (PVT) [11].

2.2. Signal pre-processing

R-events are identified in the raw ECG by using a semi-automated procedure. First, the ECG is convoluted with a Difference-of-Gaussians (DoG) wavelet that functions as a matching filter to the R-wave. Second, the information about the most recent successful

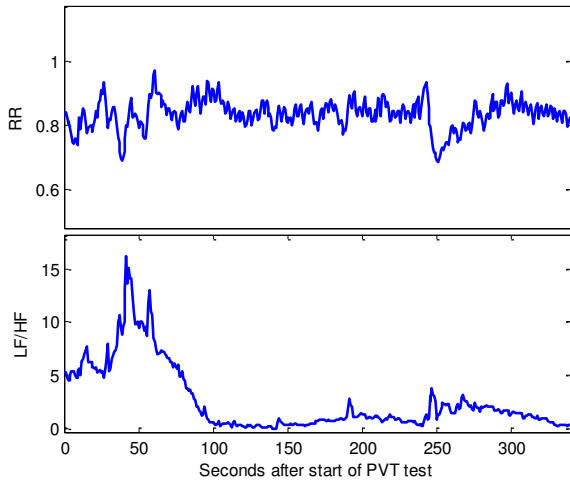


Figure 1. Time course of the RR interval and LF/HF index during one of the PVT tests (after 18 hours of CR for Subject 2). Right after the beginning of the test, the LF/HF index quickly increases, then decreases to a more relaxed, vagal-driven state.

identifications is combined to provide a probability distribution of the current detection. These two steps are further weighted together for final determination.

When the algorithm is unable to provide a single solution, the procedure stops and user intervention is requested. The scale of the wavelet is adaptively updated using a stochastic hill climber method determining a new scale according to the user's choice. Generally, it took between 20 min and 2 hours to process each continuous 52-hr ECG recording, depending on signal quality.

2.3. The point process model

A novel algorithm is applied to the R–R series to compute instantaneous estimates of heart rate and HRV from ECG recordings of R-wave events. This approach is based on point process methods already used to develop both local likelihood [12] and adaptive [13] heart rate estimation algorithms. The stochastic structure in the R–R intervals is modeled as an inverse Gaussian renewal process. The inverse Gaussian probability density is derived directly from an elementary physiologically-based integrate-and-fire model [12,13]. The model also represents the dependence of the R–R interval length on the recent history of parasympathetic and sympathetic inputs to the SA node by modeling the mean as a uniform time-sampled regression on a continuous estimate of the last p R–R intervals, where p is the autoregressive order of the model. This set of p coefficients allows for estimation of the spectral power (HRV) and further decomposition into classic low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.5 Hz) spectral components, and the ratio between the two powers (LF/HF). The point process recursive algorithm is able to estimate the dynamics of the model parameters, and consequently the time-varying behavior of each spectral index at any time resolution. This new continuous model

for deriving HRV measures has been cross-validated with standard time-frequency domain approaches for HRV analysis [1] as well as previous point process algorithms [12,13]. The dynamic response for the point process method is found to provide a significant improvement in tracking fast dynamic changes when compared to the older methods. A fixed order $p=8$ was chosen for the analysis.

Indices were updated every 5 ms using the information available up to that time point. Even when the last RR interval was not completely observed, it was predicted in the estimation of the model by means of a right censoring term [12]. While this finely sampled estimation of the indices is able to track fast changes in the autonomous nervous system (Figure 1), in this study we were particularly interested in changes occurring at a much slower scale. Therefore we also evaluated a 600 s and a 3600 s running average of these indices using a rectangular sliding window.

3. Results

The short-term sympatho-vagal balance estimates, as measured by the point process LF/HF index, mirror the complex dynamics of tasks and activities performed along the experiment. Figure 1 shows an example of the point process estimate's high temporal resolution for Subject 2. RR series and LF/HF estimates from approximately six minutes of recording are included here. Note the marked increase of sympatho-vagal balance around 25 seconds after the PVT test starts, followed by a return to a more relaxed state within just one minute. A more detailed portrayal of the short-term monitoring assessment by this index will be discussed elsewhere.

Figure 2 illustrates the long-term resolution results for the point process LF/HF index along the entire 52-hr CR for both subjects considered. The scale portrayed in Figure 1 allows us to appreciate the general trend described by the performance and alertness measures. The index is smoothed to further highlight such trends (black line). Note the high variability in both subjects in the RR series, mainly due to the large variety of tasks and activities planned during the CR. In Subject 1 a steady decrease in alertness (black asterisks) from 100 to almost 0 is observed within the first 15 hours, followed by several hours during which subjective alertness remains below 40. Forty-five hours after CR begins, a rebound in alertness is reported. In the same subject, the median reaction time from the objective performance test (PVT, red asterisks) steadily increases along the first 40 hours, then sharply declines, in excellent time correspondence with the observed increase in alertness. Note the overall decreasing trend in the first ~15 hours followed by an evident positive drift up to ~43 hours after the start of the CR. In Subject 2, the alert scale starts lower (around 50) and slowly drifts down to values around 30 in the first ~28 hours, with variations about this value after. The

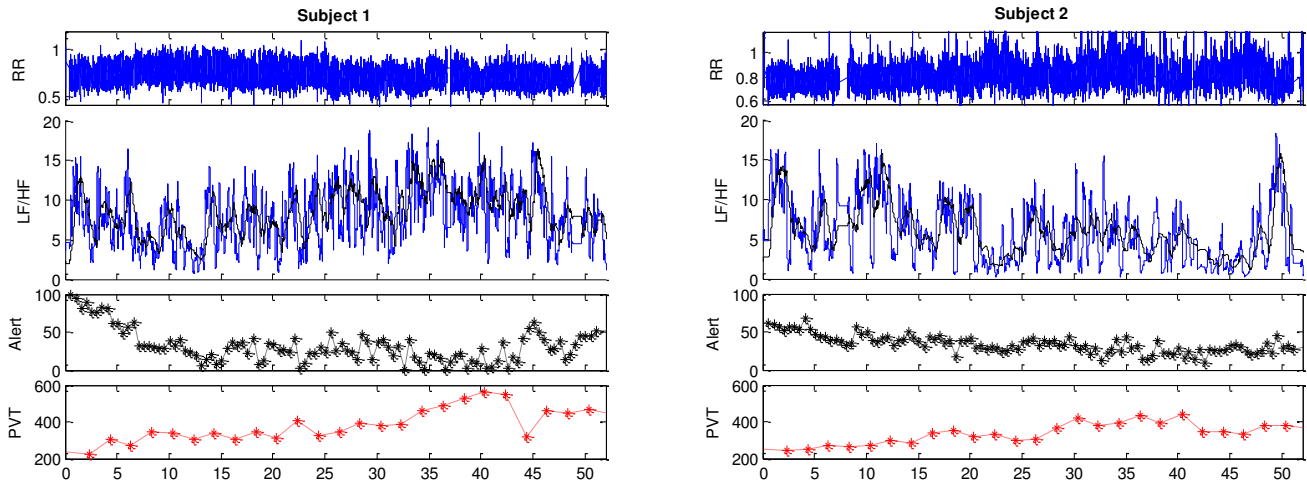


Figure 2. For each subject, the top plot is the raw RR series; the 2nd plot shows 10 min estimates of the LF/HF index (blue line) with the running average of the hour preceding a given time-point (black line); the 3rd plot presents the self-reported Alert measure taken every 30 min (black asterisks); the bottom plot shows the results from the Psychomotor Vigilance Task (PVT) as a measure of objective performance taken every two hours (red asterisks). Note that for Alert, lower values correspond to lower alertness, whereas for the PVT, higher values indicate poorer performance.

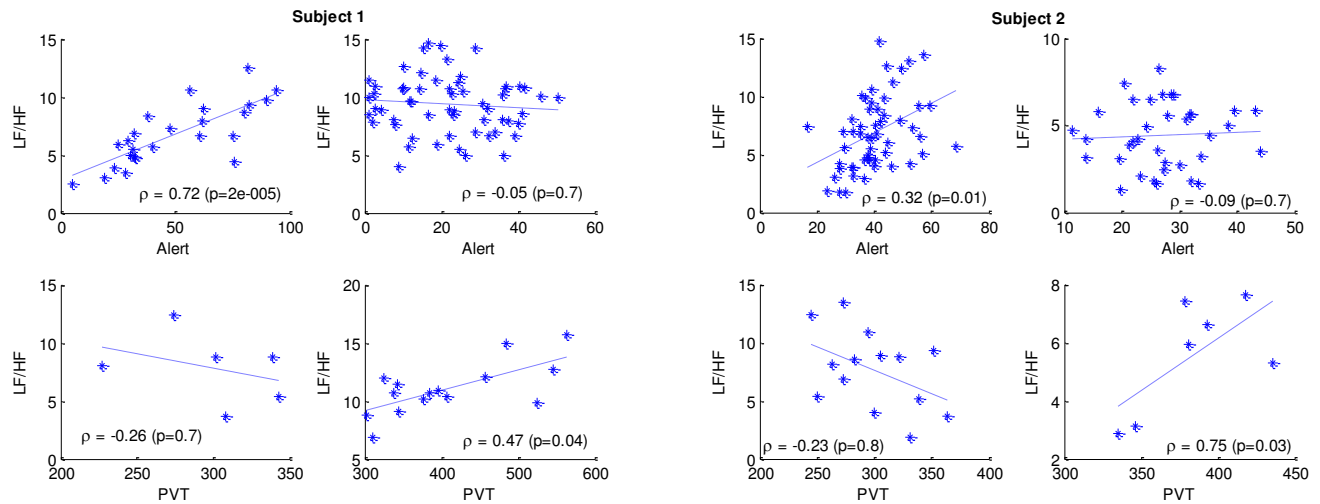


Figure 3. Scatter plots of the LF/HF balance versus the “Alert” index (upper plots) or the “PVT” response time (lower plots). For each subject, the left plots show the correlations (Spearman’s rank correlation coefficient and corresponding p-value) during the first part of the CR: note that the LF/HF index correlates positively with the Alert measure but not with the PVT. The right plots, include data from the second part of the CR: note that the LF/HF correlates positively with vigilance (PVT) measure but not with Alert.

PVT reaction time steadily increases along the first ~40 hours.

Visual inspection of the LF/HF estimates from these two subjects leads to several observations: (a) in the first ~15 hours there is a high similarity in trends between LF/HF and the alert measure in Subject 1; (b) after the first ~15 hours alertness is generally very low in both subjects; (c) in Subject 1, after the first ~15 hours, the LF/HF decreasing trend reverses and starts mirroring the increase in PVT reaction time; (d) the LF/HF index shows more prominent oscillating trends in Subject 2 than those observed for Subject 1, reaching minimum values between 21 and 26 hours and between 42 and 47 hours. In accordance to these observations, correlation analysis was

performed between 0 and 13 hours (part 1) and between 14 and 43 hours (part 2) for subject 1, and between 0 and 28 hours (part 1) and between 28 and 48 hours (part 2) for subject 2. Figure 3 portrays the results of this analysis. For both subjects, LF/HF in part 1 highly correlates with the observed decrease in Alert (best correlation in Subject 1), whereas in part 2 the sympatho-vagal index highly correlates with PVT reaction time (best correlation in Subject 2).

4. Discussion and conclusions

This paper presents a novel analysis of continuous ECG recordings during a 52-hr CR protocol during which subjects are sleep deprived. The application is mainly

aimed at demonstrating the effectiveness of our processing and modeling tools in assessing new instantaneous HRV measures from the highest resolution (milliseconds) to the longest duration (days). Our preliminary results on long-term estimates from individual subjects further reveal that during the first hours of sleep deprivation there is a considerable correspondence between the LF/HF index and subjective alertness measures. At longer times awake, an increase in LF/HF reveals an increasing sympathetic drive correlated with the worsening of objective performance measures, thus confirming previous findings that sleep deprivation ultimately leads to a significant increase of the sympatho-vagal balance [7].

This preliminary analysis provides important elements suggesting that point-process based HRV assessment be a potential real-time physiologic predictor of performance-alertness. In the future we plan to investigate LF/HF variations within each CR to assess short term effects of specific tests (such as the PVT) and/or activities on the sympatho-vagal balance.

The presented preliminary results also demonstrate the presence of high inter-individual variability effects, some of which are at scales comparable with circadian dynamics. To this extent, it is our intention to further investigate the correlation between autonomic tone and the circadian cycle, with the ultimate goal of exploring the possibility of integrating our point-process based HRV measures into mathematical models of circadian rhythms, performance, and alertness [14].

Acknowledgements

This work was supported by National Institutes of Health (NIH) Grants R01-HL084502 (R.B.); R01-DA015644 and DP1-OD003646 (E.N.B.); P01-AG09975, K02-HD045459 (E.B.K.), NCCR-GCRC-M01-RR02636, RC2-HL101340 (E.B.K.), and NSBRI (through NASA NCC 9-58) Grant HFP01604 (E.B.K.).

References

- [1] Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. *Circulation*. 1996 Mar 1;93(5):1043-1065.
- [2] Busek P, Vanková J, Opavský J, Salinger J, Nevšimalová S. Spectral analysis of the heart rate variability in sleep. *Physiological Research / Academia Scientiarum Bohemoslovaca*. 2005;54(4):369–376.
- [3] Iellamo F, Placidi F, Marciani MG, Romigi A, Tombini M, Aquilani S, et al. Baroreflex buffering of sympathetic activation during sleep: evidence from autonomic assessment of sleep macroarchitecture and microarchitecture. *Hypertension*. 2004 Apr;43(4):814–819.
- [4] Crasset V, Mezzetti S, Antoine M, Linkowski P, Degaute JP, Borne PVD. Effects of aging and cardiac denervation on heart rate variability during sleep. *Circulation*. 2001 Jan;103(1):84–88.
- [5] Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, et al. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *The American Journal of Physiology*. 1998 Sep;275(3 Pt 2):H946–950.
- [6] Vanoli E, Adamson PB, Ba-Lin, Pinna GD, Lazzara R, Orr WC. Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction. *Circulation*. 1995 Apr;91(7):1918–1922.
- [7] Zhong X, Hilton HJ, Gates GJ, Jelic S, Stern Y, Bartels MN, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. *Journal of Applied Physiology (Bethesda, Md.: 1985)*. 2005 Jun;98(6):2024–2032.
- [8] Spiegel K, Leproult R, L'hermite-Balériaux M, Copinschi G, Penev PD, Cauter EV. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *The Journal of Clinical Endocrinology and Metabolism*. 2004 Nov;89(11):5762–5771.
- [9] Klerman EB, Dijk D. Age-related reduction in the maximal capacity for sleep—implications for insomnia. *Curr. Biol*. 2008 Aug 5;18(15):1118–1123.
- [10] Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*. 1974;47(3):211–218.
- [11] Dinges DF, Powell JW. Microcomputer analyses of performance on a portable simple visual RT task during sustained operations. *Behavior research methods, instruments & computers*. 1985;17(6):652–655.
- [12] Barbieri R, Matten EC, Alabi AR, Brown EN. A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability. *American Journal of Physiology- Heart and Circulatory Physiology*. 2005;288(1):H424.
- [13] Barbieri R, Brown EN. Analysis of heartbeat dynamics by point process adaptive filtering. *IEEE transactions on BioMedical Engineering*. 2006;53(1).
- [14] Klerman EB, Hilaire MS. Review: On Mathematical Modeling of Circadian Rhythms, Performance, and Alertness. *Journal of Biological Rhythms*. 2007;22(2):91.

Address for correspondence:

Luca Citi, PhD
 Department of Anesthesia, Critical Care and Pain Medicine
 Massachusetts General Hospital – Harvard Medical School
 149, 13th Street
 Charlestown, MA 02129, USA
 E-mail address lciti@neurostat.mit.edu