PAIN-RELATED HEART RATE VARIABILITY RESPONSES IN THE CONTEXT OF EXPERIMENTAL PAIN STIMULATION


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Abstract: Objective pain assessment is still an ongoing issue in health sciences, and the analysis of Heart Rate Variability (HRV) is considered a promising tool to provide quantitative information regarding pain sensation. However, commonly used HRV analysis comprises features determined in longer time-periods (at least five minute length recordings), which might be impractical for the development of some online monitoring systems. Thus, we aimed to analyze 10 time-domain features using ultra-short HRV analysis in the context of thermal-induced painful stimulation. Electrocardiographic data from 85 participants from the Biovid Pain Database were analyzed. Ten time-domain features were extracted from pre- and post-stimulation periods using 10-second duration windows. Then, after normal distribution assessment with Lilliefors normality test, we compared intra-group variability by means of paired t-test. Three features (SDNN, RANGE and HR) significantly increased after stimulation, while two features (pNN20 and MEAN) decreased. Further, the higher the stimulation intensity, the larger the number of sensitive features. Although we suppose that the analysis of lower intensities stimulation was impaired by the short inter-stimuli interval duration, SDNN, RANGE, pNN20, MEAN and HR seem to be feasible time-domain features to assess experimental pain by means of ultra-short HRV analysis.

Keywords: Biomedical Signal Processing, Heart Rate Variability, Pain Measurement.

Introduction

Pain is an unpleasant sensation, which is related to the awareness of damage or potential tissue damage, and it is also dependent on subjective, emotional, cultural and social aspects. Nonetheless, it is still of major concern in Health policies due to its impacts on participation on daily-life and social activities, health care costs and work productivity.

The accurate assessment of pain experience is important to provide proper pain management treatments. In this sense, the analysis of some biomedical signals such as the Electrocardiogram (ECG) by means of the Heart Rate Variability (HRV) analysis appears as one out of many possibilities for the objective and quantitative assessment of the pain sensation.

Neural systems responsible for controlling cardiovascular function and pain perception have been described as close regions in the brain with superimposed structures [1], which lead researchers to propose HRV analysis as an index of how the organism provide adaptive regulation especially in case of acute experimental pain [2], [3].

In this sense, intelligent systems developed to monitor patient's pain intensity in a continuous base can benefit from HRV analysis data. However, as can be seen in [3], most studies concerning experimental pain and HRV analysis focus on the frequency-domain analysis to assess the participation of different components of the Autonomic Nervous System (ANS) in response to painful stimulation. The problem is that such methods require analysis windows with lengths greater than 5 minutes to accurately present low and very-low frequency components, hindering the development of online monitoring systems to identify fast breakthrough pain episodes.

Therefore, we aimed to evaluate the influence of experimental thermal induced pain on different time-domain HRV features extracted using 10-second duration analysis windows.

Materials and methods

For the analysis of ECG signals during painful stimulation, we used data from 85 participants, 41 men (mean 41.07±14.73 years-old) and 44 women (40.85±14.85 years-old), of the German-based Biovid Pain Database (Ethics Committee Approval: 196/10-UBB/bal) [4].

Pain induction design – As already described in [4], pain was induced by means of thermal energy applied to the backside of the right forearm while participant was sat in a chair with both arms resting in a table in front of him or her. The experiment was performed using a thermode (PHATWAY, Medoc, Israel). For each participant, pain threshold and pain tolerance were obtained, and described as the temperature in which the
heat starts to hurt and the maximum temperature the participant can stand, respectively. The maximum temperature of 50.5 °C was not exceeded in order not to harm the participant's skin integrity. Thereafter, two equally distributed intermediate values were computed. Finally, each of the four temperatures (namely P1, P2, P3, and P4, with increasing intensities) were randomly applied 20 times and sustained for four seconds, with rest intervals (baseline temperature of 32 °C) randomized between 8 and 12 seconds.

**Data acquisition** – ECG data were acquired together with other biosignals by means of a Nexus-32 amplifier (Humakarigar Pvt. Ltd., India), with a sampling frequency of 512 Hz, and event related data and were simultaneously recorded using Biotrace+ software (Mind Media, Netherlands).

**Data analysis** – HRV responses were analyzed in Matlab R2015a (MathWorks Inc., USA). Windows of 10 second-length were analyzed prior and just after each stimulus. Since inter-stimuli intervals randomly varied between 15 and 20 seconds, overlaps of up to 50% between adjacent stimuli were expected.

ECG data were filtered with 4th-order Butterworth filter with cut-off frequencies set to 20 and 50 Hz to allow for the identification of R waves and extraction of RR intervals. Then, RR intervals were analyzed in the time-domain with 10 different features feasible to ultra-short HRV analysis, as listed in Table 1.

**Table 1: Suitable time-domain Heart Rate Variability features for Ultra-Short Heart Rate Variability Analysis.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>SDNN</td>
<td>Standard deviation of all Normal to Normal Intervals within the analysis window</td>
</tr>
<tr>
<td>RMSSD</td>
<td>Root mean square of successive differences</td>
</tr>
<tr>
<td>SDSD</td>
<td>Standard deviation of successive differences</td>
</tr>
<tr>
<td>NN50</td>
<td>Number of successive Normal to Normal Intervals that differs by more than 50 ms</td>
</tr>
<tr>
<td>pNN50</td>
<td>Percentage of successive Normal to Normal Intervals that differs by more than 50 ms</td>
</tr>
<tr>
<td>NN20</td>
<td>Number of successive Normal to Normal Intervals that differs by more than 20 ms</td>
</tr>
<tr>
<td>pNN20</td>
<td>Percentage of successive Normal to Normal Intervals that differs by more than 20 ms</td>
</tr>
<tr>
<td>MEAN</td>
<td>Average value of all Normal to Normal Intervals within the analysis window</td>
</tr>
<tr>
<td>RANGE</td>
<td>Difference between maximum and minimum interval value within the analysis window</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate (in beats per minute - bpm) computed as the number of identified R waves within an analysis window times 60 seconds</td>
</tr>
</tbody>
</table>

...and divided by the window's length in seconds.

**Statistical analysis** – Lilliefors normality test was performed to assess normal distribution. Then, paired t-test was used to compare pre- and post-stimulation data.

**Results**

Regardless of the stimulus' intensity, five features were significantly affected after thermal stimulation. While SDNN (p<0.001), RANGE (p<0.001) and HR (p<0.001) increased, pNN20 (p=0.007) and MEAN decreased (p<0.001).

However, when we compared each stimulus' intensity solely, different results were found, as shown in figure 1. Mainly, the higher the intensity of the stimulus, the larger the number of HRV features that are significantly affected. P3 and P4 showed similar behaviour when compared to the overall results described above. Conversely, P2 showed only one significant feature (SDNN, which increased after stimulation), and P1 presented four significant features (SDNN, MEAN, RANGE, and HR), which presented opposite behaviours when compared to the overall results.

**Discussion**

We could observe that thermal induced pain causes significant changes in HRV analysis, even if we use ultra-short analysis windows with duration as short as 10 seconds. At least five, out of the 10 time-domain HRV features we analyzed, are sensitive to heat pain induction: SDNN, pNN20, MEAN, RANGE, and HR.

The features SDNN, RANGE and HR showed a significant increase after stimulation, whereas MEAN and pNN20 decreased. In general, differences between pre- and post-stimulation means were bigger at higher stimulation levels.

Nonetheless, we could observe that at the lowest stimulation intensity level results were usually in the opposite direction when compared to the other intensities. Since the stimuli were randomly applied, lower intensities could be following stimulation in higher intensities. Thus, we suspect that inter-stimuli intervals of 15 to 20 seconds may not be sufficient for the cardiovascular system to recover from the previous stimulation and, thus, impair the proper assessment of low-intensity stimulation data in sequence.

Contrary to our findings on ultra-short term HRV analysis, studies using time sequences longer than 5 minutes reported no differences between SDNN values after painful stimulation [5]–[10]. On the other hand, significant decreases in Mean NN-intervals (MEAN) are supported by [7] and [11]. Other studies, however, found no significant differences [5], [6], [9], [10].

In addition, two papers reported conflicting information regarding the RMSSD feature [9], [12], which presented no significant differences after painful stimulation in our study. No other papers were found...
Comparing the other significant time-domain variables (for instance, pNN20, RANGE, and HR).

![Graphs showing time-domain features](image)

Figure 1 – Comparison of pre- (blue) and post-stimulation means (yellow) of time-domain features in the context of experimental pain induction with increasing intensities. Means are compared by stimuli intensities, with increasing intensities (1 to 4). * = p<0.05.

Our main assumption regarding main differences when comparing ultra-short HRV analysis and standard HRV analysis is that time-domain responses might encompass fast responses, which tend to return to baseline values also very fast. In this sense, these responses could be masked by choosing analysis windows with longer durations such as those used in standard HRV analysis.

Once our data is originally from an existing database, we could not control the Inter-Stimuli Intervals. We believe that this was the main drawback of our study. To enable proper analysis of 10-second duration HRV analysis, the same protocol could be performed with bigger ISI, and then, the behaviour of the time-domain HRV features could be monitored to understand how long they take to return to baseline levels after painful stimulation at different intensities.

**Conclusion**

Using 10-second duration analysis windows, time-domain features as SDNN, RANGE and HR increase after painful thermal stimulation, while MEAN and pNN20 decrease. Thus, Ultra-Short HRV analysis with 10-second duration analysis windows is a suitable tool to track pain-induced changes in HRV.

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**References**


