Effective method for quantifying respiratory instability during ambulatory recordings as a subsequent marker of anxiety

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Abstract— **Ambulatory respiratory data was gathered using inductive plethysmography technology with synchronous ECG (LifeShirt®, VivoMetrics, Ventura, CA) during a study to evaluate the effect of an anxiolytic on heart rate variability and respiratory pattern as indicators of anxiety state. Positive control (PCR; post-marketing, broadly prescribed anxiolytic) and placebo (PBO) data was included in the analysis. Tidal volume waveforms were the result of a weighted sum of the abdominal and rib cage IP bands according to the qualitative diagnostic calibration method. A breath detection algorithm was run to identify the beginning and end of inhalation in these waveforms. Several types of respiratory artifact are common with ambulatory, non-controlled recordings and a consistent and reliable means is necessary to identify and manage such artifacts. An automated approach was adopted to define a *reliable* breathing index for each breath that labels that breath as contaminated by artifact or not. The root mean square of successive differences (RMSSD) were computed on the tidal inspiratory volumes and total breath times for each epoch, both for all breaths and for only those breaths that were labeled as reliable. The results indicate that when a priori automated artifact detection is included, there is a significant linear decrease in both the volume and time indices for the PCR, whilst no significant differences were noted in the PBO group. Analyzing the data without prior marking of reliable breaths showed no significant results for either group. This study demonstrates the validity of ambulatory respiratory measurements as a means to assess anxiety and establishes the need to first identify reliable breathing periods prior to the analysis of ambulatory respiratory data.**

I. Introduction

Clinical observations of changes in respiratory pattern and the associated heart rate variability in patients with anxiety disorders have stimulated much research on the subject. Except during deep non-REM sleep and under anesthesia, respiration is rarely entirely regular and moderate instability, even during quiet sitting, is to be expected [1]. This breath to breath variability reflects a 'dynamic homeostasis' and compensatory responses to continuously changing metabolic, emotional or mental disturbances [2]. However, increased levels of respiratory instability are often associated with pathology. Due to the large number of cortical and subcortical projections to the brain stem (the respiratory center), challenging stimuli are frequently emotional or cognitive and even fleeting stressful thoughts may profoundly influence breathing. Furthermore, Wilhelm et al. [3] found that respiratory variables were more sensitive indicators of anxiety than cardiovascular variables.

Ambulatory monitoring offers the opportunity to study clinical conditions such as anxiety or depression in patients' true environment. Laboratory studies generally provide less ecological relevance despite offering greater experimental control. Recently developed devices allow simultaneous ambulatory recording of a wide array of psychophysiological measures, enabling the scientific understanding of emotional processes to extend beyond the laboratory [4].

Special care is needed to accurately interpret non-controlled recordings. Interpretation of ambulatory data can be confounded by artifact associated with normal activities of daily living if measures aren't taken to appropriately address these challenges. Collecting multiple data streams such as accelerometry for movement and ECG provide a data set that can be interpreted with context and checked for internal validity. However, this approach can require substantial reviewer effort and a robust, automated technique for identifying artifact would facilitate the analysis of complex data-sets.

It is a common approach to identify artifacts by searching for outliers in the breath rates or volumes and interpolating only over these outliers. However, often undesired artifacts do not always manifest as outliers and depending on the exact indices derived from the respiratory measurements, interpolation may introduce further bias. We thus propose a more consistent and robust means of identifying and managing artifact in respiratory measurements and subsequently use this approach to form an index to assess anxiety.

II. Methods

A. Experimental

Participants in this study were all about to undergo dental surgery. This is a commonly used model to generate anxiety in subjects to evaluate the short term impact of anxiolytic treatment. From a larger data set 20 subjects were randomly

selected (10 PCR; 10 PBO). Subjects were fitted with the LifeShirt prior to the start of data collection and data was collected through the surgery and for 2 hours post-surgery. The present analysis was based on four 20 minute epochs starting at 20 minutes prior to receiving treatment to 60 mins post-treatment (start of surgery).

B. Equipment

Respiratory signals are commonly obtained by measuring movement in the thoracic and abdominal regions by inductive plethysmography (IP). The two compartment breathing model of the respiratory system shows changes in tidal volume measured at the mouth to be comparable to a weighted sum of changes in ribcage and abdominal contributions. Respiratory IP can measure tidal volume and ventilation precisely when calibrated and studies comparing calibrated respiratory IP with pneumotagraphic airflow measurements have reported correlation accuracies of r=0.96 and greater [5]. The ambulatory acquisition system used in this study is known as the LifeShirt® (VivoMetrics Inc., Ventura, CA) and it has been reliably validated to deliver accurate recordings of respiratory timing and volume outside of the laboratory. This system overcomes significant limitations of previous monitors, including their limited signal resolution and difficulty in holding chest and abdomen bands in place during recordings. It consists of a garment with embedded IP sensors for continuous monitoring of respiration, ECG, mobility, postural changes and other functions. The signals are displayed and stored on a handheld computer, and analyzed offline. The respiratory IP circuit, in brief, passes a low oscillating current through the bands creating a magnetic field that allows measuring of the self-inductance of the bands' coils which is proportional to the cross sectional area surrounded by the bands and this signal is sampled at 50Hz.

C. Analysis

The raw respiratory data is processed as follows: Both the abdominal and rib-cage bands are smoothed using a low-pass, 6th order Butterworth infinite impulse response filter with a cut-off frequency of 1.5Hz. The qualitative diagnostic calibration technique is applied to the respiratory IP output [6]. This is based on equations of the isovolume maneuver to determine the relative gain or contribution from each breathing compartment to overall tidal volume. Following calibration, a proprietary breath detection algorithm is run (Vivometrics, Inc. CA) that marks the beginning of inhalation and exhalation for each breath. The inspiratory volume is obtained by subtraction of the value of the calibrated signal at the beginning of inspiration from that at expiration. The total breath time is given by the interval between successive inhalation markings.

Identification of reliable breathing epochs is derived from the actual values of the peaks and troughs of the filtered respiratory IP waveform and not from their differences (volume or times). The idea here is that artifact free breathing will not exhibit significant variation between either successive peak or trough values over several breaths. Postural changes or sudden motion tends to shift the baseline of the waveform. Continuous motion results in large differences of peaks and troughs between each breath, as do many vocal sounds. Changes such as sighs or apneas are frequently associated with anxious states and it may not be desirable to filter these out. Frequently, these events alter only the peak values but that the values of the troughs are relative stable (this is not always true). The reliable breathing index, V_r, is derived as follows: Let N be the number of breaths, $\widehat{EI}$ is the median value of the peaks (end inspiration points) of the N breaths and $\widehat{BI}$ the median value of the troughs (begin inspiration points) of the N breaths. Let $\widehat{VI}$ be the median of the inspiratory tidal volumes for the N breaths. Then let

$$V_{peak} = \prod_{j=1}^{N} \left[\frac{\left\| EI_j - \widehat{EI} \right\|}{\widehat{VI}} < V_{thresh} \right]$$

and

$$V_{trough} = \prod_{j=1}^{N} \left[\frac{\left\| BI_j - \widehat{BI} \right\|}{\widehat{VI}} < V_{thresh} \right]$$

where BI_j and EI_j are the values of the tidal volume waveform at the j^{th} begin or end inhalation marking. V_{thresh} is a chosen threshold and $\prod$ is the product (AND) of the bracketed boolean expression. i.e. V_{peak} or V_{trough} will be false if any of the points within the window are greater than the threshold. If either V_{peak} or V_{trough} are true ($V_r = V_{peak} || V_{trough}$), then the breath at the center of the window is considered valid. We use $N = 10$ and $V_{thresh} = 0.2$ and do the calculations for each breath.

Fig 1. shows an example of artifact breath that we wish to exclude from subsequent analyses. In this case the volumes between successive breaths are clearly different and the nature of the artifact is apparent.

Fig 2. shows another example where there is a subtle shift in posture that is not detected by the accelerometer and where the volumes are relative consistent between breaths but which is also clearly artifact and must be excluded.

Fig 3. is an example of breaths that are included. Even though the peaks (volumes differ), the baseline (troughs) remains stable.

Several candidates have been proposed for the quantification of respiratory stability. The simplest of these is the standard deviation of volumes or total breath time over the analyzed interval. Other indices examine the breath to breath variability using the root mean square of successive differences (RMSSD) index. This is simply

$$RMSSD = \sqrt{\frac{1}{N-1} \sum_{j=1}^{N} \left(V\left(BI_{j+1}\right) - V\left(BI_j\right) \right)^2}$$

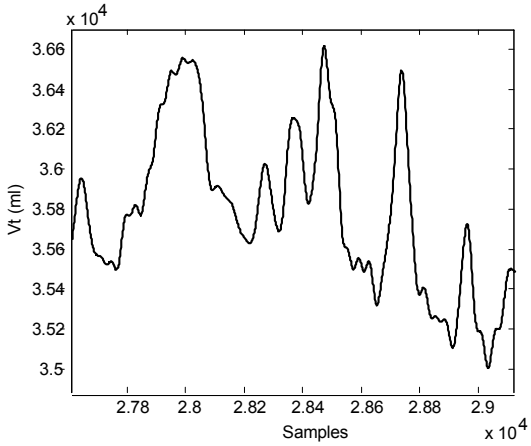

Fig. 1. Breath artifact where volumes between successive breaths differ considerably. The peaks and troughs also vary considerably between breaths.

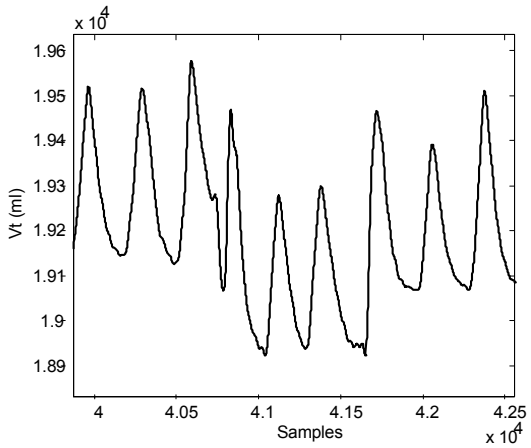

Fig. 2. Breath artifact where the volumes between succesive breaths are of similar magnitude. However the peaks and troughs clearly show a shift due to the artifact.

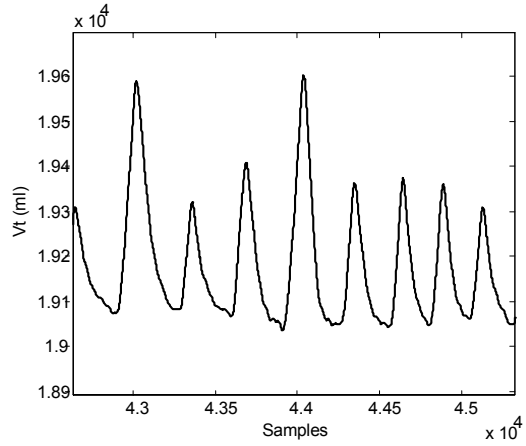

Fig. 3. Example of a breath trace that contains no artifact (troughs of each breath do not differ by much) but there is still instability between adjacent volumes.

A disadvantage of this measure is that it does not distinguish between slow changes over the entire time window and faster changes between consecutive volumes. However, it remains widely applied in the literature. The advantage of both of these indices is that the average can be formed for the analysis time only when $V_{sr} = 1$.i.e.

$$\overline{RMSSD} = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\left[\left(V\left(BI_{j+1}\right) - V\left(BI_j\right)\right) \times V_{r|_j}\right]^2}$$

Several other frequency based candidates (spectral indices or indices derived from complex demodulation) do not easily allow for the discontinuities that result from the reliable breath markings. We therefore chose the RMSSD index to determine if there were any improvements when thresholded using reliable breath markings or not.

D. Statistics

Due to individual differences, the values at each time point for each subject were normalized by the values at the first time point, so that the data set only reflected normalized changes relative to this time point. Subsequently a separate repeated measures ANOVA was run across all the time points for the placebo group and non-placebo group for each index (adjusted and non-adjusted); $RMSSD_{vol}$ and $RMSSD_{time}$.This was to determine if any statistically significant trend existed over time.

III. Results

Fig 4-7 displays graphs for the means and upper and lower quartile ranges for the adjusted and non-adjusted volume RMSSD, for both the anxiolytic and placebo groups. Similar trends were observed with the total time RMSSD but these results are not displayed here. Only the adjusted volume RMSSD for the anxiolytic group showed any significant trend over time.

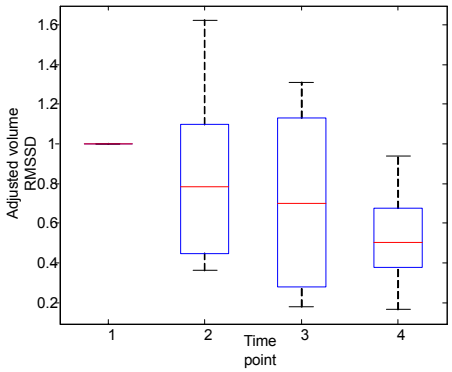

Fig. 4. Box plot for the anxiolytic group, showing mean, lower and upper quartile values of the adjusted volume RMSSD index. The whiskers show the extent of the remaining data. A signficiant linear trend was observed for this set with $p < 0.01$

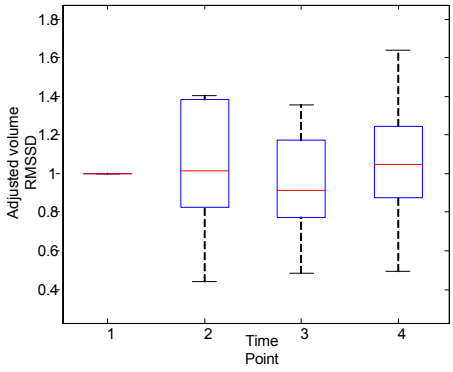

Fig. 5. Box plot for the placebo group, showing mean, lower and upper quartile values of the adjusted volume RMSSD index. The whiskers show the extent of the remaining data. No signficiant linear trend was observed for this group.

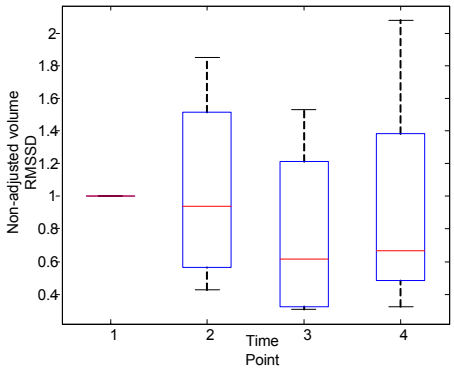

Fig. 6. Box plot for the anxiolytic group, showing mean, lower and upper quartile values of the non-adjusted volume RMSSD index. The whiskers show the extent of the remaining data. No signficiant linear trend was observed for this group.

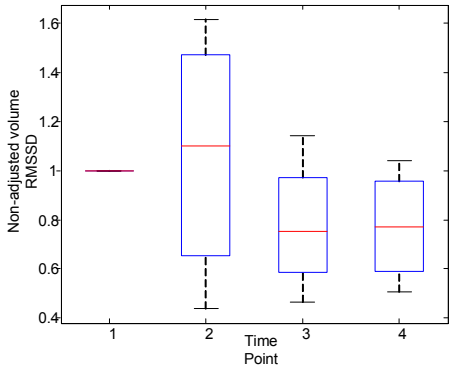

Fig. 7. Box plot for the placebo group, showing mean, lower and upper quartile values of the non-adjusted volume RMSSD index. The whiskers show the extent of the remaining data. No signficiant linear trend was observed for this group.

IV. Discussion

Results computed without pre-selection of reliable breathing epochs, demonstrated no clear trend over the time course of the positive control or the placebo group. However, when recomputed following pre-selection according to the reliable breathing index, a significant linear trend was noted for the positive control group. A decrease in the RMSSD implies less variability or more stability over time and this is the expected result due to the relaxation effect of the drug.

Further work is focusing on applying these results to other measures of regularity in time series such as entropy. It would be advantageous to have an objective means of selecting the optimal number of breaths per epoch and the optimal threshold and this could further improve the results. It is further possible that an adaptive scheme may be a more optimal solution.

V. Conclusion

This study demonstrates that ambulatory recordings of respiration may be of value to assess anxiety. Confident data interpretation requires a consistent means of selecting acceptable portions of the entire data set that are free from context artifact. A suitable candidate for automated pre-screening of respiratory data is the 'reliable breathing index'. When applied to the resultant data subset, standard indices that reflect the stability of a data stream, were able to significantly separate the effects of an anxiolytic drug versus that of a placebo. Additionally, the automated and robust identification of respiratory artifact will enable a more reliable evaluation of respiratory associated physiologic measures, such as heart rate-variability, collected during patients' normal activities of daily living.

VI. References

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