ASSESSMENT OF SURGICAL STRESS USING HEART RATE AND PLETHYSMOGRAPHIC PULSE WAVE AMPLITUDE VARIABILITY

Matti Huiku[*], Mark van Gils[**], Ilkka Korhonen[**], Minna Kymäläinen[*], Petri Kärkäs[*], Panu Takala[*], Kimmo Uutela[*] and Arvi Yli-Hankala[***]

[*] GE Healthcare Finland, Helsinki, Finland
[**] VTT Information Technology, Tampere, Finland
[***] Department of Anaesthesia, Tampere University Hospital, Tampere, Finland

Mark.vanGils@vtt.fi

Abstract: Stress free anaesthesia can be provided with timely and adequate administration of hypnotic and analgesic drugs. Our goal was to develop a measure for the surgical stress in a patient. 60 patients were anesthetized with propofol and remifentanil target controlled infusion with rocuronium paralysis. We recorded physiological parameter data and calculated off-line heart rate (RRI) and plethysmographic amplitude (PPGA) variability parameters. The beat-to-beat RRI and PPGA time series were investigated in different time scales. The original time series were normalized using histogram transformation, which reduces the inter-patient variability by adjusting the measured parameter values to the same fixed range and distribution in all patients. Sympatho-vagal ratio and estimates for the irregularity of the respiratory modulation were calculated synchronized to artificial ventilation. These parameters were regressed with the estimated severity of surgical stimulation, remifentanil effect site concentration, and their combination. The parameters were ranked according to the mean regression coefficient divided by the standard deviation over the patient dataset. The best performing parameters were the normalized RRI and PPGA, which are the promising candidates for a surgical stress index.

Introduction

Balanced anaesthesia demands control of a patient's hypnosis and analgesia. During general anaesthesia the level of hypnosis can be assessed based on the electroencephalography (EEG) signal [1, 2]. Currently no objective on-line measurement exists for the adequacy of analgesia. Demands for monitoring the level of analgesia are increasing due to better understanding of the benefits of balanced stress free anaesthesia. In balanced anaesthesia the analgesic and hypnotic drugs are administered according to the patient's individual needs in varying surgical conditions.

Inadequate analgesia may result in fast cardio-vascular stress responses in heart rate, blood pressure, and peripheral blood circulation and more sustained change in the cardio-vascular and metabolic state by increased endocrine secretion of stress related hormones and substances [3-5]. These changes during surgery and in post-operative period may delay the patient recovery and even increase morbidity [6, 7].

Heart rate variability (HRV) is a measure of the activity of the autonomic nervous system (ANS) and thereby may be applicable to assess the level of surgical stress during anaesthesia. Components of HRV are controlled by the parasympathetic and sympathetic nervous systems. The sympathetic nervous system prepares body for high stress situations, while the parasympathetic system restores the normal body functions by lowering heart rate. These two branches of ANS control the body functions in characteristically different time scales. The respiratory component of HRV, also called Respiratory Sinus Arrhythmia (RSA), is mainly due to parasympathetic vagal control, while the slower components have mainly sympathetic origin. With increasing stress the sympathetic activity increases, and the sympatho-vagal balance tends to shift towards sympathetic dominance marked by large sympathetically controlled slower components in HRV.

HRV analysis is an established tool in studies of the autonomic nervous system [8, 9]. However, during general anaesthesia, these studies are much more scarce. Yli-Hankala et al have observed that in positive pressure ventilation RSA has an opposite phase to normal spontaneous breathing [10]. Under forced ventilation the separation in frequency domain is imperfect [11], and hence, nonlinear methods would be needed. Kato et al have studied spectral analysis of HRV and sympatho-vagal balance during isoflurane anaesthesia [12]. Seitsonen et al have found that no single component of HRV can describe the nociceptive-antinociceptive balance in a patient, but instead a multi-parameter solution is needed [13]. They further suggest a combination parameter using HR, plethysmographic notch amplitude, and Response Entropy (RE) [1] for predicting the responsiveness of a patient at skin incision.

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Optimally, the sympathetically and parasympathetically controlled components of HRV should be separated in the analysis of stress responses. The methods provided by HRV analysis may apply for studies of the plethysmographic and blood pressure variabilities, as well. Suppression of the plethysmographic pulse wave amplitude (PPGA) is a measure for increased sympathetic activity and the PPGA variability analysis could thus complement the HRV analysis [14, 15].

Our objective was to study whether different HRV and PPGA variability parameters and methods could provide a measure for the adequacy of analgesia during surgery of an anaesthetised patient.

Material and Methods

Subjects and protocol. The study was approved by the local ethical committee of Tampere University Hospital. Written informed consent was obtained from each patient. We anaesthetised 60 female patients with propofol-remifentanil target controlled infusions and rocuronium-induced paralysis. The patients were intubated and thereafter over-pressure ventilated until extubation. The level of hypnosis was targeted to State Entropy SE=50 [16] at incision and maintained by a substantially constant propofol infusion. Remifentanil (Rem) concentration was adjusted to 1, 3, or 5 ng/ml for skin incision and the Rem level was subsequently varied between these concentrations with about 15 minutes intervals.

Data acquisition. Our aim was to find parameters that correlate with clinical assessment of the surgical stress of a patient and that are easily available in standard anaesthesia monitors. Physiological parameters with electrocardiography (ECG), photoplethysmography (PPG) and airway pressure and CO2 waveforms were recorded continuously during entire anaesthesia (GE Healthcare S/5 Collect with S/5 iCentral). A dedicated research nurse annotated all anaesthesia events including intubation, incision and certain painful surgical phases in a text file. The changes in the drug infusions, the cumulative infused drug amounts and other patient medications were timely marked in the same file. All recorded data without patient identification were stored for off-line analysis (Matlab version 6.5 Release 13).

Data pre-processing and time series calculation. R-wave peaks were automatically detected from the ECG waveform and the beat-to-beat R-to-R intervals (RRI) were calculated and manually corrected when necessary. Plethysmographic waveform amplitudes (PPGA) were extracted pulse-to-pulse. False pulse detections (artifacts, etc) were automatically marked and excluded from further analysis. Time marks for the beginning of each inspiratory ventilation cycle were detected using the airway pressure or capnographic CO2 waveforms. A synchronization waveform was constructed using the inspiratory time points. The PPGA and RRI data were synchronized to the ventilation by interpolating these time series to include 16 regular interval time points in each ventilation cycle starting at the inspiratory start (first interpolated) point.

Sympathetic and parasympathetic features were extracted off-line from the RRI and PPGA time series. We employed different methods to quantify the response features in different time scales.

Data normalisation. In order to study the very slow (dominantly sympathetic) components of variability we first searched for methods to eliminate the inter-patient differences in the absolute values of the original cardio-vascular parameters. We normalized the original beat-to-beat RRI and pulse-to-pulse PPGA time series using a histogram transformation [17] to obtain the normalized parameters, RRI_{norm} and $PPGA_{norm}$. Our normalization scheme used the RRI and PPGA data history of the individual patient and the typical parameter value distribution in a large patient group to adjust the individual mean values and value distribution to the same range for every patient (Fig. 1). The *a priori* distribution was taken from all the patients in our study by pooling all data together. This distribution was superimposed with the parameter value distribution collected from the individual patient to form a combined distribution function. At each time moment, the combined distribution consisted of the *a priori* distribution weighted by 0.3, and the previous individual distribution, weighted by 0.7. The individual distribution only contained parameter data (RRI or PPGA) after anesthesia induction and the loss of consciousness. A cumulative distribution function was calculated based on the combined distribution. The normalization was performed by mapping the original input parameter value to the percentage output in the cumulative distribution function.

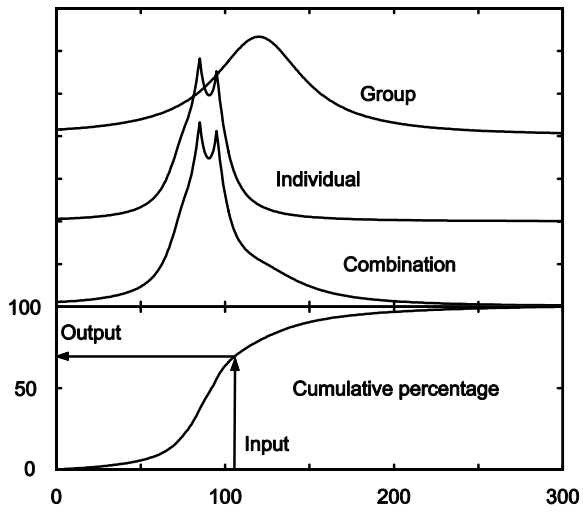

Figure 1: Histogram normalization.

In the histogram normalization the group distribution essentially defines the allowable range for the original parameter values. The combination distribution adjusts the output parameter distribution between 0 and 100 so that the median individual input value roughly corresponds to the output value 50, and

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the lower and upper quarter limit inputs to 25 and 75, respectively.

The normalization with the weights of 0.3 and 0.7 for the group and individual history data was tailored to reflect the long-lasting changes of the cardio-vascular state in a patient in one numeric scale without inter-patient variability.

In addition to this long-term normalisation, to emphasize the changes in the cardio-vascular state in a shorter time scale, we performed the normalization using a 5-minute parameter history data. The 5-min history data still extend over relative long time scale in comparison to a typical respiration cycle. This normalization scheme used weights 0.2 for the group distribution and 0.8 for the 5-minute distribution, and rejected all other data history. In comparison to using the full data history, this normalization brings more responsiveness to the output parameter, and allows a fast adaptation to different intra-surgical phases, thereby considerably decreasing both inter- and intra-patient variability.

Separation of respiratory and nonrespiratory variability and parameter calculation. The ratio of the low (LF, 0.05-0.15 Hz) to high frequency (HF, >0.15 Hz) signal power, the sympatho-vagal ratio RRI LF/HF, is affected by the forced over-pressure ventilation of a patient. We tried to reduce this artificially induced interference by calculating the LF signal variability after carefully removing the respiration waveform from the RRI (and PPGA) time series. We employed the respiration-synchronized time series to extract the LF component from the original RRI and PPGA time series. The time series were first detrended in a 60 sec time window. A differential signal between the time series points in the same phase of the respiration cycle was calculated point-by-point. The differential signal was then low pass filtered, after which a cumulative sum of the averaged differences was calculated. This time series was delayed by one half of the respiration cycle and scaled by 1/16 to get the LF component. This component was subtracted from the synchronized composite signal to get the residual HF signal.

The sympathetic (LF) and vagal (HF) power ratio was calculated point-by-point as standard deviation (SD) ratio of the LF and HF signal components over two ventilation cycles.

We continued the analysis of the PPGA and RRI time series by splitting the residual HF component to it's regular respiration modulation and irregular beat-to-beat noise parts. We used the Walsh-Hadamard (W-H) transform [17] to characterize the regularity within one respiration cycle. The interpolated HF time series was transformed using a 16*16 W-H matrix. The analysis of the regularity was performed using the weight coefficients (a1, a2, ..a16) of the 16 W-H base arrays. The average of the W-H coefficients (<a2>, <a3>, …<a16>) over 8 respiration cycles was used to estimate the regular part of the respiration modulation. The irregularity, $PPGA_{irreg}$ and RRI_{irreg} , was estimated as the ratio of the current residual power of the W-H coefficients and the power of the average coefficients, i.e.

$$A^k_{irreg} = \sum_{j=2..16} (a^k_j - < a^k_j >)^2 \; / \; \sum_{j=2..16} < a^k_j >^2 ,$$

in which $A_{irreg} = PPGA_{irreg}$ or RRI_{irreg} and a_j the jth W-H coefficient in the respiration epoch k.

We also estimated the irregularity of the respiration modulation in RRI as RSA_{irreg} (irregularity of the respiration sinus arrhythmia modulation). RSA_{irreg} was calculated as the SD of the HF signal difference between the actual signal and the signal delayed by one respiration cycle.

In order to compare our analysis of the HR and PPGA variability to standard methods in HRV we performed Poincare analysis as reported by Seitsonen et al.

Our parameters are summarized in Table 1.

Table 1: Variability parameters. In Histogram transformation (Full) and (5 min) refer to the normalization schemes, in which either full data history or 5 min data history, respectively, were employed. The subscript norm is for the parameters calculated using either of the normalization schemes. The parameters without the subscript norm have been calculated using the original beat-to-beat or respiration-synchronized time series.

Parameter	Time scale of variability	Variability mechanism
$PPGA_{norm}$, RRI_{norm} (Full)	Whole anaesthesia	Neural and endocrine sympathetic activation
$PPGA_{norm}$, RRI_{norm} (5 min)	Minutes	Neural and endocrine sympathetic activation
RRI LF/HF, RRI_{norm}LF, RRI SD2, PPGA SD2	> One respiration cycle	Mainly neural sympathetic activation
$RSA_{norm\ irreg}$, RRI SD1, $RRI_{norm\ irreg}$, $PPGA_{norm\ irreg}$, PPGA SD1	<= One respiration cycle	Neural sympathetic activation and/or parasympathetic deactivation

Statistical analysis. We correlated the parameters by linear regression with the remifentanil effect site concentration (targets adjusted to 1, 3 or 5 ng/ml) and the estimated intensity of stimulation. The remifentanil effect site concentration was calculated off-line based on the on-site clinical annotations of the target controlled infusion targets and total drug amounts. We

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used the pharmacokinetic model of Minto et al [18] to obtain continuous time series for the remifentanil levels (Rem). The severity of stimulation (Stim) was graded to 0, 1, 2, or 3, corresponding to no, moderate, severe and intense noxious stimulation, respectively (all levels assessed based on clinical annotations of the surgical events). The surgical stress (SS) experienced by the patient was estimated as the difference of the stimulus and remifentanil scores (SS=Stim –Rem/2).

The candidate parameters were ranked by the t-values of their regression coefficient to Rem, Stim and SS over the data during surgery. The regression slope coefficient was first calculated for each individual anaesthesia case, i.e. one patient. The mean and standard deviation of the regression slope over all anaesthesia cases was then calculated. The t-value was defined as the mean divided by the standard deviation in the whole dataset, i.e. all patients. The ranking was set based on the t-value of the regression to SS. The two normalization schemes were ranked separately.

Results

The largest t-value of the PPGA parameters was obtained for $PPGA_{norm}$ in both normalization schemes (The full normalization in Fig. 2 and the 5-min normalization in Fig. 3). Among the RRI parameters the sympatho-vagal ratio RRI LF/HF performed the best in the full data history normalization. Also the RRI LF (RRI_{norm} LF) calculated using either of the normalization schemes showed a high t-value.

With 5 min data history RRI_{norm} was the best of all parameters. The t-value was clearly better than with the full data history. Especially the correlation of RRI with the stimulus intensity improved as compared to using all history data in normalisation. Similar effect could not be observed in PPGA. The irregularity parameters $RSA_{norm\ irreg}$ and $PPGA_{norm\ irreg}$ correlated well with stimulus, but rather poorly with remifentanil. In RRI SD1 and PPGA SD2 the correlation to stimulus and remifentanil had the same sign, which made the overall t-value poor to SS. The t-values improve when the variability is calculated over long time scales.

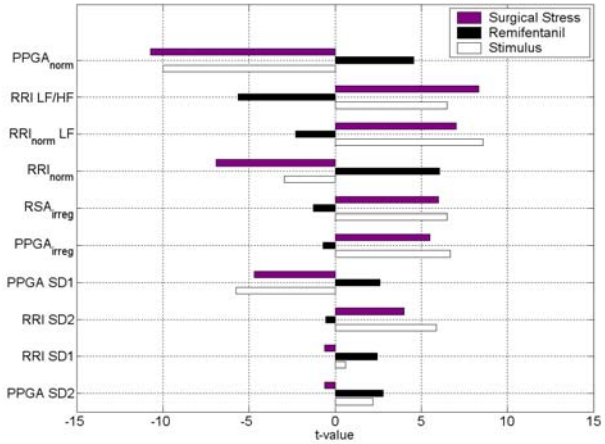

Figure 2: Some of the best parameter candidates calculated using the full data history normalization scheme. SD1 and SD2 Poincare parameters are for comparison and calculated from the original unprocessed beat-to-beat time series.

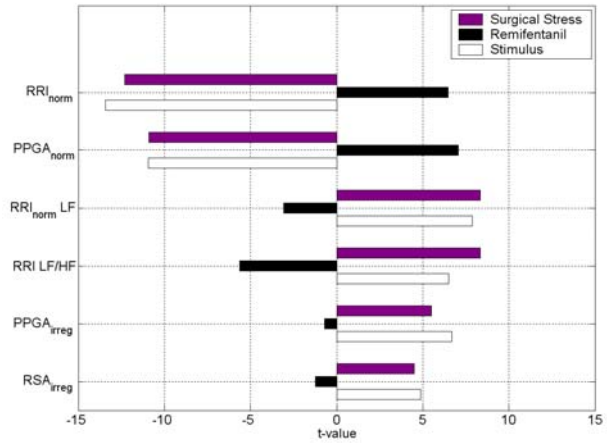

Figure 3: Some of the best parameter candidates calculated using the 5-min data history normalization scheme. The parameters are as in Fig. 2 except that the SD parameters are not shown.

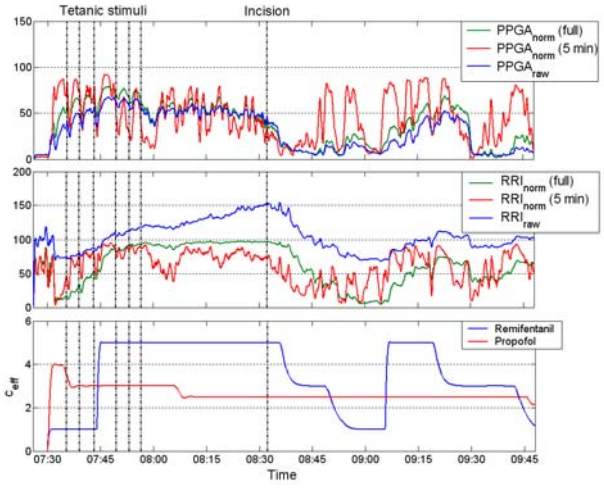

Figure 4: The time behaviour of the normalized and raw PPGA and RRI parameters in one typical anaesthesia and surgery. Artificial electric tetanic stimuli (50 Hz, 50 mA, 30 sec) are given to the patient ulnar nerve in the beginning of anaesthesia. Remifentanil effect site concentration is in ng/ml and propofol in microg/ml.

Figure 4 shows an example of the data in one patient. The responses to electric tetanic stimuli are clearly larger with the 5 min normalization in comparison to the full normalization and the raw PPGA and RRI responses. Especially in RRI the responses are considerably smaller at higher remifentanil concentration than at lower remifentanil level. At skin incision the PPGA decreases and heart rate (inverse of RRI) increase. Again the responsiveness is highest with the 5-min normalization. The PPGA and RRI parameters decrease with decreasing remifentanil concentration. Thereafter, with

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increasing concentration the candidate parameters recover, but stay somewhat smaller than before the start of surgery. During surgery the PPGA and RRI parameters with the 5-min normalization show considerably larger responsiveness than with the full data normalization and the raw parameters.

Discussion

We studied the beat-to-beat heart rate and photoplethysmographic waveform amplitude variabilities during general anaesthesia. Our goal was to find suitable parameter candidates to develop a new combined measure for the surgical stress of a patient. This parameter, a surgical stress index, could be used to adjust the analgesic medication during surgery to provide stress free anesthesia for all patients. The surgical stress index together with a measure of the level of hypnosis would help the anesthetists to give personalized anesthesia according to patients' real needs.

Sympathetic responses can originate from the increased endocrine secretion of cathecolamines (epinephrine and nor-epinephrine) and stress related hormones (cortisol, ACTH, etc) and the neurally mediated autonomic nervous system activation. The humoral sympathetic responses appear as very slow variation or a sustained change of the level of the PPGA and RRI time series. The ANS neural activation often shows as fast responses in the cardio-vascular parameters. Sympathetic neural activation is dominating at frequencies corresponding to time scales longer than about 10 sec while the parasympathetic activation causes the main part of the variability at higher frequencies, typically at respiration time scales. Our processing of the original RRI and PPGA time series was tailored to probe the variabilities in different time scales and to assess which types of variabilities best describe the state of the autonomic nervous system.

A good surgical stress index shall both track the changes of the level of stimulation and the level of antinociception provided by analgesic medication. In this respect $PPGA_{norm}$, RRI_{norm} and RRI LF/HF were promising variables in this study. These parameters are calculated over long time scales and may reflect the changes of the sympathetic tone in the autonomic nervous system. The changes of the sympathetic tone may origin from the altered level of stress related hormones or rather persisting change of the neural sympathetic activity in ANS. The irregularity parameters RSA_{irreg}, $PPGA_{irreg}$, PPGA SD1 and RRI SD2 most probably probe the rapid change in the neural sympathetic activity. The correlation to the level of stimulus is relatively good, but these parameters seem not so well follow the level of analgesic medication in a patient. These parameters seem suitable for detecting nociceptive events and indicating these to the care-givers. The irregularity parameters may indicate a change in the nociceptive-antinociceptive balance, if the number of nociceptive events is counted in certain time window. The increase of these counts could suggest inadequate analgesic medication in similar manner as the normalized PPGA and RRI.

The t-values of our parameter candidates seem to be higher in the 5 min normalization scheme. Therefore, it would be reasonable to combine $PPGA_{norm}$ and RRI_{norm} with this normalization scheme into an index of surgical stress. However, this conclusion may be premature, because a fast adaptation (within 5 min) during surgery makes the interpretation of the more responsive index values difficult. For instance, it would be more vague to assign a fixed threshold value to suggest more analgesic drug infusion in a patient. The normalization using the full patient history is less responsive and seems safer in this respect. With full patient history a normalized parameter value, say 75, would have roughly the same meaning in all phases of the surgery.

A surgical stress index could be combined from the normalized RRI and PPGA with or without the shorter time scale HRV and PPGA variability parameters. In patient monitoring it would be reasonable to favour robustness over peak performance in the final combination index. The short-term variability parameters may be, in somewhat adverse way, more sensitive to certain special situations during anaesthesia than the basic PPGA and RRI parameters. For instance, such situation could be heart arrhythmias or some artifacts in the signal, which may affect considerably the short term response, but change only little or transiently the long term parameter.

Further clinical evaluations with different combination of drugs, with interfering medications and in different types of anaesthesia are needed to solve the final structure of the surgical stress index. A prototype for a surgical stress index was developed based on this study. This index is currently subjected to further clinical studies.

Conclusion

HRV and PPGA variability parameters were correlated with the estimated surgical stress and its components during general anesthesia. The study suggests that an objective measure for surgical stress can be constructed using only cardio-vascular parameters RRI_{norm} and $PPGA_{norm}$, which are normalized using the past history of the parameter values in the individual patient. A prototype index is now in further clinical evaluations.

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