34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Real-Time Cardiorespiratory Coherence Detects Antinociception During General Anesthesia

Chris J. Brouse[1]*, *Student Member, IEEE*, Walter Karlen[1], Guy A. Dumont[1], *Fellow, IEEE*, Dorothy Myers[2], Erin Cooke[2], Jonathan Stinson[2], Joanne Lim[2], J. Mark Ansermino[2]

Abstract— **Heart rate variability (HRV) may provide anesthesiologists with a noninvasive tool for monitoring nociception during general anesthesia. A novel real-time cardiorespiratory coherence (CRC) algorithm has been developed to analyze the strength of linear coupling between heart rate (HR) and respiration. CRC values range from 0 (low coherence, strong nociception) to 1 (high coherence, no nociception). The algorithm uses specially designed filters to operate in real-time, minimizing computational complexity and time delay. In the standard HRV high frequency band of 0.15 – 0.4 Hz, the real-time delay is only 5.25 – 3.25 s. We have assessed the algorithm's response to 60 anesthetic bolus events (a large dose of anesthetics given over a short time; strongly antinociceptive) recorded in 47 pediatric patients receiving general anesthesia. Real-time CRC responded strongly to bolus events, changing by an average of 30%. For comparison, three traditional measures of HRV (LF/HF ratio, SDNN, and RMSSD) responded on average by only 3.8%, 14%, and 3.9%, respectively. Finally, two traditional clinical measures of nociception (HR and blood pressure) responded on average by only 3.9% and 0.91%, respectively. CRC may thus be used as a real-time nociception monitor during general anesthesia.**

I. INTRODUCTION

Anesthesiology is commonly regarded as the practice of autonomic medicine. Noxious stimuli during surgery cause the autonomic nervous system (ANS) to invoke a stress response, increasing sympathetic tone and decreasing parasympathetic tone [1]. An excessive and prolonged sympathetic response increases the risk of suffering from perioperative complications, delays recovery, and is a key factor in postoperative morbidity [2]. Anesthesiologists control the stress response (nociception) by administering analgesic drugs (antinociception).

There is currently no clinically proven and routinely used monitor of the ANS. Anesthesiologists are guided by observation and interpretation of trends in patients' vital signs, most importantly heart rate (HR) and blood pressure. These are only indirect measures of nociception. Confounding factors such as pre-existing medical conditions and inter-patient variability cause difficulties in such indirect estimations of the ANS. An automated nociception monitor that directly assesses ANS activity would be very useful for general anesthesia, providing anesthesiologists with feedback about the adequacy of analgesia in real-time. Heart rate variability (HRV) shows promise as a nociception monitor [3], [4].

We have previously developed a nociception monitoring algorithm called wavelet transform cardiorespiratory coherence (WTCRC). The algorithm measures ANS activity by analyzing respiratory sinus arrhythmia (RSA) [5]. WTCRC can detect nociception during general anesthesia [6], [7].

Unfortunately WTCRC is unsuitable for real-time analysis. The algorithm is based on the continuous wavelet transform (CWT), which simultaneously analyzes signals across a wide range of times/frequencies. This makes it an ideal tool for visualizing coherence in the joint time/frequency plane, and exploring the relationship between HR and respiration. The CWT is very computationally inefficient, however, performing many redundant calculations that are not required to produce an index of nociception. Furthermore, WTCRC exhibits significant real-time delay, which limits its usefulness in the clinical application of nociception monitoring.

In this work, we will describe a modified cardiorespiratory coherence (CRC) algorithm that is better suited to real-time analysis. This real-time CRC algorithm eliminates the computational redundancy of its forebear, and uses specially designed filters to minimize real-time delay. We will demonstrate that this new algorithm responds strongly to analgesic drugs (antinociception) during general anesthesia, and that it outperforms traditional measures of nociception.

II. METHODS

A. Real-Time Cardiorespiratory Coherence

The real-time CRC algorithm is a custom adaptation of our existing WTCRC algorithm [5], [6], [7], which is itself based on prior theoretical work on coherence analysis [8], [9]. CRC begins by analyzing the HR and respiration waves using a customized complex Morlet basis function (filter). This filter is a complex exponential modulated by a Gaussian:

$$\Psi(t) = \pi^{-\frac{1}{4}} e^{2\pi i f_c t} e^{-t^2 f_b}, \tag{1}$$

where f_c is the filter's center frequency and f_b is the bandwidth. The bandwidth term is defined as:

$$f_b = 2f_c/f_s, \tag{2}$$

where f_s is the sampling frequency. As f_b decreases, so does the filter's frequency bandwidth. Note that this relationship is opposite to that in the standard complex Morlet definition.

This custom analyzing filter tracks the RSA as it moves across the time/frequency plane. We use the respiratory

This work was supported in part by the Michael Smith Foundation for Health Research (MSFHR) and the Natural Sciences and Engineering Research Council of Canada (NSERC).

[1]Department of Electrical & Computer Engineering, University of British Columbia, Vancouver, BC, Canada

[2]Department of Pediatric Anesthesia, BC Children's Hospital, Vancouver, BC, Canada

*Corresponding author, email: chrisb@ece.ubc.ca

frequency (f_r) as the filter's center frequency ($f_c = f_r$). This is where the RSA power exists in the frequency domain. As f_r varies over time, f_c changes to track the RSA.

The filter length depends on the respiratory frequency. As f_r decreases, f_c and f_b decrease accordingly. The Gaussian modulator in (1) becomes narrower in frequency and wider in time (by the Heisenberg-Gabor uncertainty principle). This tradeoff is modeled after the principles of wavelet analysis.

Real-time delay depends on the filter length. Longer filters produce longer delay. The delay is caused by the right half of the filter, which operates on future (non-causal) signal values. We can mitigate the delay by truncating the filter in time, trading error for improved time localization. We truncate the filter where the Gaussian modulator edge falls below e^{-2}, which is similar to the cutoff criterion in [8] and [9]. This produces a variable real-time delay, given by:

$$t_{delay} = \sqrt{f_s / f_c}. \tag{3}$$

The filter is applied to the tachogram (HR time series) and respiration signals to calculate their individual powers and cross powers. Tachogram, respiration, and cross powers are denoted as $P_t^{TT}(f_c)$, $P_t^{RR}(f_c)$, and $P_t^{TR}(f_c)$ respectively.

The powers are then smoothed in time with the left half of a Gaussian window ($e^{-t^2/2\sigma^2}, \quad t \leq 0$). By using only the left half, we make the smoothing operation causal, and do not introduce any additional real-time delay. The σ parameter defines the level of smoothing. We use $\sigma = 5$ to approximate the smoothing of the existing WTCRC algorithm [6]. In future work, σ could be adjusted to tune the results.

Finally, the algorithm calculates the coherence estimator:

$$\hat{C}_t^2(f_c) = \frac{\left|\left\langle P_t^{TR}(f_c)\right\rangle\right|^2}{\left\langle\left|P_t^{TT}(f_c)\right|\right\rangle \left\langle\left|P_t^{RR}(f_c)\right|\right\rangle}, \tag{4}$$

where the angled brackets denote the smoothing operator.

The result is a series of real-time coherence values at the time-varying respiratory frequency. Coherence can range from 0 (no coherence, strong nociception) to 1 (perfect coherence, no nociception or strong antinociception).

B. Clinical Protocol & Data Collection

Following ethics approval and informed consent, data were collected from 47 healthy pediatric patients receiving general anesthesia during dental surgery. Subjects were aged 3-6 years, had ASA physical status I or II, were free of cardiorespiratory disease, and were not taking medications that alter autonomic function. Subjects were anesthetized with propofol and remifentanil. Surgeries provided multiple periods of nociceptive stimuli, including dental dam insertions, tooth extractions, cavity drillings, etc. The anesthesiologist could deliver bolus doses of anesthetics at her discretion, if she decided the patient was responding too strongly to the surgical stimulation. A bolus is a large dose of anesthetics given over a short time, and is strongly antinociceptive.

Physiological data were recorded throughout each case. The electrocardiogram (ECG) and capnometry (CO_2) waves, as well as the respiratory frequency (f_r) (from capnometry) and mean noninvasive blood pressure (NIBPmean) trends, were recorded using Datex/Ohmeda S/5 Collect software (GE Healthcare, Helsinki, Finland). The ECG was recorded at 300 Hz, CO_2 at 25 Hz, f_r at 1/10 Hz, and NIBPmean at 1/180 Hz. A research assistant annotated the data in real-time with markers identifying anesthetic bolus events.

C. Data Analysis

Data were manually inspected and selected for *post hoc* analysis in Matlab (The Mathworks, Natick, MA). Case annotations were searched to find all recorded anesthetic bolus events. Bolus events were only retained for analysis if they occurred during the stable phase of anesthesia, when the patient was mechanically ventilated, and when the respiration and ECG waves were free of significant artifacts. In total, 60 anesthetic bolus events were retained for analysis.

Heart rate and respiration signals were prepared for coherence analysis. Data segments were extracted around each bolus event. The 60 s immediately preceding the bolus event was labeled the *nociceptive period*. The bolus was given 30 s to take effect, after which the following 60 s was labeled the *antinociceptive period*. In each segment, a 120 s buffer was provided before the start of the nociceptive period and after the end of the antinociceptive period, to ensure the analysis was not corrupted by edge artifacts. Fig. 1 shows an example analysis segment. ECG R-peaks were detected using a filter bank algorithm [10], and errors were manually corrected to create a gold standard beat series. Each beat series was converted into a tachogram, and then resampled onto an evenly-spaced 4 Hz grid using Berger's algorithm [11]. The respiration CO_2 wave was downsampled to 4 Hz using standard low pass filtering and decimation. The f_r trend was upsampled to 4 Hz using a repeater.

The percent change in CRC was calculated in all bolus events in pseudo real-time. The tachogram, respiration, and f_r were analyzed sample-by-sample to simulate a real-time environment in each data segment. The resulting CRC was averaged over the nociceptive and antinociceptive periods. The percent change in average CRC from the nociceptive to the antinociceptive period was calculated. Finally, percent changes were averaged over all 60 anesthetic bolus events.

Alternative measures of nociception were also calculated for comparison. The change in WTCRC (the non-real-time coherence algorithm) was calculated to provide a reference measure of coherence. The change in low frequency to high frequency HR power (LF/HF ratio), standard deviation of normal HRs (SDNN), and root mean square of successive differences in HRs (RMSSD) were calculated as traditional HRV measures. Finally, the change in average HR (HRmean) and NIBPmean were calculated as traditional clinical nociception measures. Since NIBPmean was only sampled every 180 s, we used the last sample in or before the nociceptive period, and the first sample in or after the antinociceptive period. In analyzing the LF/HF results, 18 of the 60 bolus events were excluded because the respiratory frequency was in the LF band (< 0.15 Hz). We have previously shown that the LF/HF ratio cannot function under these conditions [5].

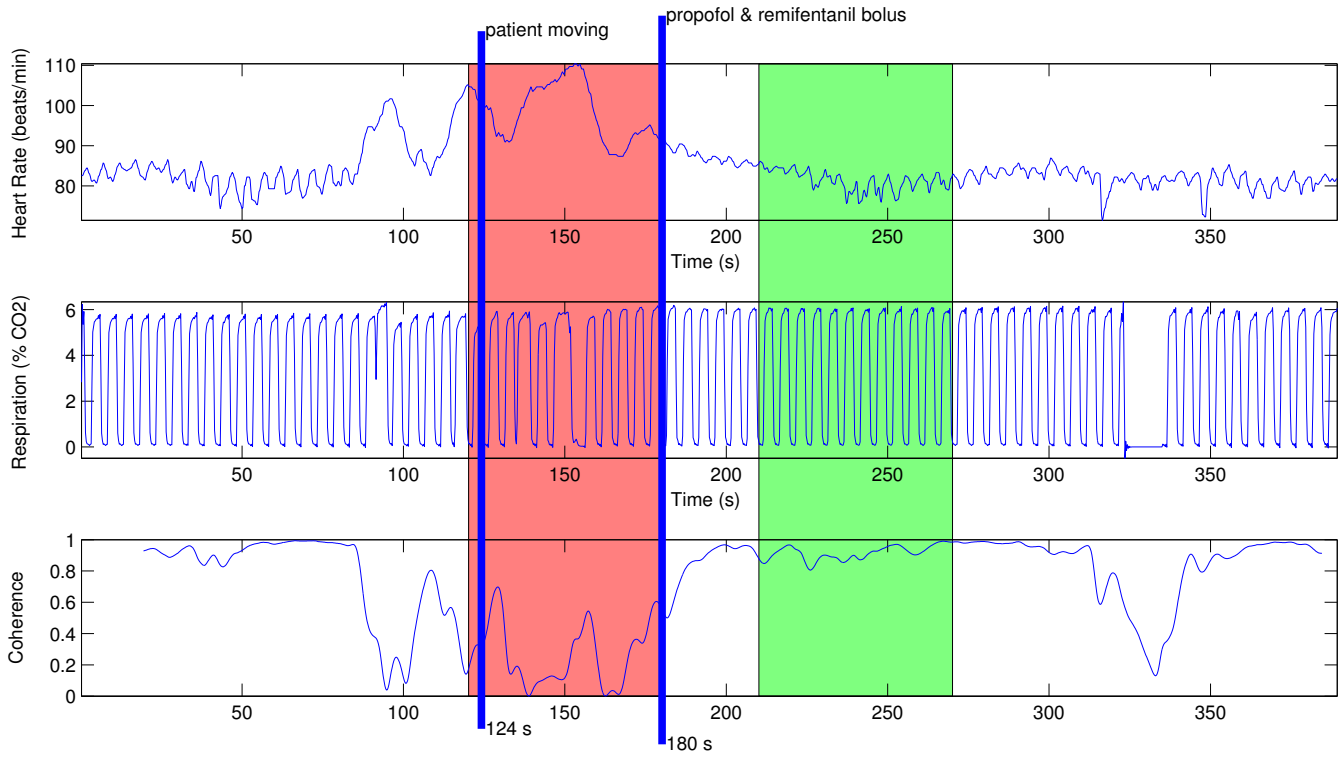

Fig. 1. Example real-time CRC analysis. Top plot: HR; middle plot: respiration (CO_2); bottom plot: real-time CRC. Vertical blue lines denote clinical events. Red and green highlighting denotes the nociceptive and antinociceptive periods, respectively. Notice that the CRC is missing near the end of the time series. This is caused by the real-time delay. In this example, the respiratory frequency is 0.2 Hz, which produces a real-time delay of 4.5 s. The missing CRC at the start of the time series is caused by the combined length of the analyzing and smoothing filters. This only affects the very beginning of any analysis. Finally, notice the effect of a recording artifact in the respiratory wave at approximately 320 – 335 s.

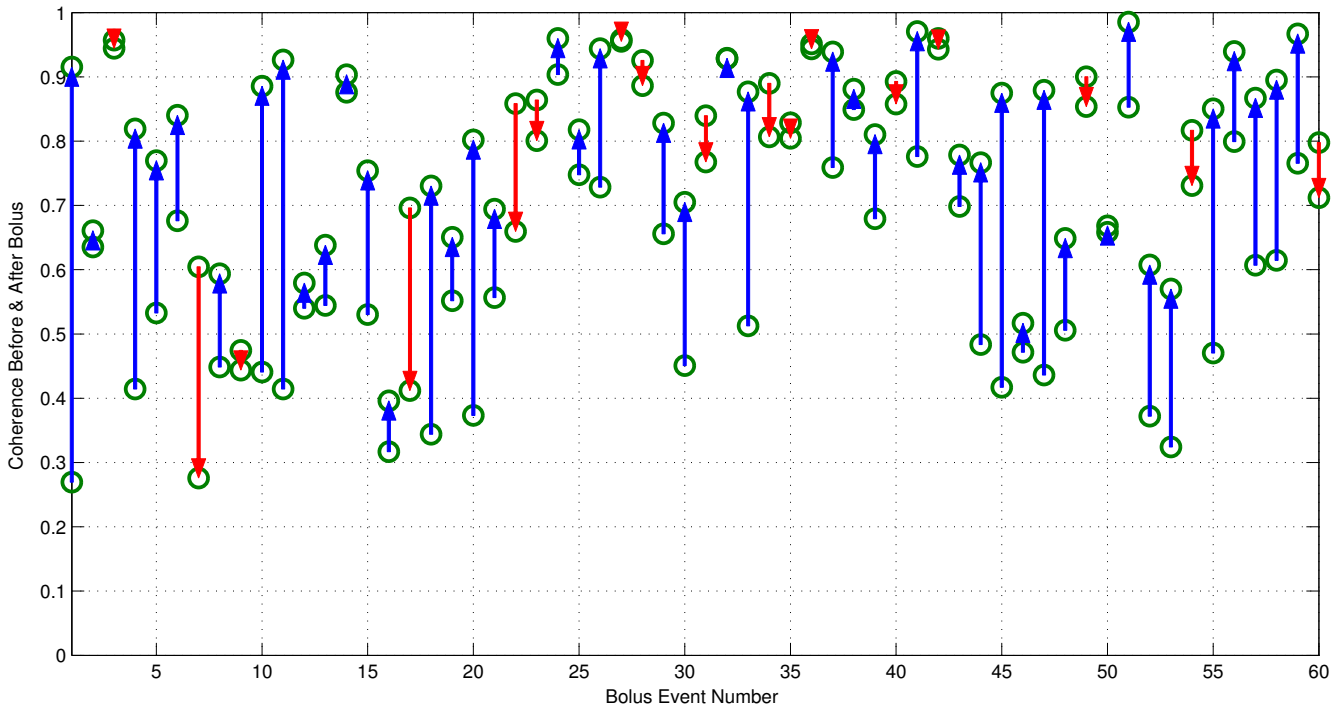

Fig. 2. Change in real-time CRC for each anesthetic bolus event. Line length denotes the magnitude of the change. Arrowheads and color denote the direction of the change. Blue indicates an increase in CRC (expected direction), red indicates a decrease (wrong direction).

III. RESULTS

Fig. 1 illustrates an example real-time CRC analysis of a single anesthetic bolus event. Fig. 2 presents the real-time CRC results across all anesthetic bolus events. Fig. 3 illustrates the average response of each nociception measure. Real-time CRC responded to an anesthetic bolus by 30% on average, and WTCRC responded by 32%. Traditional measures of HRV — LF/HF ratio, SDNN, and RMSSD — responded by 3.8%, 14%, and 3.9% respectively. The traditional clinical measures of nociception — HRmean and NIBPmean — responded by 3.9% and 0.91% respectively.

Real-time CRC achieved a real-time delay ranging from 5.25 – 3.25 s in the HRV HF band (0.15 – 0.4 Hz).

IV. DISCUSSION & CONCLUSION

We have developed a novel real-time cardiorespiratory coherence algorithm for monitoring nociception during general anesthesia. The algorithm measures ANS activity by analyzing the strength of linear coupling between HR and respiration. This is one measure of RSA. We have adapted our previous work on WTCRC to create the real-time CRC algorithm.

Real-time CRC uses specially designed filters to minimize the real-time delay. The algorithm tracks the RSA as it moves in the time/frequency plane by changing the center frequency and bandwidth of the analyzing filter. As the respiratory frequency decreases, the bandwidth decreases and the filter grows longer in time. The real-time delay thus increases as the respiratory frequency decreases. The customized causal Gaussian smoothing filter does not contribute any additional delay. The CRC algorithm was designed to produce very small delay across a wide range of respiratory frequencies. In the standard HRV HF band (0.15 – 0.4 Hz), the CRC filters produce a real-time delay of only 5.25 – 3.25 s. This allows the algorithm to respond very quickly in its intended clinical application of real-time nociception monitoring.

Real-time CRC compared very favorably to other measures of nociception in our analysis (Fig. 3). WTCRC responded slightly more strongly (32% compared to 30%), but we believe this is a reasonable tradeoff considering it does not operate in real-time. The traditional measures of HRV exhibited much weaker responses, as did the traditional clinical measures of nociception.

Our experiment underestimates the true performance of all algorithms. It assumes that each bolus dose of anesthetics was delivered in response to strong nociception. In some cases, however, the anesthetics appear instead to have been delivered *in anticipation of* nociception. In these events, the ANS state changes in the wrong direction, reducing the overall response average. Under real clinical conditions, all algorithms should perform better than reported here.

We have shown that real-time CRC responds strongly to antinociception in pediatric patients receiving general anesthesia. Specially designed analyzing and smoothing filters allow CRC to be measured with only a small real-time delay. These advances open up the possibility of using CRC for real-time nociception monitoring during general anesthesia.

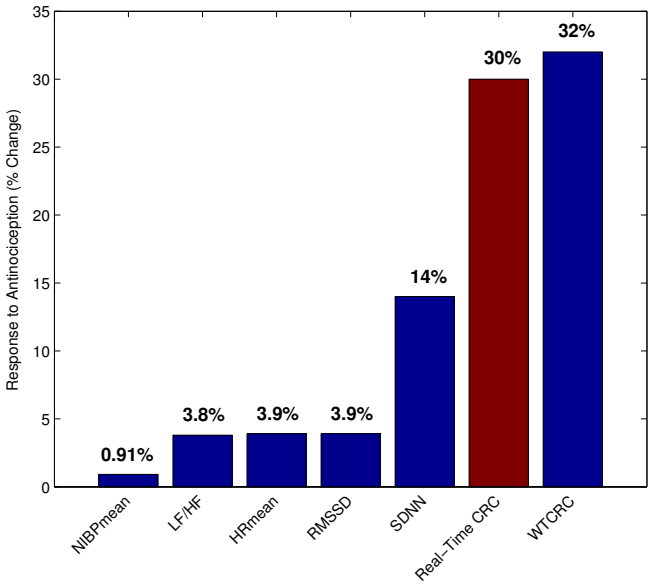

Fig. 3. Average response to antinociception, by algorithm.

V. ACKNOWLEDGMENTS

The authors acknowledge the contributions of Carolyne Montgomery to the clinical study design, and the Department of Pediatric Anesthesia at BC Children's Hospital for its assistance in conducting the study. Special thanks to the dental operating room staff for their boundless patience.

REFERENCES

[1] J. Johnson, L. Grecu, and N. Lawson, "Autonomic Nervous System: Physiology and Pharmacology," in *Clinical Anesthesia*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2009, pp. 326–69.

[2] H. Kehlet, "Multimodal approach to control postoperative pathophysiology and rehabilitation," *Brit J Anaesth*, vol. 78, pp. 606–17, 1997.

[3] E. Seitsonen, I. Korhonen, M. van Gils, M. Huiku, J. Lötjönen, K. Korttila, and A. Yli-Hankala, "EEG spectral entropy, heart rate, photoplethysmography and motor responses to skin incision during sevoflurane anaesthesia," *Acta Anaesth Scand*, vol. 49, 284–92, 2005.

[4] R. Logier, M. Jeanne, A. Dassonneville, M. Delecroix, and B. Tavernier, "PhysioDoloris: a monitoring device for Analgesia / Nociception balance evaluation using Heart Rate Variability analysis." in *Conf Proc IEEE Eng Med Biol Soc*, 2010, pp. 1194–7.

[5] C. J. Brouse, G. A. Dumont, D. Myers, E. Cooke, and J. M. Ansermino, "Wavelet Transform Cardiorespiratory Coherence for Monitoring Nociception," in *Computing in Cardiology*, 2010, pp. 713–6.

[6] C. J. Brouse, W. Karlen, D. Myers, E. Cooke, J. Stinson, J. Lim, G. A. Dumont, and J. M. Ansermino, "Wavelet transform cardiorespiratory coherence detects patient movement during general anesthesia," in *Conf Proc IEEE Eng Med Biol Soc*, vol. 33, 2011, pp. 6114–7.

[7] C. J. Brouse, W. Karlen, G. A. Dumont, D. Myers, E. Cooke, J. Stinson, J. Lim, and J. M. Ansermino, "Measuring Adequacy of Analgesia with Cardiorespiratory Coherence," in *Proceedings of the 2012 Society for Technology in Anesthesia Annual Meeting*, 2012.

[8] K. Keissar, L. R. Davrath, and S. Akselrod, "Coherence analysis between respiration and heart rate variability using continuous wavelet transform." *Phil Trans R Soc A*, vol. 367, pp. 1393–406, Apr. 2009.

[9] A. Grinsted, J. C. Moore, and S. Jevrejeva, "Application of the cross wavelet transform and wavelet coherence to geophysical time series," *Nonlinear Proc Geoph*, vol. 11, pp. 561–566, 2004.

[10] V. X. Afonso, W. J. Tompkins, T. Q. Nguyen, and S. Luo, "ECG beat detection using filter banks," *IEEE Trans Biomed Eng*, vol. 46, no. 2, pp. 192–202, Feb. 1999.

[11] R. D. Berger, S. Akselrod, D. Gordon, and R. J. Cohen, "An Efficient Algorithm for Spectral Analysis of Heart Rate Variability," *IEEE Trans Biomed Eng*, vol. 33, no. 9, pp. 900–4, 1986.