Point Process Respiratory Sinus Arrhythmia Analysis during Deep Tissue Pain Stimulation

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Abstract

We present an analysis of autonomic nervous system responses to deep tissue pain by using an instantaneous point process assessment of Heart Rate Variability (HRV) and Respiratory Sinus Arrhythmia (RSA). Ten subjects received pressure stimuli at 8 individually calibrated intensities (7 painful) over three separate runs. An inverse Gaussian point process framework modeled the R-R interval (RR) by defining a bivariate regression incorporating both past RRs and respiration values observed at the beats. Instantaneous indices of sympatho-vagal balance and RSA were estimated combining a maximum-likelihood algorithm with time-frequency analysis. The model was validated by Kolmogorov-Smirnov goodness-of-fit and independence tests. Results show that, in comparison to the resting period, all three pain runs elicited a significant decrease in RSA by over 21% (p=0.0547, 0.0234, 0.0547) indicating a reduced parasympathetic tone during pain, with RSA estimates negatively correlated with the calibrated stimulus intensity levels (slope = -0.4123, p=0.0633).

1. Introduction

The autonomic nervous system (ANS) is modulated to provide an adaptive response to the pain experience. The pain experience usually increases heart rate (HR) [1–3] and decreases heart rate variability (HRV) [4–6]. Cain et al. reported lower HF power and higher LF/HF ratio in women with irritable bowel syndrome who have severe gut pain [4]. Storella et al. found increase in HRV with the relief of chronic pain which was attributed to the restoration of cardiovascular health [5]. A study on new-born infants reported a clear stress response provoked when the heel was squeezed for blood sampling, indicated by an increased HR and a decreased spectral power in the HF band [6]. Campbell et al. reported long term relationships between pain sensitivity and the autonomic tone [7], and found that average pain sensitivity is associated with HF component and LF/HF ratio of HRV, suggesting increased sympathetic and reduced parasympathetic tone among individuals less sensitive to pain. In addition to the frequency domain methods, time domain methods of HRV analysis have also been used in pain/analgesia evaluation [8]. To date, we have not seen an attempt to link continuous estimates of Respiratory Sinus Arrhythmia (RSA) with evoked pain administration.

In this paper, we present a maximum likelihood point process algorithm for instantaneous estimation of HRV and RSA during short-term pain administration. The proposed method is capable of achieving continuous-time estimates accounting for rapid dynamic changes in both respiratory and autonomic influences on cardiovascular control. The algorithm is applied to a pain administration protocol where short-term pressure stimuli were used to generate pain experience in ten subjects.

2. Methods

2.1. Pain protocol

The experimental protocol consisted of a series of pressure stimuli (each 14s long, 2s ramp up, 10s at target pressure, 2s ramp down) which were delivered on the left calf using a velcro-adjusted pressure cuff connected to a rapid cuff inflator. The cuff inflator was adapted to ramp up more gradually to target pressure over 2 seconds, to minimize abrupt subject motion. Ten seconds after the end of each stimulus, subjects used a button box to complete two pain rating scales, both on 0-100 numerical scales: pain intensity (0 = 'no pain', 100 = 'the most intense pain tolerable') and pain unpleasantness (0 = 'neutral', 100 = 'extremely unpleasant'). Subjects received each of the p0-p70 (p0 = 'no pain', p70= 'highest target pressure/pain') stimuli three times, for a total of 24 stimuli. Of note, stimulus pressure had a highly significant linear effect on both ratings of pain intensity and unpleasantness. The stimuli were delivered in a pseudorandom order in three separate

runs, 8 stimuli per run. All physiological signals, including ECG and respiration, were collected at 400Hz using Chart Data Acquisition Software on a laptop using the Powerlab System (ADInstruments, Colorado Springs, CO). Informed consent was obtained from all participants, and the protocol was approved by the Human Research Committee of Massachusetts General Hospital.

2.2. Point process algorithm

As autonomic inputs to the sinoatrial (SA) node are part of the cardiovascular control circuitry, the heartbeat variations are dynamic, or time-varying [9]. We model the heartbeat occurrences (R-waves on the ECG) with a history dependent, inverse Gaussian parametric point process model. Of note, the inverse Gaussian process characterizes the integrate-and-fire model of heart beat generation [9]. Assuming that in a given observation interval $(0, T]$ K successive pulses are recorded: $0 < u_1 < u_2 < \ldots < u_K \leq T$, after any beat-timing u_k the waiting time until the next R-event obeys a history dependent inverse gaussian probability density $f(t)$ given by

$$f(t|u_k) = \left[\frac{\theta(t)}{2\pi(t-u_k)^3}\right]^{\frac{1}{2}} \exp\left\{-\frac{1}{2}\frac{\theta(t)[t-u_k-\mu_{RR}(t)]^2}{\mu_{RR}^2(t)(t-u_k)}\right\}, \quad (1)$$

where t is at any time satisfying $t > u_k$, and $\mu_{RR}(t) > 0$ is the mean of the distribution, which is an estimation of the instantaneous mean R-R interval (RR). $\theta(t) > 0$ is the shape parameter of the inverse gaussian distribution. The standard deviation of the above probability model is given by

$$\sigma_{RR}(t) = [\mu_{RR}^3(t)/\theta(t)]^{\frac{1}{2}}. \quad (2)$$

For RR measured in seconds, $r = c/(t-u_k)$, where $c = 60s/min$, gives the estimation of heart rate in beats per minute (bpm). By using a standard change of variables formula [10], we get the mean and standard deviation of the heart rate probability density are given by [9]

$$\mu_{HR}(t) = c\left(\frac{1}{\mu_{RR}(t)} + \frac{1}{\theta(t)}\right), \quad (3)$$

$$\sigma_{HR}(t) = c\left[\frac{2\mu_{RR}(t)+\theta(t)}{\mu_{RR}(t)\theta^2(t)}\right]^{\frac{1}{2}}. \quad (4)$$

Instantaneous estimates of heart rate and heart rate variability are characterized by $\mu_{HR}(t)$, and $\sigma_{HR}^2(t)$, respectively.

We further model $\mu_{RR}(t)$ as a bivariate autoregressive (AR) model incorporating past RR and respiration values accounting for the lasting effects of the autonomic inputs to the SA node as well as the respiration influence on heart beat dynamics,

$$\mu_{RR}(t) = a_0(t) + \sum_{k=1}^{p} a_k(t)RR_{t-k} + \sum_{k=1}^{q} b_k(t)RP_{t-k}. \quad (5)$$

The original respiration signal (RP) is re-sampled at the beat events, so that both respiration and RR are synchronized.

RSA can then be defined as the transfer function from RP to RR,

$$H_{12}(\omega, t) = \frac{\sum_{k=1}^{q} b_k(t)z^{-k}|_{z=e^{j2\pi f_s}}}{1-\sum_{k=1}^{p} a_k(t)z^{-k}|_{z=e^{j2\pi f_s}}}. \quad (6)$$

We then use the time-varying respiration spectrum $P_{RP}(\omega, t)$ to estimate the dynamic respiratory frequency $\omega_{RP}(t)$ where maximum respiration power is concentrated at each time instance, i.e.,

$$\max_{\omega}[P_{RP}(\omega, t)] = P_{RP}(\omega_{RP}, t). \quad (7)$$

The RSA gain is estimated by evaluating (6) at ω_{RP},

$$RSA_{gain}(t) = |H_{12}(\omega_{RP}, t)|. \quad (8)$$

A local maximum likelihood method [11] is used to estimate the unknown time-varying parameter set $\xi = \{\{a_k\}_{k=0}^{p}, \{b_k\}_{k=1}^{q}, \theta\}$. In estimating ξ at time t, we take a local likelihood interval $(t-l, t]$, where l is the length of the local likelihood observation window. Within $(t-l, t]$, we may observe n pulses, $t-l < u_1 < u_2 < \ldots < u_n \leq t$. Then, we consider the local joint probability density of $u_{t-l:t}$, where $u_{t-l:t} = \{u_1, \ldots, u_n\}$. The log-likelihood associated with the joint probability density is given by

$$\log f(u_{t-l:t}) = \sum_{j=2}^{n} w(t-u_j)\log f(u_j - u_{j-1}) + w(t-u_n)\log\int_{t-u_n}^{\infty} f(\nu)d\nu, \quad (9)$$

where $w(t-u_j) = \alpha^{t-u_j}$, $0 < \alpha < 1$, is a weighting function for the local likelihood estimation [9, 11], and the second term represents the likelihood of the partially observed interval since the last observed heartbeat u_n. To maximize the local log likelihood given in (9) we use a Newton-Raphson method, and obtain the local maximum likelihood estimate of ξ.

Goodness-of-fit of the proposed model is evaluated using a Kolmogorov-Smirnov (KS) test based on the time-rescaling theorem [12]. The test uses the conditional intensity function $\lambda(t) = f(t)/[1-\int_{u_n}^{t} f(\nu)d\nu]$ to transform beat events into independent observations on the interval $[0, 1]$, and the KS plot allows to test the agreement of the transformed observations and the ideal uniform probability density. The transformed quantiles' autocorrelation function is further computed to check independence of the transformed intervals. The KS distance is defined as the maximum distance of the KS plot from the diagonal.

3. Results

The proposed maximum likelihood point process algorithm was applied to each subject during three pain runs, as well as during the preceding rest epoch. Optimal model parameters ($p = 4$, $q = 6$, $l = 90$s, and $\alpha = 0.98$)

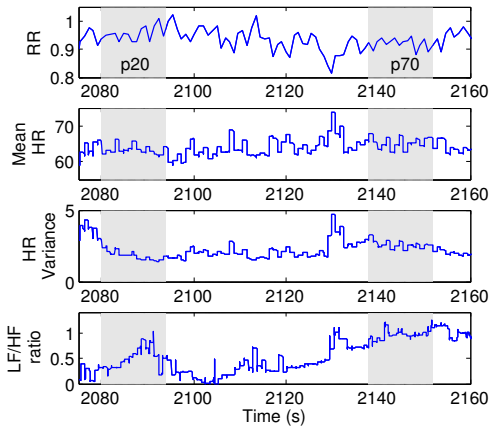

Figure 1. From top to bottom, original RR series and continuous estimates of HR, HRV, and LF/HF ratio for a 90s segment during a pain run for one representative subject. Shaded areas indicate periods where pain is administered.

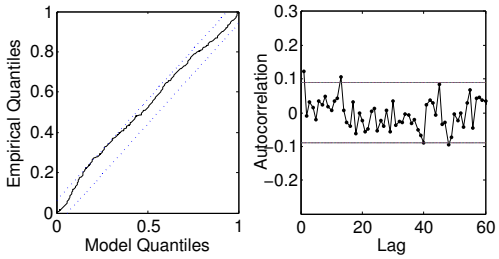

Figure 2. KS plot and Autocorrelation function for the example in Figure 1. Dashed lines indicate the 95% confidence bounds.

were found empirically from a discrete set within reasonable ranges, by minimizing both the Akaike Information Criterion for maximum likelihood estimation and the KS distance on the KS plot. Figure 1 shows the original RR series together with the estimated mean heart rate, heart rate variability, and LF/HF ratio. Dotted lines show periods where pain is administered, i.e. two periods corresponding to target pain intensities of 20 and 70 respectively. While HRV slightly decreases during the pain administration, which agrees with previous findings, we observe an increase in LF/HF ratio during pain compared to the immediately preceding period, suggesting reduced vagal inputs during pain. The KS plot and autocorrelation function shown in Figure 2 verifies the goodness-of-fit of the model for the run considered in Figure 1, as both KS distance and autocorrelation stay within the 95% confidence interval.

Figure 3 shows the original respiration signal together with the estimated instantaneous respiratory frequency, coherence between respiration and RR at the respiratory frequency, and the dynamic RSA gain from the same run considered above. Respiration is fairly constant, and respiratory frequency varies between $0.3 - 0.34$Hz. We observe

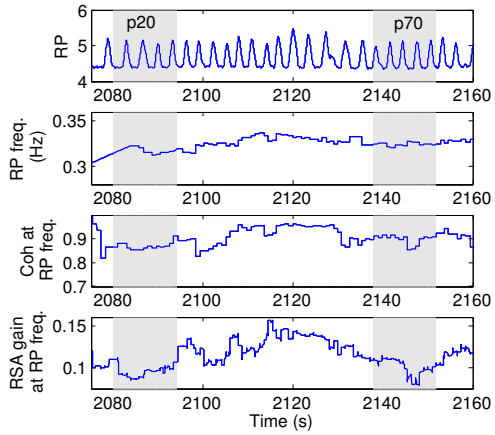

Figure 3. From top to bottom, original respiration signal, respiratory frequency, coherence between respiration and RR, and dynamic RSA estimation at the respiratory frequency for the same example as in Figure 1.

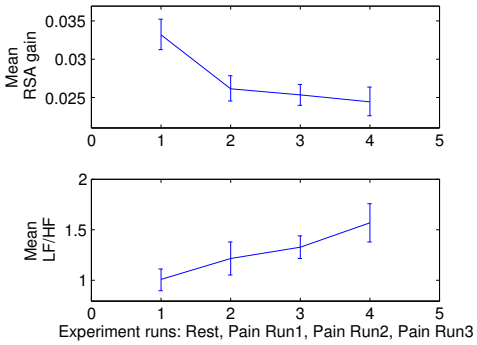

Figure 4. Mean LF/HF ratio and RSA gain averaged for all subjects within the Rest epoch and the Pain Run epochs.

a high coherence (> 0.8), which indicates that respiration and RR are highly correlated at the respiratory frequency. Importantly, we observe a decrease in RSA gain during pain administration. During the second pain epoch (target intensity of 70), RSA gain drops to even lower values as compared to the first epoch with target intensity of 20, suggesting that higher pain be associated with lower RSA.

Statistical averages of mean RSA and LF/HF estimates for all the subjects during rest and the three pain runs are given in Figure 4. Results show that, in comparison to the resting period, all three pain runs elicited a significant decrease in RSA by over 21% (p=0.0547, 0.0234, 0.0547) pointing at an overall reduced parasympathetic tone during pain. Also, in comparing the RSA quantification with the sympatho-vagal balance indices, we found that the LF/HF ratio expectedly increased during pain runs compared to the rest, but that the increment was not statistically significant (p=0.7344, 0.0977, 0.4961).

Figure 5 shows the correlation between estimated RSA gain and LF/HF with the calibrated stimulus intensity lev-

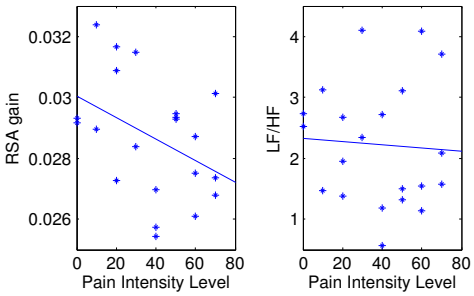

Figure 5. Mean LF/HF ratio and RSA gain estimations during the application of pain at different intensities.

els. RSA negatively correlates with the pain levels (slope = -0.4123, p=0.0633), suggesting the reliability of the proposed RSA estimation as a pain indicator. On the other hand, the standard LF/HF ratio shows insignificant correlation with the stimulus level intensity (slope = -0.0609, p=0.7932).

4. Discussion and conclusions

An inverse Gaussian point process model of heartbeat interval dynamics was proposed to derive continuous estimates of RSA during a short-term pain administration experiment. Overall, a decrease in RSA was found for the recordings when pain was administered as compared to the resting stage, in line with previous findings suggesting reduced vagal tone during pain experience. The results also show a negative correlation between the RSA estimates and the target pain intensities. In comparing our RSA quantification with the standard sympatho-vagal balance indices, we found that the novel RSA assessment provides higher significance and sensitivity than any other time-varying instantaneous autonomic measure as computed within the proposed point process framework (including LF/HF). These encouraging preliminary results indicate that the proposed method may be able to differentiate pain stages and fast transitions in protocols where pain is administered in short windows of time.

Future analysis will include assessing the correlations between RSA estimation and subjects' perspective of intensity and unpleasantness ratings of the pain. Also, future improvements to the model may consider frequency-dependent filters consistent with autonomic modulation physiology in order to obtain more direct estimates of vagal tone. Additionally, the introduction of a multivariate model with arterial blood pressure as further covariate will enable to disentangle the closed-loop blood pressure control dynamics from the respiratory-driven effects. A precise dynamic RSA assessment could ultimately provide a reliable measure of autonomic tone for assessing and characterizing pain experience.

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