Pain and Stress Measurement During General Anesthesia Using the Respiratory Sinus Arrhythmia

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Abstract. The measurement of stress and pain during general anesthesia is a not sufficiently solved problem. Currently the anesthetist uses his experience to ensure an appropriate pain medication. Underdosing can lead to unwanted high activation of the sympathetic autonomous nervous system and endocrine systems. The consequences might be cardiovascular instabilities, damage of the organism or a neurogenic shock. Overdosing can lead to critically slow heart rates and low blood pressures. Since the correct dose is important, a reliable pain measurement would benefit a good outcome of the patient.

The respiratory sinus arrhythmia, a slight oscillation in the heart beat interval caused by breathing, is directly proportional to the calming parasympathetic part of the autonomous nervous system. Since this system controls the relation between physical stress and relaxation it can give valuable information about the patient’s stress or pain level.

With the Analgesia Nociception Index an algorithm was proposed to measure pain via the respiratory sinus arrhythmia. This algorithm has been modified to reduce the signal to noise ratio and to increase the validity during general anesthesia with the possibilities of a modern fully networked operating room. The results are summarized in this paper.

Keywords
- pain, respiratory sinus arrhythmia, heart rate variability, Analgesia Nociception Index, Spectral Analgesia Index

1. Introduction

Different approaches towards the measurement of pain have been proposed in the literature in the last few years. The span reaches from statistical model based algorithms over physiology based approaches towards machine learning algorithms.

With the Noxious Stimulation Response Index (NRSI) from Lugnibuehl et al. [1] a pain index was introduced that doesn’t measure the pain level in the exact case. It rather uses a pharmacokinetic model based prediction of the effect side concentration of opioid analgesics and the hypnotic Propofol to make a statistical statement about probability of a patient’s reaction onto a painful event.

A vital parameter based statistical pain measurement approach was made by Wennervirta et al. [2]. They collected the photoplethysmographic (PPG) waveforms of 26 patients during general anaesthesia. An increase in blood pressure, movement or coughing was considered to be a nociceptive event and was treated with opioid analgesics. Through the computation from correlations between a painful event and the characteristics in the PPG signal, the heartbeat interval (HBI) and the amplitude of the pulswave (PPGA) were identified to be the most pain sensitive. With the Surgical Stress Index (SSI) an pain index was introduced that describes the patient’s pain on a scale from zero to hundred based on these observations:

\[
SSI = 100 - (0.7 \cdot PPGA + 0.3 \cdot HBI)
\]

Machine learning approaches have for example been used to detect patterns in the facial expression of neonates that reflect their pain level. Ghelami et al. [3] described how relevance vector machine (RVM) learning techniques can be used to compute the affiliation of facial expressions to classes of “pure” and thus easy identifiable facial expression. The probability of the affiliation to a specific class directly translates into the intensity of an expression.

While all of these approaches try to describe pain, they lack in their physiological explainable background. A parameter that describes a persons pain level through well investigated physiological phenomenons is the Analgesia Nociception Index (ANI) that was suggested by Logier et al. [4]. This pain index uses a small resonance in the signals of the cardio vascular system that originates from a steady breathing. The cardiovascular system is controlled by the autonomous nervous system, which consists of two antagonistic parts: The sympathetic and the parasympathetic nervous system. The slower sympathetic branch increases the heart rate, blood pressure and respiration in stressful events, whereas the fast parasympathetic part reduces all those functions and augments regeneration and digest. The overall delay of the cardiovascular system and the parasympathetic
nerve branches is small enough for the central nervous system to react onto the changing thoracic blood pressure due to respiration. This leads to small oscillations in all measurable signals of the cardio vascular system, which are directly depending on the actual parasympathetic tone. For high stress levels the sympathetic tone is high and the parasympathetic tone is neglectable. Because the delay of the sympathetic nerve branches is much longer no oscillations are measurable. The oscillations can e.g. be measured in the heart rate variability (HRV), which represents the spacing between two consecutive heartbeats. Here they are called respiratory sinus arrhythmia (RSA) [5].

Through this mechanism the activation of the parasympathetic tone and thus the patient’s stress level can be observed. During general anesthesia, where the patient’s consciousness is deactivated trough hypnotics, mainly the exposure to pain leads to physical stress reactions. So the height of the RSA is directly linked to the patient’s pain level.

To quantify pain in an easily interpretable scale Logier et al. used the normalized heart rate variability to observe the RSA phenomenon. The normalization was done by dividing the signal trough the signals 2-norm in a defined window. They filtered the signal with a band pass filter between 0.15 Hz and 0.4 Hz so that in the noise free case only the heart rate variations due to respiratory modulation remain as a sine signal with respiratory frequency and varying amplitude. To recover the amplitude, which directly corresponds to the pain level, they calculated the upper and lower envelope of the signal and computed the area $AUC$ between them in windows of 16 s. The minimal of these areas in a 64 s sliding window $AUC_{min}$ was used to compute the pain index after the following formula:

$$ANI = 100 \cdot \frac{\alpha \cdot AUC_{min} + \beta}{12.8}$$

(2)

Where the parameters were chosen to $\alpha = 5.1$ and $\beta = 1.2$

This approach shows some space for improvements:

1. The actual respiratory frequency is not taken into account. It is determined by the respirator and thus available for the computation trough the possibilities of a modern, fully connected operation room. We will use the actual respiratory frequency to reduce noise in the index signal.

2. The time delay of the index is quite high as a result of a relatively long window length of 64 s. With our new index we will reduce the window length and obtain a faster responding index.

3. The static scaling factors of the index presented in [4] don’t hold a interpretable meaning and lead to bad comparability of different patients. We will use a training phase to calculate the scaling factors uniquely for every patient, so that the index fulfills specific norm requirements.

2. Materials and Methods

In this section the algorithmic foundation towards the improved evaluation of the RSA out of the HRV signal is presented. Firstly, we will show how data from different medical devices can be combined for pain measurement using modern network based interoperability concepts in the operating room IT-infrastructure. Secondly, we will explain how the HRV and the current respiratory rate can be computed out of the ECG-, PPG-signal, respective the capnometry-signal using the ADAPIT-algorithm, proposed by Yu et al. [6].

Thirdly, we will explain the functionality of our new pain index and discuss the possibilities for normalization lastly.

The proposed system is based on a manufacturer independent networked operating room, which is currently developed in the OR.NET project [7]. In such a modern operating room vital signs can be acquired from different devices and can be merged to obtain e.g. a measure for pain, even if the signals don’t origin from the same medical device. This can be achieved by a secure, robust network architecture that connects standalone medical devices using standard state of the art internet protocols. Furthermore, the so called Open Surgical Communication Protocol (OSCP) is able to communicate with hospital IT systems, which enables the system to acquire further information about the patient, like age, size, sex and weight. With these possibilities our pain index system doesn’t need any physical connection to the patient.

Because We base our approach towards pain measurement onto the interpretation of the respiratory disturbance of the cardiovascular system, we can use the ECG, PPG or invasive blood pressure signals of the networked operating room. Since ECG and PPG are mostly assessed in standard monitoring setups, we compute the HRV based on these signals. Trough the networked operating room we could use the artery blood pressure or in postoperative care contactless PPG imaging (PPGi®) for instance as well [8]. The fusion of different signals from different sources leads to a more robust pain measurement.

For the HRV assessment beat-to-beat intervals are required which can be determined from ECG as well as from PPG signals [9]. Therefore regarding the ECG signal the R-peak is ideally suited. In the PPG signal the maximum of the pulse wave can be used. The capnogram of an artificially ventilated patient is periodic and has a characteristic plateau at every cycle. The occurrences of these characteristics can be detected over time with the ADAPIT-algorithm proposed by Yu et al. [6].

This algorithm filters the vital parameter signal with a median filter of specific length different signals (ECG: 55 ms; PPG: 550 ms, CO2: 1 s) and subtracts the result from the original signal. The result is a residual signal that only has high frequent components and no baseline variations. Every peak that now is greater than a threshold is considered to be a characteristic value as first approximation. In a second filter step a new threshold is chosen to be the half
of the median of all detected signal maximums. All now as valid detected signal peaks are aligned with a string of markers with period P in the way that the period time P may not change more than a half P between two consecutive cycles. All aligned peaks are marked as detected characteristic

The respiratory sinus arrhythmia is a phenomenon that can best be seen in the frequency representation of the HRV. Figure 1 shows the frequency components from the HRV-signal of a patient during general anesthesia. The spectrogram representation was achieved by calculating the short-time fast Fourier transform (FFT) of the HRV with a Hamming window of length L = 30 s and a window overlap of 28 s. Explicitly notable is the maximum at the breathing frequency (around 0.2 Hz), which is caused by the RSA. A slight less prominent maximum at the double frequency can be interpreted as the second harmonic of the RSA due to the nonlinear excitation through the respirator. The evaluation of the RSA height is straightforward: We evaluate the amplitude $A_{RSA}$ of the frequency components that are the nearest to the given respiratory frequency $f_{RSA}$:

$$A_{RSA}(t) = HRV(f_{RSA}(t), t)$$

$$f_{RSA}(t) = \min |f(t) - f_{resp}(t)|$$

Depending on the strength of the RSA compared to the noise floor the obtained $A_{RSA}$ is more or less reliable. Moreover the noise energy might change over time. The varying noise floor at the breathing frequency is directly superposed with the useful RSA signal and thus leads to variations in $A_{RSA}$, which doesn’t originate from a changed parasympathetic tone. To reduce this disturbance we calculate the expected noise value $\mu$ inside the band of possible respiratory frequencies, subtract it from $A_{RSA}$ and set all values smaller than zero to zero:

$$A_{eff}(t) = \begin{cases} A_{RSA}(t) - \mu(t), & \text{if } A_{RSA}(t) - \mu(t) > 0 \\ 0, & \text{else} \end{cases}$$

$$\mu(t) = \frac{1}{f_{RSA} - 0.125\,\text{Hz}} \int_{0.15\,\text{Hz}}^{0.4\,\text{Hz}} HRV(f_{RSA}(t), t) df + \frac{1}{f_{RSA} - 0.025\,\text{Hz}} \int_{0.375\,\text{Hz}}^{0.5\,\text{Hz}} HRV(f_{RSA}(t), t) df$$

The least possible value of the effective RSA-amplitude $A_{eff}$ is now bounded to zero, which straightforwardly means that no RSA has been detected. To obtain an inter-patient comparable index value out of $A_{eff}$, we need to scale it properly. Since we don’t know the maximum RSA magnitude for a specific patient, which occurs theoretically in a state of total relaxation, the scaling of $A_{eff}$ into a desired value range of $[0, 100]$ poses some problems. In the following we provide a possible approach for this problem.

In Figure 3 we can see that the time series of $A_{eff}$ can be split into two different components: one slowly changing baseline and one faster changing component with almost constant magnitude. The baseline was calculated by applying a median filter of length 300 s onto the signal from Figure 2. We obtained the faster changing signal components by simply subtracting the baseline from the original signal.

We observed that the baseline is highly dependent on the administration of analgesics and on the amount of painful events. From this we conclude, that this component probably shows the patient’s base stress level. The interpretation of the high frequent residual is more complex. Through the evaluation of the study we found that the properties of the residual signal of different patients were quite similar reference to mean frequency and variations in magnitude, but had different expected magnitudes. With normalizing the index onto the expected magnitude of the residual signal we assume to have found a common basis for a good comparability between different patients. Basing on these observations we introduce the Spectral Analgesia Index (SAI):

$$SAI = \alpha \cdot A_{eff} \quad \text{with} \quad \alpha = 6 \cdot E(|A_{eff,res}|)^{-1}$$

For an approximation of the expected value of $A_{eff,res}$ we use a training phase of 5 min. The factor six in 5 has been empirically chosen. With our study data this constant allowed the best mapping onto the range of the ANI.
3. Results

With some specific examples we compare the performance of the new found SAI with the original ANI. Through the evaluation of study data obtained from patients in an post anesthesia care unit we conclude that the pain measurement via the RSA is not valid in awake, non ventilated patients.

The two shown operating procedures in Figure 4 and Figure 5 show clearly the difference between the original ANI and the modified version. While the baseline of the original ANI rather shows the trend of the patient’s pain constitution, the SAI reacts strongly on certain operation events. Especially the reactions onto morphine analgesics are remarkable. After every analgesics dose we observed an increase in the SAI index value. Painful events mostly cause a decrease in the index value. We can see that the modified index reacts faster onto the different events. If the ANI shows a amplitude change due to a painful event or due to analgesic applications, it happens a few minutes later. The higher frequent residual variations obtained from both indexes are quite similar.

Evaluating the spectrograms of all study participants leads to the insight that an interpretable RSA is often not given. In many cases the RSA is just below the SNR threshold; in some operations the RSA fully disappears in the signal noise.

4. Discussion

In this section we will discuss our results and give a short outlook. Firstly, we will discuss the origin of the differences between ANI and SAI and their advantages and disadvantages in different scenarios. Secondly, we will debate the possibilities for the huge differences between the RSA manifestation in different subjects and will highlight further study fields and possibilities for improvement.

The reason for the time delay from the ANI compared to the SAI can be explained by the averaging effect of the ANI algorithm, where from a 64 s window only the smallest 16 s sub-window is taken into account. The SAI algorithm only uses a 30 s sliding hamming window for its frequency analysis, which yields a more instantaneous behavior.

The ANI does not often show low or high index scale values, in contrast to the SAI, which is logically pinned to the zero value. So in patients with non detectable RSA the ANI delivers a nonzero index value, which is obviously not valid. The SAI on the other side yields an index value of zero, which is more realistic. Nevertheless it has to be deter-
mined whether or not the missing RSA comes from extreme stress or other reasons. The determination of the general validity of the RSA is an important field of study.

In the HRV of awake patients the RSA is not as easily detectable as in artificially ventilated patients. The reason is that the normal respiratory drive yields no real steady state respiratory frequency, especially in pain- and stressful situations. Because we further don’t know the current respiratory rate the classical ANI is advantageous in this situation, since it averages over all possible respiratory frequencies. If the index values of the ANI are valid at all for awake patients is questionable in the end, since we don’t know if only the RSA has a significant influence in the evaluated frequency interval. An approach towards the HRV analysis in awake patients could be made with amplitude-frequency demodulation algorithms, which wouldn’t only lead to the amplitude information $A_{RSA}(t)$ but to the current respiratory rate as instantaneous frequency as well. That the RSA is measurable in awake patients as well is implied by Figure 6 with a slight shadow at 0.2 Hz.

Another important thing worth a deeper investigation is the different manifestations of the RSA at different patients. The way an anesthetist performs the anesthesia is probably influential. We found that the most interventions with a good detectable RSA were in short chronologically distance, which could imply that they were performed by the same team or setting. The age, the sex and the physical condition of the subject could be influential as well. We found that the strongest RSA signals in the study originated from young patients, mostly males, but make statistically significant statements these phenomena have to be investigated on larger scale.

5. Summary

From the discussion we conclude that the general occurrence of the RSA has to be studied more in detail to have a certain base for any algorithmic pain measurement. If a RSA is detected with an appropriate signal to noise ratio we believe that it’s observation yields a easy and valid way towards an automated stress and pain analysis. For the pain and stress analysis during general anesthesia we think with the SAI we have found a good index for the measurement of pain. For awake patients the existing algorithms don’t serve the purpose. New approaches e.g. via a amplitude-frequency demodulation [10] could be more promising.
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References


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