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Real-Time Cardiorespiratory Coherence is Blind to Changes in Respiration During General Anesthesia

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Abstract— **Purpose. A novel real-time cardiorespiratory coherence (CRC) algorithm has been developed to monitor nociception during general anesthesia. CRC uses custom designed filters to track and analyze the respiratory sinus arrhythmia (RSA) as it moves in time and frequency. CRC is a form of sensor fusion between heart rate and respiration, estimating the strength of linear coupling between the two signals. The aim of this study was to estimate the effect of changes in respiration rate (RR) and peak airway pressure (PPaw) on CRC. The response of CRC was compared to a prior offline wavelet-based algorithm (WTCRC) as well as traditional univariate heart rate variability (HRV) measures. A nociception index was created for each algorithm, ranging from 0 (no nociception) to 100 (strong nociception).**

Methods. Following ethics approval and informed consent, data were collected from 48 children receiving general anesthesia during dental surgery. The times of change in RR and PPaw events were noted in real-time. A total of 43 RR and 35 PPaw change events were analyzed post hoc in pseudo real-time. The nociception index averages were compared between a baseline period and a response period around each event. A Wilcoxon rank-sum test was used to compare changes.

Results. The change in RR changed the CRC nociception index by an average of -2.2 [95% CI from -10 to 4.7] ($P > 0.3$), and the change in PPaw changed the CRC nociception index by an average of 5.4 [-1.0 to 11] ($P > 0.1$). The changes were smaller than those of many traditional HRV measures.

Conclusions. Real-time CRC was blind to the changes in respiration, and was less sensitive than many of the traditional HRV measures. A nociception index based on CRC can thus function across a wider range of respiratory conditions than can many traditional univariate HRV measures. The real-time CRC algorithm shows promise for monitoring nociception during general anesthesia.

I. INTRODUCTION

Anesthesiology includes 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 peri-operative complications, delays recovery, and contributes to postoperative morbidity [2]. Anesthesiologists must control the stress response (nociception) by administering analgesic drugs (antinociception).

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The ANS is currently not routinely monitored. Anesthesiologists are guided by observation and interpretation of trends in patients' vital signs, including heart rate (HR) and blood pressure. These are only indirect and insensitive measures of nociception or the ANS, and are not well correlated with nociception. Confounding factors such as pre-existing medical conditions and inter-patient variability challenge the anesthesiologist to administer the correct amount of drug to suppress nociception in each individual. An automated nociception monitor that directly assesses ANS activity would be very useful for general anesthesia, providing anesthesiologists with feedback about the adequacy of antinociception. Heart rate variability (HRV) shows promise as a noninvasive nociception monitor [3], [4], [5].

HRV reflects the autonomic state, and is typically measured in the time and frequency domains. Frequency domain measures traditionally rely on fixed frequency bands, assuming that the respiration rate (RR) falls between 0.15 - 0.4 Hz (9 - 24 breaths/min). When the RR falls outside of this range, traditional HRV measures may fail. We aim to eliminate this assumption in our work.

We have previously developed cardiorespiratory coherence (CRC) algorithms for monitoring nociception. Initially, a wavelet transform CRC (WTCRC) algorithm was developed for offline analysis using the continuous wavelet transform. Then a real-time CRC algorithm was developed for online analysis using custom-designed filters to minimize real-time delay. We have previously shown that the CRC correlates to a traditional frequency domain HRV measure [6], that it can detect patient movement (a sign of strong nociception) [7], and that it responds to nociceptive and antinociceptive stimuli [8], [9]. However, further validation studies are required.

In this work, we will measure the response of CRC to changes in RR and peak airway pressure (PPaw), and compare its responses to those of traditional time and frequency domain HRV measures. A nociception monitor should be blind to changes in respiration.

II. METHODS

A. Nociception Indices

CRC is a measure of the linear coupling between HR and respiration. It is a cross correlation between these two signals in the time and frequency domains. CRC analyzes the HR and respiration signals in time/frequency, correlates them, and smooths the results.

An analyzing filter tracks the respiratory sinus arrhythmia (RSA) as it moves across the time/frequency plane. RSA is a

healthy heart arrhythmia driven by respiration, that has been shown to reflect the autonomic balance [10]. The analyzing filter is a complex Morlet function with variable center frequency and bandwidth. We use the respiratory frequency (f_r) as the filter's center frequency. This is where the RSA power exists in the frequency domain. As f_r varies over time, the filter's center frequency and bandwidth change to track the RSA. The filter measures the HR power (denoted $P_t^{HR}(f_r)$), respiration power ($P_t^{Resp}(f_r)$), and cross power ($P_t^X(f_r)$).

The coherence estimator is calculated as:

$$\hat{C}_t^2(f_r) = \frac{\left|\left\langle P_t^X(f_r)\right\rangle\right|^2}{\left\langle\left|P_t^{HR}(f_r)\right|\right\rangle\left\langle\left|P_t^{Resp}(f_r)\right|\right\rangle}, \quad (1)$$

where the angled brackets denote a smoothing operator using a causal Gaussian smoothing filter. The CRC nociception index is then calculated as:

$$\text{CRC} = 100 \text{ x } (1 - \hat{C}^2). \quad (2)$$

The result is a series of real-time CRC values at the time-varying f_r. CRC can range from 0 (perfect coherence, no nociception) to 100 (no coherence, strong nociception).

Traditional time and frequency domain HRV measures were calculated for comparison. The low frequency (LF) power, high frequency (HF) power, normalized LF and HF (LFnu, HFnu), LF/HF ratio, standard deviation of normal-to-normal beats (SDNN), and root mean square of successive differences (RMSSD) were tested. Nociception indices were created for these measures by mapping them to a range of [0 100] using tuning values derived from our dataset. The procedure is fully described in [11].

B. Clinical Protocol & Data Collection

Following ethics approval and informed consent, data were collected from healthy pediatric patients receiving general anesthesia during dental surgery. Subjects were aged 3-6 years, had ASA physical status I or II (i.e. healthy patients), were free of cardiorespiratory disease, and were not taking medications that alter autonomic function. Subjects were anesthetized with propofol and remifentanil.

The RR was changed from 8 to 16 breaths/min and the PPaw was changed from 15 to 12 cmH_2O once during each case. These were two separate events, occurring at two different times. The level of nociception is unknown and variable both before and after the change in RR and PPaw (since the changes occurred during surgery). The changes in RR and PPaw themselves are neither nociceptive nor antinociceptive, so we expect that the level of nociception should be, on average, unchanged.

Physiological data were recorded throughout each case. The electrocardiogram (ECG), capnometry (CO_2), and airway pressure (Paw) signals, as well as the respiratory frequency (f_r) (derived from capnometry) trend, were recorded using Datex/Ohmeda S/5 Collect software (GE Healthcare, Helsinki, Finland). The ECG was recorded at 300 Hz, CO_2 and Paw at 25 Hz, and f_r at 0.1 Hz. A research assistant annotated the data in real-time with markers identifying the times of change in RR and PPaw events.

C. Data Analysis

The study sample size was based on the precision of a receiver operating characteristic (ROC) curve that has not been utilized in this analysis. The data analyzed in this study have been included in previous publications [6], [7], [8], [9].

Data were manually inspected and selected for *post hoc* analysis in Matlab (The Mathworks, Natick, MA). Case annotations were searched to find all recorded change in RR and PPaw events. Events with significant ECG or CO_2 artifacts were excluded from analysis.

HR and CO_2 signals were prepared for analysis. Data segments were extracted around each event. A *baseline period* consisted of a 60 s analysis window ending 60 s before the event. A *response period* consisted of a 60 s analysis window starting 60 s after the event. This allowed for a 60 s buffer before and after the event, to ensure the analysis was not corrupted by cross contamination. The analysis windows were padded with 120 s of data on each end, to ensure the analysis was not corrupted by edge artifacts. ECG R-peaks were detected using a filter bank algorithm [12], and errors were manually corrected to create a gold standard beat series. Each beat series was converted to a HR signal and resampled onto an evenly-spaced 4 Hz grid using Berger's algorithm [13]. The CO_2 signal was downsampled to 4 Hz using standard low pass filtering and decimation. The f_r was upsampled to 4 Hz using a repeater.

The change in the nociception indices was calculated in all events in pseudo real-time. The HR, CO_2, and f_r signals were analyzed sample-by-sample to simulate a real-time environment in each data segment. The resulting nociception index values were averaged over the baseline and response periods. The change in average value from the baseline to the response period was calculated. Finally, changes were averaged separately over all change in RR and PPaw events.

A 95% confidence interval was estimated about the mean changes, using a corrected percentile bootstrapping method (the *bootci* function in Matlab). A Wilcoxon rank-sum test was applied to estimate the statistical significance of the mean changes. A Bonferroni correction was applied to account for the multiple significance tests performed. Nine tests were performed in each experiment, leading to a corrected significance level of $0.05/9 = 0.0056$. Responses below this level were considered statistically significant.

III. RESULTS

The 48 subjects (22 male, 26 female) had a median (IQR [full range]) age of 3.7 (0.68 [3.0 - 6.8]) years, weight of 16 (3.0 [12 - 24]) kg, and height of 101 (6.5 [92 - 114]) cm.

A total of 43 change in RR events were analyzed. One was excluded due to significant ECG artifacts, where the HR was impossible to discern. Two were excluded due to significant artifacts in the CO_2 signal. One was missing due to a failure of the data recording equipment. One was missing because the case ended early.

Measure	Mean Baseline	Mean Change	95 % CI	P-value
CRC	34	-2.2	-10 to 4.7	> 0.3
WTCRC	14	0.28	-5.2 to 5.3	> 0.1
LF	59	-9.2	-13 to -5.6	< 0.008
HF	55	-8.2	-11 to -5.5	> 0.05
LFnu	74	-29	-37 to -22	< 0.000004*
HFnu	82	-26	-33 to -19	< 0.000002*
LF/HF	67	-16	-20 to -12	< 0.000002*
SDNN	18	1.4	-0.74 to 3.8	> 0.4
RMSSD	19	5.1	1.8 to 8.7	> 0.3

TABLE I

RESPONSE TO A CHANGE IN RR FROM 8 TO 16 BREATHS/MIN. ASTERISKS (*) DENOTE STATISTICALLY SIGNIFICANT RESULTS WITH A BONFERRONI CORRECTION.

Measure	Mean Baseline	Mean Change	95 % CI	P-value
CRC	32	5.4	-1.0 to 11	> 0.1
WTCRC	16	4.1	-0.95 to 9.1	> 0.05
LF	59	-2.8	-7.7 to 1.4	> 0.3
HF	37	5.3	2.8 to 8.4	> 0.1
LFnu	43	4.1	-3.6 to 12	> 0.2
HFnu	54	5.2	-1.2 to 12	> 0.1
LF/HF	51	2.6	-1.5 to 6.4	> 0.1
SDNN	27	-5.9	-11 to -2.1	> 0.2
RMSSD	33	-7.2	-14 to -2.7	> 0.2

TABLE II

RESPONSE TO A CHANGE IN PPAW FROM 15 TO 12 CMH_2O. ASTERISKS (*) DENOTE STATISTICALLY SIGNIFICANT RESULTS WITH A BONFERRONI CORRECTION.

A total of 35 change in PPaw events were analyzed. Two were excluded due to significant ECG artifacts, where the HR was impossible to discern. One was missing due to a failure of the data recording equipment. Four were missing because either the start or end PPaw was clinically unachievable. Six were missing because the case ended early.

The CRC nociception index did not change significantly in response to a change in RR, changing by an average of -2.2 [95% CI from -10 to 4.7] ($P > 0.3$). It also did not change significantly in response to a change in PPaw, changing by an average of 5.4 [-1.0 to 11] ($P > 0.1$). Real-time CRC was less sensitive to the stimuli than were many of the traditional HRV measures. Full results in Tables I, II, and Figs. 1, 2, 3.

IV. DISCUSSION & CONCLUSION

The results of this study demonstrate that a nociception index based on real-time CRC is blind to changes in RR and PPaw. CRC was less sensitive to these stimuli than some traditional time and frequency domain HRV measures. A nociception index should be blind to these changes, since they are not nociceptive.

CRC is unique in combining information from the HR and respiration signals, operating as a form of sensor fusion. CRC makes no assumption on the location of the RSA, completely eliminating the concept of fixed frequency bands. The algorithm tracks the RSA as it moves in time and frequency using the respiration frequency calculated from the respiration signal (e.g. CO_2). CRC has information on the exact location of the RSA. We have previously shown that CRC continues to function when the respiration frequency is low (< 0.15 Hz), while the LF/HF ratio fails [6]. This limitation extends beyond the LF/HF ratio.

Reliance on fixed frequency band limits caused the traditional frequency domain HRV measures to respond to the change in RR. For each change in RR event, the baseline RR was 8 breaths/min (0.133 Hz). In this condition, the RSA was not present in the expected HF band, but was instead mostly in the LF band. This condition distorts the frequency domain measures, leading to an amplified LF, LFnu, and LF/HF ratio, and an attenuated HF and HFnu. The corresponding nociception indices are artificially high, and not true reflections of the autonomic state. This condition led to statistically significant responses in LFnu, HFnu, and LF/HF. In addition, responses in the LF and HF were nearly statistically significant. Respiration in the LF band is not just a theoretical condition. Slow respiration is often used during general anesthesia. Fixed frequency bands are therefore a significant limitation.

The PhysioDoloris Analgesia Nociception Index (ANI) (MetroDoloris SAS, Loos, France), another HRV-based nociception monitor, may suffer the same limitation. The ANI measures changes in the magnitude of RSA. The algorithm applies a wavelet bandpass filter to the HR signal to isolate the RSA, then calculates the area under the RSA curve (AUC). The ANI is calculated as a weighted fraction of the smallest short-term AUC to longer-term AUC. The design of the wavelet filters assumes that the RSA will exist in the frequency range of 0.167 - 0.667 Hz [4]. The low RR condition in our experiment exceeds the filter design of the ANI. Another nociception monitor, the Surgical Stress Index (SSI) (GE Healthcare, Helsinki, Finland), may also suffer this limitation. It is based partly on the photoplethysmogram amplitude, which may be affected by respiration [5]. However, we have not shown any such effect in our experiments.

While our results show that CRC is not significantly affected by a change in RR, the experiment was only performed on the range of 8 - 16 breaths/min. It is possible that there is a small effect that may only become measurable at greater changes in RR. Furthermore, while we have shown that CRC can operate across a wider range than the traditional frequency domain HRV measures, this range is not unbounded. The respiration and HR can only couple across a finite frequency range. If the patient breathes too slowly or two quickly, the HR will be unable to couple to the respiration and coherence will drop to zero (CRC nociception index of 100). The exact lower and upper RR bounds are unknown, and probably vary across the population. Age, health, and individual physiology all likely contribute to variation in RSA coupling bounds. These bounds could be tested in the future, by ramping the RR under otherwise steady state conditions and observing the resulting change in CRC.

CRC may have responded to a change in PPaw, though the response was too small to be statistically significant. While the mean change was small (5.4), the nociception index

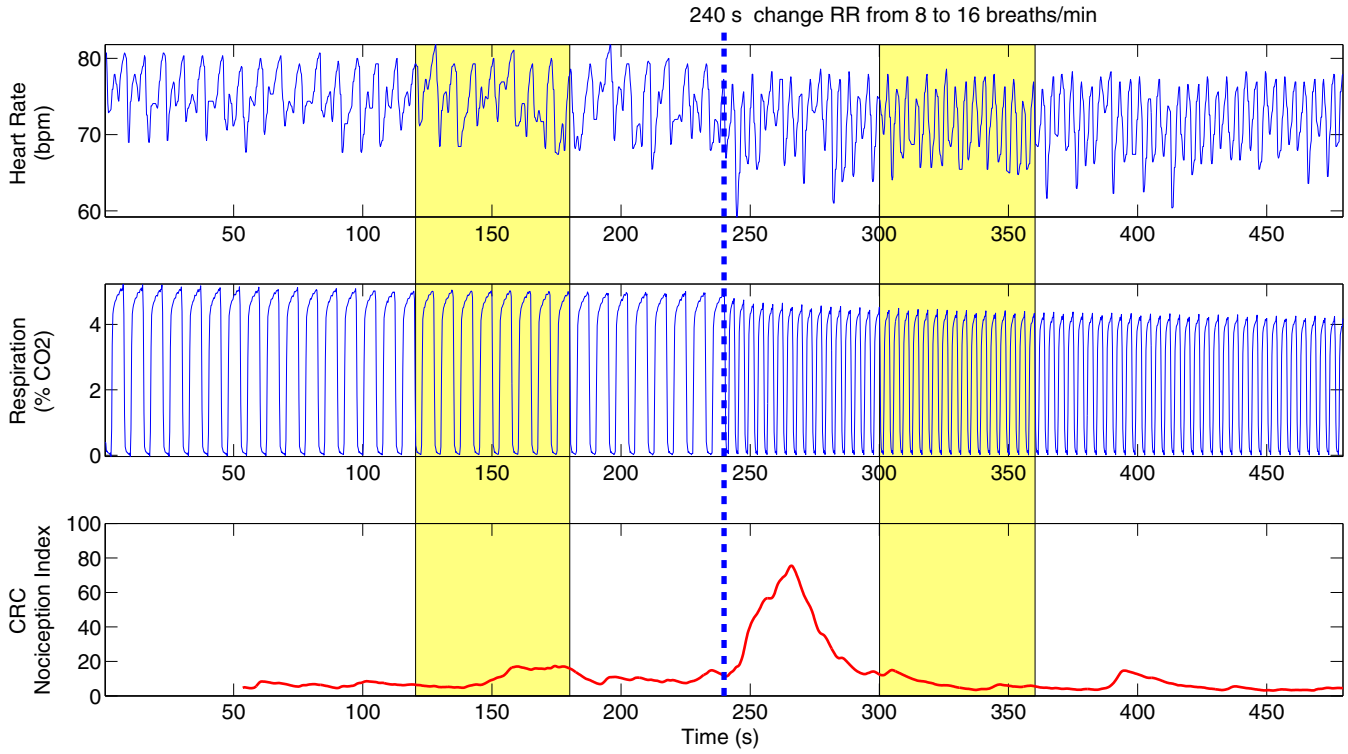

Fig. 1. Example change in RR event, analyzed with real-time CRC. Vertical lines denote clinical events. The yellow vertical bands (both left and right) represent the baseline and response periods, respectively. The nociception index is approximately the same in the period preceding the change in RR as it is following it. The transient increase in the nociception index immediately following the change in RR is caused by a delay in the analyzing filter tracking. For this brief period, the real-time CRC algorithm is looking for the RSA at the wrong frequency. The missing CRC data at the beginning of the window corresponds to the combined length of the analyzing and smoothing filters. This is not directly related to the real-time delay.

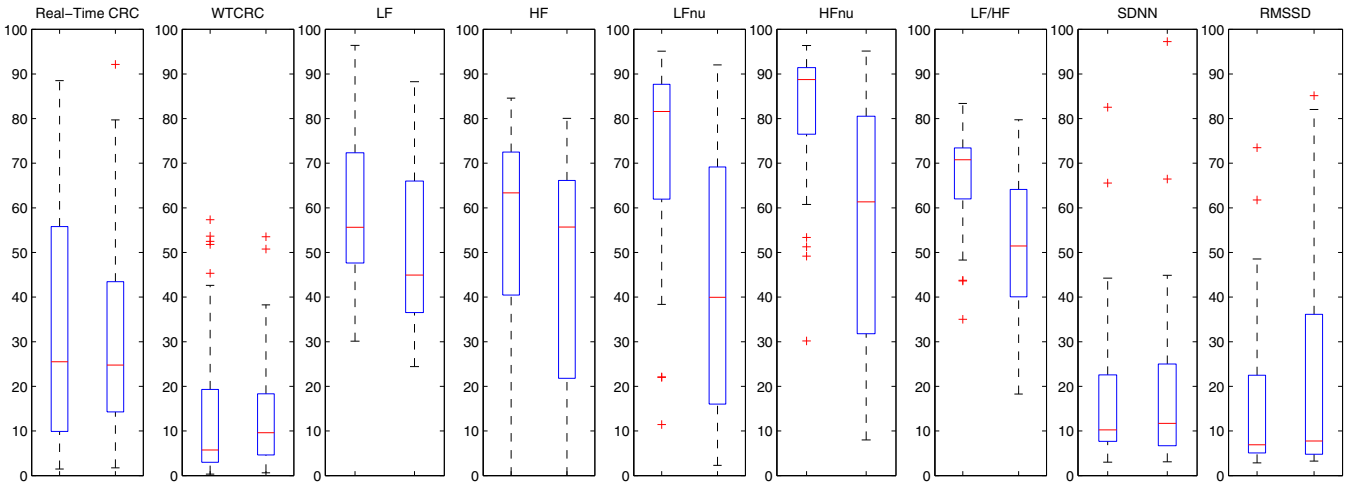

Fig. 2. Boxplots of responses to a change in RR for all measures. The boxes represent the index levels before (left) and after (right) the change in RR. The central red bar represents the median (second quartile). The box edges are the first and third quartiles. The whiskers extend 1.5x the interquartile range (IQR) beyond the box edges. Points beyond the whiskers are drawn as red plus symbols (+), and may be considered outliers. Such possible outliers were not excluded from analysis.

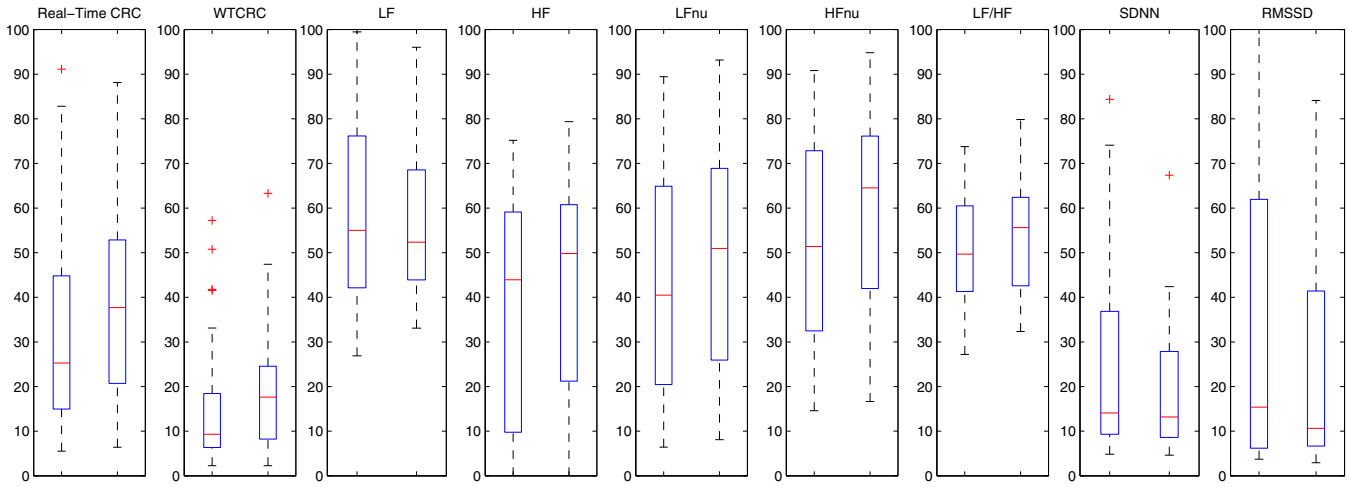

Fig. 3. Boxplots of responses to a change in PPaw for all measures. The boxes represent the index levels before (left) and after (right) the change in PPaw. The central red bar represents the median (second quartile). The box edges are the first and third quartiles. The whiskers extend 1.5x the interquartile range (IQR) beyond the box edges. Points beyond the whiskers are drawn as red plus symbols (+), and may be considered outliers. Such possible outliers were not excluded from analysis.

increased in most of the events (26/35 or 74%). There is a theoretical mechanism to explain this effect. The air pressure in the lungs provides an external perturbation to the ANS. The perturbation acts both directly (through stretch receptors in the lungs) and indirectly (through changes in intrathoracic pressure and thus baroreflex). The cyclic perturbation causes corresponding oscillations in HR (i.e. RSA). When the PPaw is decreased, the perturbation effect is likewise decreased. In the extreme, when the PPaw drops to zero, there is no perturbation, no RSA, and thus no coherence. Decreasing the PPaw may actually decrease coherence, and thus increase the CRC nociception index. This hypothesis could be tested in the future, by decreasing the PPaw under otherwise steady state conditions and observing the resulting change in CRC.

Future work will involve improving artifact handling. CRC is sensitive to false or missed beats in the ECG, which are manifested as strong discontinuities in the HR signal. HR artifacts typically lead to a strong false increase in the CRC nociception index. Artifacts in the respiration signal produce a similar result. Robust artifact detection and rejection will be essential for a nociception monitor in clinical practice.

CRC shows promise as a real-time monitor of nociception during general anesthesia. CRC responds to both nociception and antinociception, and operates over a wider range of respiratory conditions than do many traditional HRV-based measures. In the future, CRC could provide anesthesiologists with feedback about the adequacy of analgesia in real time, increasing patient safety during surgery.

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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] R. Huhle, M. Burghardt, S. Zaunseder, N. Wessel, T. Koch, H. Malberg, and A. Heller, "Effects of awareness and nociception on heart rate variability during general anaesthesia," *Physiological Measurement*, vol. 33, no. 2, pp. 207–17, Feb. 2012.

[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] M. M. R. F. Struys, C. Vanpeteghem, M. Huiku, K. Uutela, N. B. K. Blyaert, and E. P. Mortier, "Changes in a surgical stress index in response to standardized pain stimuli during propofolremifentanil infusion," *Brit J Anaesth*, vol. 99, no. 3, pp. 359–67, Sept. 2007.

[6] 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.

[7] 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.

[8] C. J. Brouse, W. Karlen, G. A. Dumont, D. Myers, E. Cooke, J. Stinson, J. Lim, and J. M. Ansermino, "Real-Time Cardiorespiratory Coherence Detects Antinociception During General Anesthesia," in *Conf Proc IEEE Eng Med Biol Soc*, 2012, pp. 3813–3816.

[9] C. J. Brouse, W. Karlen, G. Dumont, D. Myers, E. Cooke, J. Stinson, J. Lim, and J. Ansermino, "Monitoring Nociception During General Anesthesia with Cardiorespiratory Coherence," *J Clin Monit Comput*, p. (submitted).

[10] J. A. Taylor, C. W. Myers, J. R. Halliwill, H. Seidel, and D. L. Eckberg, "Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans," *Am J Physiol Heart Circ Physiol*, vol. 280, no. 6, pp. 2804–14, June 2001.

[11] C. J. Brouse, "Monitoring Nociception During General Anesthesia with Heart Rate Variability," Ph.D. dissertation, University of British Columbia, 2013.

[12] 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.

[13] 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.