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Pain / Analgesia evaluation using heart rate variability analysis

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Abstract— **The optimization of analgesic drugs delivery during general anesthesia requires to evaluate the pain / analgesia balance. Heart Rate Variability analysis has been shown in several studies to measure the Autonomic Nervous System tone, which is strongly influenced by anesthetic drugs. Recording RR series during general anesthesia enabled us to observe that the Respiratory Sinus Arrhythmia pattern changed when a surgical stimulation was painful, even though the patient was not conscious. We developed a pain / analgesia evaluation algorithm based on the magnitude analysis of the respiratory patterns on the RR series. The parameters computed from this algorithm were recorded in thirty nine patients during general anesthesia. We retrospectively compared our parameters at different levels of analgesia during surgical stimulation, and found that they were related to pain / analgesia and relatively independent from other anesthesia related events like hypnosis and haemodynamic conditions.**

Keywords— **Analgesia Monitoring, Pain Evaluation, Heart Rate Variability**

I. INTRODUCTION

Taking into account pain level during medical procedures is an approach to improve quality care which implies the optimization of analgesic drugs prescription.

In case of conscious adult patients, the pain evaluation is performed using the Analog Visual Scale (AVS). AVS consists in a 10 centimeters graduated ruler equipped with a cursor moved by the patient. Beside the fact that such a measure gives subjective and punctual information, it can't be used for unconscious patients, for example during General Anesthesia (GA) or in critical care units.

GA uses hypnotic and analgesic drugs to allow painful surgical procedures. Clinical parameters such as Heart Rate (HR) and Arterial Blood Pressure (ABP), which are currently used for monitoring under GA, are neither sensitive nor specific of pain / analgesia. On the other hand, the powerful drugs used in such cases are associated to the constant risk of overdose, so that the anesthesiologist must constantly search the minimal dose to make the surgical procedure possible.

Several studies have shown that Heart Rate Variability (HRV) analysis gives information related to the Autonomic Nervous System (ANS) activity [1, 2, 3], which is strongly influenced by anesthetic drugs. Some authors described a global anesthesia depth index (hypnotic level) based on the HRV analysis [4]. However, no one described an index related to pain / analgesia during GA.

We have developed an instantaneous HRV analysis method, non invasive and user-friendly, based on the ECG signal acquisition [5, 6]. This analysis method enabled us to design parameters related to the influence of pain on the ANS activity. We tested them in a clinical trial, which consisted in HRV measurements during surgical procedures under GA. This clinical trial showed the significant relation between our parameters and pain / analgesia.

II. METHODOLOGY

Our method to evaluate pain / analgesia during GA is based on a time analysis of HRV. Recording RR series during GA allowed us to observe the change of patterns in relation to surgical stimulation. We noted that, when anesthesia is well stabilized, the RR series is only modulated by Respiratory Sinus Arrhythmia (RSA), so that a ventilatory pattern appears at regular intervals on the RR series (figure 1a). These patterns become irregular or chaotic (figure 1b) as soon as anesthesia is disturbed by any external event. Especially, we found that painful events, such as surgical incision, induced a decrease of the patterns magnitude.

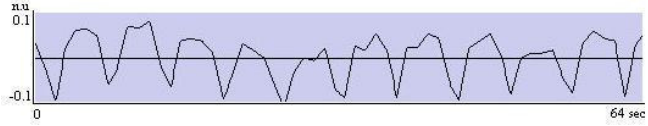

Fig. 1a: RR series in case of well stabilized anesthesia.

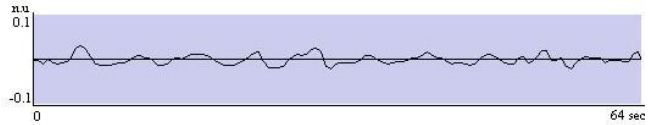

Fig. 1b: RR series in case of painful event.

According to these observations, we developed an analgesia level evaluation algorithm based on the magnitude analysis of the respiratory patterns on the RR series [7, 8, 9], as described below.

RR series acquisition:

An instantaneous RR value represents the time interval between two R waves of the electrocardiogram (ECG). The RR series is obtained from the ECG signal, which is digitized at a sampling rate of 250 Hz, using an R wave detection algorithm. The accuracy of the instantaneous RR values is +/- 4ms. In order to obtain equidistant RR samples, the RR series is re-sampled at 8 Hz using a linear interpolation algorithm.

RR samples windowing, filtering and normalizing:

In order to compute the parameters issued from the respiratory patterns, the RR samples are isolated into a 64 s moving window (512 samples). Since the method is based on the respiratory pattern changes measurements, samples are band pass filtered from 0.1 Hz to 1 Hz to obtain a signal representing respiratory effects on RR series. The band pass filter is built using a numerical high pass filter with a cutting frequency of 0.1 Hz linked with a numerical low pass filter with a cutting frequency of 1 Hz. In order to obtain parameters values free of inter patients variability, the signal is normalized within the moving window. The normalization algorithm consists of computing the norm value S according to the following formula:

$$S = \sqrt{\sum_{i=1}^{N} (RR_i)^2}$$

Where RRi represents the RR series samples values, N the number of samples in the window.

In a second time, each sample of the window is divided by the norm value S.

Area Under the Curve (AUC) parameters computation:

We evaluate the respiratory pattern changes by computing the area under the RR series curve values. In that way, each minimum point within the moving window is detected. Then, in order to get time analysis compatible with a respiratory cycle, the moving window is divided into 4 sub-windows of 16 seconds each (128 samples). Inside each sub-window, the area under the curve between x axis and the minimum points is computed, giving 4 areas values A1, A2, A3 and A4 (figure 2).

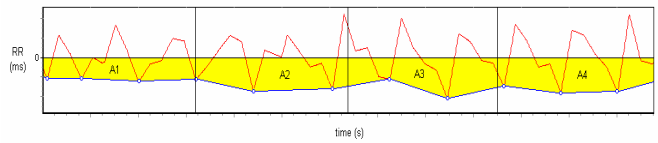

Fig. 2: RR series area under the curve computation.

From these 4 areas values two parameters are extracted to be tested within the clinical trial:

AUCmean, which represents the mean value of A1-A4

AUCmax, which represents the maximum value of A1-A4

Continuous measurement:

Continuous measurement of AUCmean and AUCmax parameters can be assumed by moving the 64 s window after each calculation. The sampling rate of the final parameters depends of the window moving period. In practice, a 5 s moving period would give an acceptable trend curve of the parameters values.

III. CLINICAL TRIAL

After institutional approval, we prospectively included patients who were to undergo GA for surgical procedure in the University Hospital of Lille in two different surgical units. The patients enrolled in the first unit (group 1) had GA for percutaneous spermatozoid sampling in order to achieve in-vitro fertilization. The patients enrolled in the other unit (group 2) needed GA for teeth extraction.

Anesthetic Protocol:

GA was induced and maintained by propofol administered via a target controlled intra venous anesthesia device (Diprifusor®) associated with a Bi Spectral Index (BIS™) monitoring that enabled us to keep hypnosis constant by maintaining the BIS™ values between 40 and 60. An opioid was administered Intra Venously (IV) together with propofol at induction of GA. Heart Rate (HR) and Systolic Blood Pressure (SBP) were monitored continuously during GA. An additional opioid IV bolus was administered during the course of GA in case of haemodynamic response to the surgical stimulus (rise of HR or SBP of 30% from baseline with baseline = measurements after GA induction, before start of surgery), as usually done during GA. ECG recording did not interfere with management of GA. The two trials differed only by the opioid used, sufentanil in group 1 and alfentanil in group 2. All events like induction of GA, surgical incision, painful stimulus, additional opioid injection or hypnotic target concentration were noted every 5 minutes, as were monitoring values: HR, SBP, BIS™. All patients were

intubated and ventilated at a rate of 10 cpm. Inspired gas was a mixture of nitrous oxide in oxygen 50%/50%.

Statistical Analysis:

We distinguished four subgroups by dividing each group in patients who reacted to surgical stimulation (gr1-R and gr2-R) and therefore needed additional opioid administration and those who did not (gr1-noR and gr2-noR). We compared clinical parameters between the different subgroups, and the parameters calculated from the RR series. We used the non parametric Mann Whitney and Kruskal Wallis tests to test differences between continuous data. The statistical tests were considered significant at a p value lower than 0.05.

IV. RESULT

I) Patients

We included 19 patients in group 1 and 20 patients in group 2 (Table 1). None suffered acute bleeding during GA, and none required the injection of parasympathetic blocking agent (atropine). Two patients in group 1 and 15 patients in group 2 (group 2-R) showed a sufficient increase in HR or SBP to necessitate additional opioid administration.

	Group 1	*Group 2*
N	19	20
Reaction/no reaction	2 / 17	15 / 5
Years	33 [23, 46]	22,5 [18, 30]
BMI (kg/m²)	24 [20, 29]	21 [20, 28]
ASA status I/II	11/8	17/3
Usual SBP (mmHg)	120 [110, 140]	110 [100, 130]

Table 1: Epidemiologic data in groups 1 and 2

II) Clinical measures under GA

We observed haemodynamic differences between group 1 and group 2, as shown in figure 3. This was related to overall depth of analgesia, which was deeper in group 1 than in group 2, as assessed by the number of patients who needed additional opioid administration. BIS™ was slightly lower in group 1 than in group 2, but this had no consequence on depth of analgesia. The hypnotic part (propofol) of GA was almost the same in gr1 and gr2. When comparing group 2 subgroups, we found no difference in SBP (Mann Whitney, p=ns), but HR was significantly higher in gr2-R than in gr2-noR (Mann Whitney, p=0.0001), which was in accordance with the anesthetic protocol.

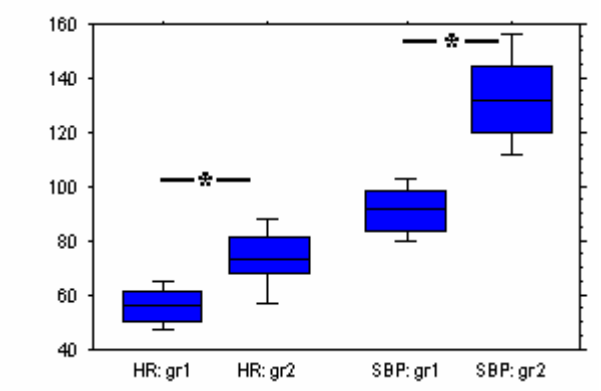

Fig. 3: Box Plot of HR and SBP in gr1 and gr2 (* p<0.05)

III) HRV measures under GA

AUCmean and AUCmax were significantly lower in group 2-R than in group 1-noR and group 2-noR (Mann Whitney U-test, p<0.0001 in both cases), as shown in figure 4. This shows that these indexes were related to the nociception / analgesic balance.

There was no difference for AUCmean and AUCmax between gr1-noR and gr2-noR (Mann Whitney U-test, p=ns), which shows that these indexes were not influenced by haemodynamic conditions [7].

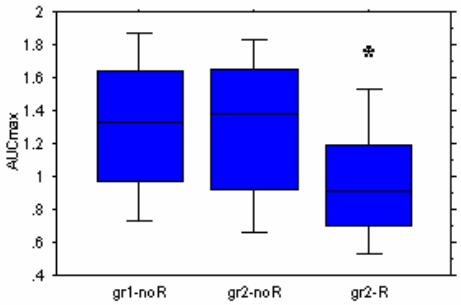

Fig. 4: Box Plot of AUCmax per stimulation in all subgroups (* p<0.05)

V. CONCLUSION

On line pain / analgesia evaluation during GA could be of precious help to optimize analgesic drugs delivery and to limit the risk of toxicity effects. The HRV analysis based algorithm we have developed, which principal outcome is to highlight RSA effects on the RR series changes, seems to be a true way to elaborate an analgesia monitoring system. Particularly, measuring the area under the curve of the filtered and normalized RR series within 16 seconds sub-windows, allowed us to elaborate the AUCmean and AUCmax parameters which have been tested running a clinical trial. This trial showed a significant level difference of AUCmean and AUCmax between two groups of patients,

one needed additional opioid administration and the other did not. This level difference shows that AUCmean and AUCmax are related to the nociception / analgesic balance.

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