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Heart Rate Variability analysis for newborn infants prolonged pain assessment.

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Abstract— **Pain management is a general concern for healthcare quality. In the particular context of neonatal care, it's well known that an efficient pain management will decrease mortality and morbidity of newborn infants. Furthermore, the plasticity of developing brain is vulnerable to pain and/or stress, that in turn may cause long term neurodevelopmental changes, including altered pain sensitivity and neuroanatomic and behavioural abnormalities. During neonatal intensive care stay, large number of painful procedures are performed, the majority of which are not accompanied by adequate analgesia. Optimal management requires competent pain assessment which can be especially difficult to perform in this non verbal population. We have developed an instantaneous heart rate variability (HRV) analysis method, non intrusive and user-friendly, based on the ECG signal acquisition. This analysis method enabled us to design parameters related to the influence of pain on the Autonomic Nervous System (ANS) activity. This paper presents the application of this method, previously validated for adults under general anesthesia, to the domain of newborn infants prolonged pain assessment.**

Keywords— **Newborn infants, Pain Evaluation, Heart Rate Variability**

I. Introduction

Concern about short and long-term adverse consequences of early pain exposure in newborn infants gives motivation to develop valid and reliable measures of infant pain.

Various pain assessment scales have been developed, mainly based on both behavioral and physiological indicators of pain:

- **Neonatal Facial Coding System (NFCS)**: For short term pain evaluation. It's based on 9 items describing newborns facial expression.
- **Amiel-Tison score**: This score is used to evaluate postoperative pain for children between 0 and 7 months. It's based on 10 items describing facial and corporal motricity, cry and relationship with healthcare provider.
- **Newborn short term pain scale (D.A.N):** For newborn or preterm infant short term pain evaluation. It's based on 3 items describing facial and corporal motricity and pain vocal expression.
- **Preterm Infant Pain Profile (P.I.P.P):** For preterm infant short term pain evaluation. It's based on 7 behavioral and physical items.
- **Pain and comfort newborn pain evaluation scale (E.D.I.N):** For long term pain and/or comfort measurement. It's based on 5 behavioral items (facial and corporal motricity, relationship with healthcare provider, sleep, etc…) evaluated on one hour intervals.

These scoring systems allow bedside evaluation and help decision taking for managing pain. However, those different pain scales have some limitations:

- reliability has been questioned even when performed by well-trained nurses, in particular in distinguishing pain and discomfort;
- some pain scales require prolonged clinical observation of the infants, especially for assessing prolonged pain;
- pain scoring is intermittent, with a risk not to take into account some painful episodes during the inter-rating period.

Compared to acute pain, prolonged pain may be largely unrecognized in the newborn infants and therefore untreated. Many conditions exist in neonatal intensive care unit during which newborn infants may experienced prolonged pain. Examples include mechanical ventilation, nasal lesions during nasal continuous positive airway pressure, abdominal distension, necrotizing enterocolitis or pain after a surgical procedure. Although newborn prolonged pain can be assessed by using the EDIN scales, it may be underestimated because pain scoring is performed usually twice or 3 times a day in clinical setting.

Previous studies clearly showed that systems controlling cardiovascular functions are closely coupled to systems associated with perception of pain [1, 2]. Heart Rate Variability (HRV) is a well-established non-invasive measure of cardiac autonomic control [1, 3]. HRV is mediated primarily by changing levels of parasympathetic and sympathetic outflow from the central nervous system to the sinoatrial node of the heart. Studies using selective pharmacological blockade of the cardiac sympathetic and parasympathetic receptors have shown that fluctuations in heart rate (HR) above 0.15 Hz and centered at the respiratory frequency, are mediated exclusively by changes in parasympathetic outflow, whereas lower frequency changes are mediated by both changes in parasympathetic and sympathetic outflows [4, 5]. In adults, growing evidence

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highlights that pain, fear or anxiety result in a decrease in the HRV, in particular the high frequency (HF) power (> 0.15Hz), indicating a drop in vagal tone during unpleasant stimuli or emotion [6, 7, 8, 9]. In infants, a decreased spectral power in the high frequency band has been observed during routine heel lancing procedure, suggesting a decrease in parasympathetic output during acute nociceptive stimuli [1, 10]. To the best of our knowledge, the specific autonomic control mechanisms that underline cardiac response to painful stimuli in the newborn infant are not known.

We have developed an instantaneous heart rate variability (HRV) analysis method, non intrusive and user-friendly, based on the ECG signal acquisition [11]. This analysis method enabled us to design parameters related to the influence of pain on the Autonomic Nervous System (ANS) activity. The aim of this study was the application of this method, previously validated for adults under general anesthesia [9], to the domain of newborn infants prolonged pain assessment. To test method ability to detect prolonged pain, we compared the obtained parameters to the behavioral EDIN score.

I. Methods and Materials

Our method to evaluate pain is based on a time analysis of HRV. Recording heart period (time interval between two cardiac cycles) during general anesthesia allowed us to observe the change of patterns in relation to surgical stimulation. We noted that, when anesthesia is well stabilized, heart period is only modulated by Respiratory Sinus Arrhythmia (RSA), so that a ventilatory pattern appears at regular intervals on the heart period time series (fig. 1a). These patterns become irregular or chaotic (fig. 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 pattern magnitude.

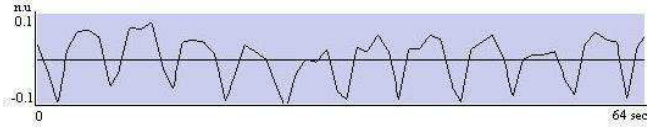

Fig. 1a: heart period in case of well stabilized anesthesia.

Fig. 1b: heart period in case of painful event.

According to these observations, we developed a pain level evaluation algorithm based on the magnitude analysis of the respiratory patterns on the heart period series [11], as described below.

A - RR series acquisition:

The 250 Hz digitized electrocardiogram (ECG) is used to automatically detect R waves [12], and thus measure heart periods, which is the time between two R waves of the ECG (RR intervals).

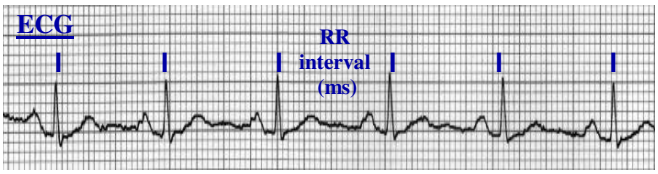

Fig 2 : ECG recording. R waves are detected, and intervals between two adjacent R waves are measured.

RR intervals series are filtered in real time using a filtering algorithm that effectively removes inaccuracies induced by artefact [13]. The resulting RR series were re-sampled at 8 Hz using a linear interpolation algorithm and then isolated into a 64 seconds moving window (512 samples) for RR series analysis. For reliable inter patients comparability, the signal is normalized within the moving window using the squared vectorial norm of the windowed RR series (which is related to the variance of the series). 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.

$$RR_i = RR_i / S$$

B - RR series filtering:

Since the method is based on the magnitude analysis of the respiratory patterns on the RR series, RR samples are high pass filtered above 0.15 Hz (corresponding to the parasympathetic HR activity).

As it allows analyzing non-stationary signals, wavelet analysis have already shown its ability in many biomedical applications and more particularly in RR series 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. In order to develop the band pass filter, we chose to use a 4-coefficients Daubechie wavelet [14] which is very similar in shape to the RSA RR series modulation pattern. 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. The following table shows the wavelet filter cutting frequency as a function of the wavelet level.

Table 1 shows that to design a 0.15Hz to 2.6667 Hz band pass filter, the wavelet levels 1 to 5 must be kept (0.167 Hz to 2.667 Hz) to apply the reverse wavelet transform. In that way, from a classical RR series recording, a signal which is only related to RR high frequency variations (RRhf) is obtained.

Table 1: Daubechie wavelet cutting frequencies as a function of wavelet level.

Level	Scale	Pseudo Frequency (bpm)	Pseudo Frequency (Hz)	Frequency domain
1	2	160	2.6667	HF
2	4	80	1.3333	HF
3	8	40	0.6667	HF
4	16	20	0.3333	HF
5	32	10	0.1667	HF
6	64	5	0.0833	LF
7	128	2.5	0.0417	LF
8	256	1.25	0.02085	VLF

C – Indexes computation:

The parasympathetic tone is assessed by computing the area under the RRhf series curve values as shown in figure 3. Local minima and maxima are detected, and the areas A1, A2, A3 and A4 are measured as the area between the lower and upper envelopes in each 16 sec sub-window.

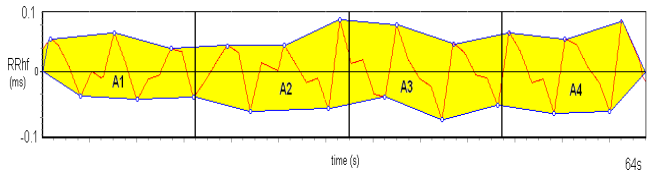

Fig. 3 Local minima and maxima detection and A1, A2, A3, A4 computation.

We defined 3 different HRV indexes related to parasympathetic activity, representing the minimum, the maximum and the mean values of the A1, A2, A3 and A4 areas:

- AUCmin = min(A1,A2,A3,A4).
- AUCmax = max(A1,A2,A3,A4).
- AUCmean = mean(A1,A2,A3,A4).

Continuous measurement of the indexes 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 1 s moving period gives an acceptable trend curve of the parameters values.

C – Clinical trial

To test the ability of our HRV analysis method for newborn prolonged pain assessment, we recorded RR series on newborns infants between their second and third hour of life. At the same time, the EDIN score was evaluated. As an EDIN score up to 5 is considered as an indicator of long term pain, we then divided the population in two groups: "No Pain" (EDIN < 5) and "Pain" (EDIN ≥ 5). We computed our indexes for each recorded RR series and extract the 1 hour mean values for each index. We tested the difference between the two groups using the Mann Whitney non-parametric statistical test. The statistical tests were considered significant at a p value of 0.05.

II. Results

We included 41 newborns; 22 were born by non instrumental procedure and 19 using instrumental ones. 27 newborns showed an EDIN < 5 ("No Pain" group) and 14 showed an EDIN ≥ 5 ("Pain" group). Most of the EDIN ≥ 5 was measured in the instrumented population (11/14) confirming the fact that instrumental extraction is a risk factor for prolonged pain in the newborn infant.

Table 2: Indexes values as a function of the group. Values are median (25–75% interquartile range). Statistical analysis = Mann Whitney U- test.

	No Pain (EDIN<5)	Pain (EDIN≥5)	p value
Heart rate	130 (120-141)	127 (120-142)	NS
AUCmax	**1.55 (1.34;1.83)**	**1.32 (1.16;1.42)**	**0.024**
AUCmin	0.63 (0.49-0.77)	0.65 (0.41-0.83)	NS
AUCmean	1.03 (0.86-1.16)	0.92 (0.69-1.09)	NS

Despite having similar basal mean heart rate, AUCmax was significantly lower in the "Pain" group than in the "No Pain" group (Mann Whitney U-test, $p<0.05$), as shown in fig. 4. There was no difference for AUCmin and AUCmean between the "Pain" group and the "No Pain" group (Mann Whitney U-test, p=ns).

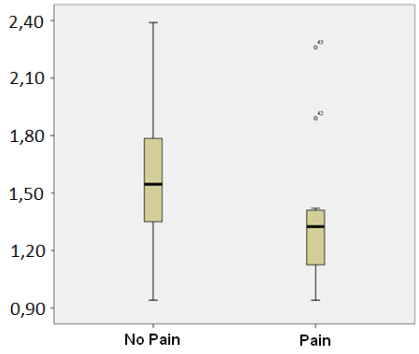

Fig 4: AUCmax in group "No Pain" (EDIN score < 5) and in group "Pain" (EDIN score ≥ 5). Mean AUCmax is significantly higher in the group "No Pain" than in the group "Pain" ($p<0.05$). A high EDIN score ≥ 5 is usually considered as indicative of prolonged pain in the newborn infant.

The corresponding difference in HRV can be graphically appreciated in Fig 5 showing individual tracings of RR series

after normalization and filtering in an infant with low EDIN score and an infant with high EDIN score. Compared to panel A, variability of RR series is decreased in Panel B.

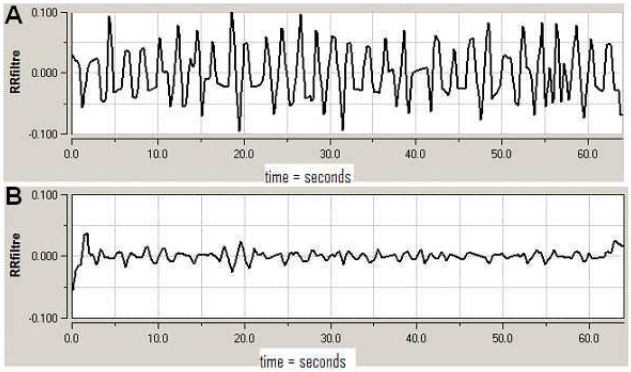

Fig. 5: Individual tracings of RR series (after normalization and band pass filtering of the RR samples from 0.16 Hz to 2.6 Hz) in 2 full-term newborn infants. Panel A: infant with mean EDIN score = 2 (considered as indicative of minimal pain). Panel B: Infant with mean EDIN score = 7 (considered as indicative of significant pain).

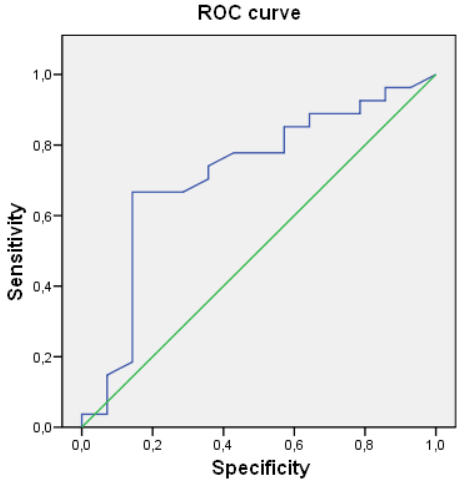

Fig. 6: Receiver operating characteristic curve of AUCmax for EDIN score up to 5 expressed as sensitivity as a function of specificity.

III. CONCLUSION

This paper presents the application of a HRV analysis method to the particular domain of newborn infants prolonged pain evaluation. This real time analysis method allows to obtain several indexes (AUCmax, AUCmin and AUCmean) related to the influence of pain on the ANS. If this method has already been validated for acute pain evaluation of adult patients under general anesthesia [9], the proof of concept still had to be done for prolonged pain as well as for newborn infants.

The clinical study presented in this paper indicates that prolonged pain is associated with a decreased AUCmax HRV index in full-term newborn infants. Low AUCmax identifies with a good sensitivity infants with significant prolonged pain (Fig. 6).

Even if further clinical studies comparing newborn infants who underwent surgical procedure and controls are required to assess whether AUCmax can be used as an indicator to assess prolonged pain in the newborn infants, a quantitative and continuous assessment of AUCmax can constitute an efficient solution for prolonged pain detection.

We propose that a decreased AUCmax, might help to identify infants potentially experiencing pain, and could be used as an alert signal to prompt the nursing staff for clinical pain scale scoring.

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