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Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia

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Abstract— **The optimization of analgesic drugs delivery during general anesthesia (GA) requires to evaluate the pain/analgesia balance. Heart Rate Variability (HRV) analysis has long been shown to measure the autonomic nervous system tone, which is strongly influenced by anesthetic drugs. Power spectrum measurements are widely used to assess HRV low (LF) and high frequency (HF) ranges, related to the sympathetic and parasympathetic systems. We have developed an original graphic measurement technique (EnvTOT) of the ventilatory influence on the RR series. Measurements on simulated RR series showed that the graphic assessment is independent from respiratory rate, while LF and HF spectral measurements are over- and underestimated for respiratory rates lower than 12 cycles min^{-1}. Clinical measurements on 49 patients during GA showed that normalized HF power was strongly related to hemodynamic responsiveness during GA, and was strongly correlated with normalized EnvTOT measurements. A real time computation of the RR series could therefore help medical staff to anticipate hemodynamic responsiveness and the analgesia/nociception balance during GA.**

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

I. INTRODUCTION

General anesthesia (GA) combines the use of hypnotic and analgesic drugs in order to achieve a certain level of non-responsiveness to surgical stimulation. Numerous ways of assessing the depth of hypnosis have been described and validated during the last decade, thus enabling anesthesiologists to continuously adapt the regimen of hypnotic drugs to the patient's need. On the other hand, there are only few and unreliable ways to assess the analgesia/nociception balance in an unconscious patient.

Some authors have suggested that Heart Rate Variability analysis (HRV) may prove useful in order to measure the sympathetic and parasympathetic tones during GA, which would indirectly help to assess the analgesia/nociception balance [1]. HRV measurements can be made on the RR series computed from the recording of a three lead ECG. Power spectrum measurements have been classically made using a Fast Fourier Transform, and more recently thanks to a Fast Wavelet Transform (FWT) which is best suited for non stationary signals [2, 3, 4].

A major difficulty for the medical staff is to interpret the results of power spectrum measurements, because of the great number of influences that occur during GA and surgical procedure : shifts in the analgesia/nociception balance are not the only ones influencing the sympathetic and parasympathetic tones.

We have therefore developed a graphic measurement of the ventilatory influence on the RR series, in order to give both a qualitative and a quantitative measurement of HRV [5, 6]. This method seemed promising when tested on adult patients under general anesthesia, but needed further validation.

1. 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 [5]. We found in particular that painful events such as surgical incision induced a decrease of the patterns magnitude.

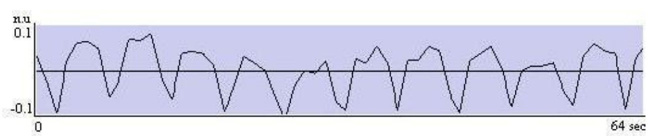

Fig. 1a: RR series in case of well stabilized anesthesia.

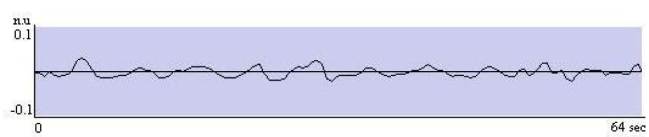

Fig. 1b RR series in case of painful event.

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

RR series acquisition:

An instantaneous RR value represents the time interval between two R waves of the electrocardiogram (ECG, fig. 2). 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 [7].

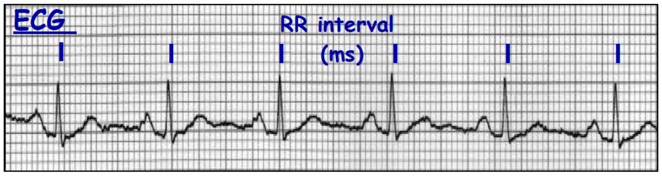

Fig 2. ECG recording. R waves are detected, and intervals between two adjacent R waves are measured.

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, normalizing and filtering:

In order to compute the RR series analysis, the RR samples are isolated into a 64 seconds moving window (512 samples). To obtain parameters values free of inter patients variability, the signal is normalized within the moving window. In a first step, the normalization algorithm consists of computing the mean (M) value.

$$M = \frac{1}{N}\sum_{i=1}^{N}(RR_i)$$

Where RR_i represents the RR samples values and N the number of samples in the window.

Then the mean value M is subtracted from each sample of the window.

$$RR_i = (RR_i - M).$$

The resulting *RR* series is then used for the norm (S) value computation.

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

.

Finally, each resulting *RR* sample is divided by the norm value S.

$$RR_i = RR_i / S$$

Since the method is based on the magnitude of the respiratory pattern measurements, RR samples are band pass filtered from 0.15 Hz to 0.5 Hz, which is the frequency band related to RSA, using a wavelet based numerical filter.

As it allows analyzing non-stationary signals, wavelet analysis has already shown its ability in many biomedical applications and more particularly in RR analysis. Usually, such a method is used to compute the signal energy distribution. However, wavelet transform can also be used as a band-pass filter when classical FIR and IIR filters show their limits. Indeed, wavelet based filters allow to isolate one or several frequency domains of the signal without any phase shift.

To realize the band pass filter, we chose to use a 4 coefficients Daubechie wavelet.

Applying a direct wavelet transform to the RR series allows to obtain its time-scale representation in different wavelet energy levels. Each level is related with a particular frequency domain. Applying then a reverse wavelet transform using only selected levels allows to retrieve a filtered signal in the time domain, lacking in frequencies corresponding to the non used wavelet levels. Figure 3 shows the wavelet filter cutting frequency as a function of the wavelet level.

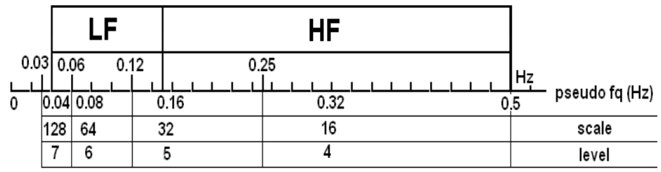

Fig 3. Wavelet analysis : wavelet levels lead to pseudo-frequencies. HF measurements are made using levels 4 and 5. LF measurements are made using levels 6 and 7. Total power is LF+HF.

This figure shows that to design a 0.15 Hz to 0.5 Hz band pass filter, the wavelet levels 4 and 5 must be kept (0.16 Hz to 0.67Hz) to apply the reverse wavelet transform.

Area Under the Curve (AUC) parameters computation:

We evaluated the heart respiratory interaction by measuring its area of influence on the RR series (yellow surface, fig 4): after detection and connection between the local minima and the local maxima, the surface thus delineated is measured (EnvTOT). When measured on a normalized RR series, the result is given in normalized units (EnvTOTnu).

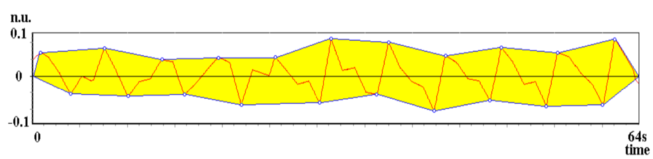

Fig. 4: normalized RR series : computation of EnvTOTnu as area (yellow) under the curve.

Simulated RR series and power spectrum measurements:

Using an ECG recording and the afferent RR series of a patient during general anesthesia and positive pressure ventilation, we used one ventilatory pattern (fig 5) and generated several simulated RR series at various respiratory rates (8, 10, 12 and 15 cycles.min^{-1}) and three amplitudes (x1 original amplitude; x2 double; x3 triple). Spectral measurements were made using the FWT.

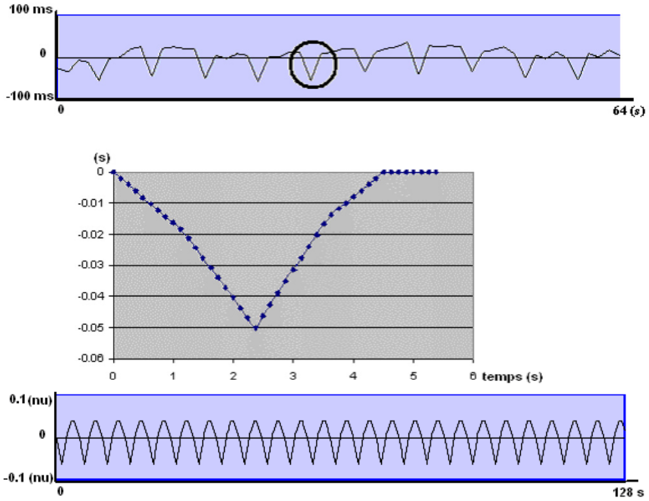

Fig 5. Upper panel real case RR series during GA respiratory pattern are clearly visible. Middle Panel : extraction of one respiratory panel. Lower panel : example of simulated RR series by pasting respiratory patterns next to each other - respiratory rate in this case is 12 cycles.min^{-1}.

Real case measurements during general anesthesia:

After institutional approval, we included 49 adult patients, scheduled to undergo general anesthesia for various surgical procedures under the same anesthetic protocol : propofol using a Diprifusor™ (TCI-Diprifusor™, Zeneca Ltd,) target device, continuously adapted to the measured Bispectral Index (BIS™, Aspect A-2000 XP™ v3.31), positive pressure ventilation at 10 cycles.min^{-1}. In group 1, patients underwent spermatozoid sampling for in vitro fertilization. In group 2, they underwent teeth extraction. In group 3, they underwent Ear-Nose-Throat surgery. Opioid differed between the groups : sufentanil in group 1, alfentanil in group 2 and remifentanil in group 3. All patients were free of autonomic nervous system altering disease. At induction of GA, opioid and propofol were administered together, and the trachea was intubated. Additional opioid boluses were administered only in case of hemodynamic reactivity, defined as an increase of heart rate or systolic blood pressure of more than 30% from the baseline. These events were recorded, and RR series up to 10 min before them were analyzed. The HRV measurements up to 5 min ("lightAnalg") and up to 10 min ("earlyLightAnalg") before hemodynamic responsiveness were compared with a baseline measurement ('noStim") made before surgical stimulation under GA.

Statistical analysis

ANOVA for repeated measurements with subsequent Fisher's PLSD test were used. P values less than 0.05 were considered statistically significant. StatviewTM (v4.55, Abacus concept Inc, Berkeley, CA) was used for the statistical analysis. Unless otherwise specified, results are presented as medians (interquartile).

IV. RESULTS

Results of simulated RR series:

Respiratory influence on the RR-series at respiratory rates of 8, 10, 12 and 15 cycles.min^{-1} is measured by the wavelet levels 4 and 5. The RR series simulating a 8 cycles.min^{-1} ventilation, theoretically in the LF range, is near the junction between wavelet levels 5 and 6. Unlike Fourier transform, wavelet analysis shows an important overlap between levels, leading to an underestimation of HF/(HF+LF) and an overestimation of LF/(HF+LF) for the 8 and 10 cycles.min^{1} RR series (fig 5 lower panel, left). On the other hand, EnvTOT measurements are not influenced by the respiratory rate, but only by the amplitude of the pattern. Ventilatory pattern amplitudes (x1 x2 x3) are clearly visible on figure 6 (upper panel) for spectral and graphic measurements, but disappear when spectral measurements (fig 6 lower panel, left) or EnvTOT measurements (fig 6 lower panel, right) are normalized. EnvTOT(nu) measurements could therefore be superior to spectral ones, because of their independence from respiratory frequency on simulated RR series.

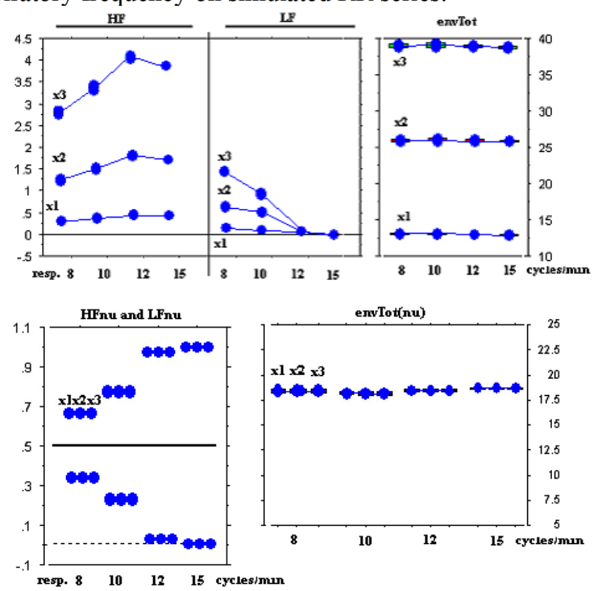

Fig 6. Upper panel : left - HF and LF measurements on simulated RR series at 8, 10, 12 and 15 cycles/min. Right - graphic measurements ; Lower panel : left - normalised spectral measurements HF/(HF+LF) and LF/(HF+LF) ; right - normalised graphic measurements EnvTOT(nu)

Results of RR series analysis during general anesthesia

Forty nine patients were included (group 1 : n=19; group 2 : n=18; group 3: n=12). Only 19 patients showed at least one hemodynamic change compatible with the "lightAnalg" status ; some patients presented these changes up to 4 times, thus leading to 51 sequences : "noStim"-"earlyLightAnalg"-"lightAnalg". Spectral measurements during these 51 sequences are shown figure 7. We found that absolute power spectra (HF and LF) are less sensitive to hemodynamic reactivity than normalized power spectra (HFnu and LFnu), and that LFnu behaved symmetrically to HFnu.

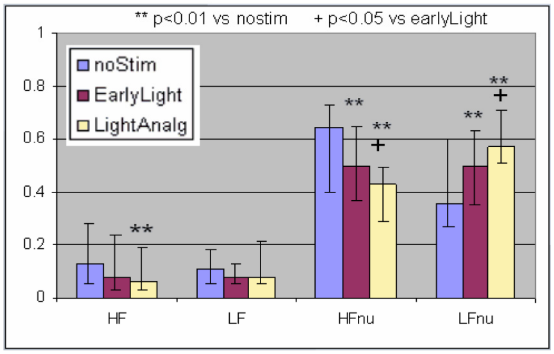

Figure 7. Raw and normalized spectral measurements during GA. "noStim" measurements are made under GA before surgical stimulation. "EarlyLight" and "LightAnalg" are measured respectively during the 10 min and during the 5 min preceding hemodynamic responsiveness to surgery. ANOVA and Fisher's PLSD test.

Furthermore, the graphic measurements EnvTOTnu showed a strong correlation with HFnu (r^2=0.86, p<0.01), as shown in figure 8.

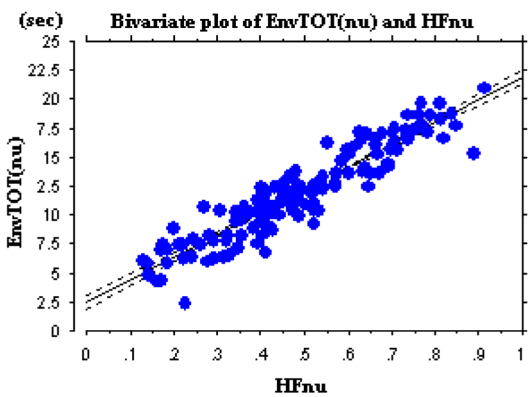

Figure 8. Bivariate plot between EnvTOTnu and HFnu during GA.

Continuous measurement

ECG acquisition, R wave automatic detection and RR series filtering using FWT and EnvTOTnu calculation have been implemented. A continuous monitoring of EnvTOTnu during general anesthesia is now possible (fig 9) on a gliding ECG window of 64 sec, with a 4 sec moving period.

Fig 9. Real time monitor (Tablet PC) with ECG real time acquisition, RR series computation and filtering, and EnvTOTnu measurement.

The normalized RR series gives thus the medical staff a real time qualitative information about the ventilatory influence on the RR series. The EnvTOTnu computation is stored and displayed as a trend during anesthesia, so that "lightAnalg" periods of time can be detected and compared with the "noStim" ones.

V. CONCLUSION

We have shown on simulated RR series that normalized spectral measurements can be under evaluated when the respiratory rate is lower than 12 cycles.min^{-1}, while graphic measurements (EnvTOT) are not influenced by respiratory rate. EnvTOT could therefore be better suited for clinical HRV measurements than spectral ones.

Measurements made on 49 adults during general anesthesia showed that HFnu is strongly related with the analgesia/nociception balance, and could be used to predict hemodynamic reactivity due to the lack of analgesia. We found that HFnu was also strongly correlated with EnvTOTnu.

ECG recording and RR series automatic computation in order to achieve a real time measurement of EnvTOTnu on a handheld tablet PC has been implemented, and needs now further clinical evaluation.

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