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Automated analgesic drugs delivery guided by vagal tone evaluation: Interest of the Analgesia Nociception Index (ANI).

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Abstract — **Analgesic drugs delivery optimization constitutes one of the main objectives of modern anesthesia. Indeed, their over or under determination constitutes a risk for anesthetized patient in terms of hemodynamic reactivity or post-operative hyperalgesia. Nowadays, new physiological indexes allow anesthesiologists to evaluate the balance between the analgesia level and the noxious stimulus importance. ANI is an index related to the autonomic nervous system activity based on heart rate variability analysis. Its ability for the analgesia / nociception balance evaluation has been established bringing evidences about its helpfulness for analgesic drug delivery. In this article, we describe a device for automatic analgesic drugs administration based on the ANI evolution during surgical procedures under general anesthesia. We hypothesized that such a device could improve the quality and safety of anesthesia by reducing adverse cardiovascular events and delivered analgesic drugs doses.**

Keywords—**Automated drugs delivery, Heart Rate Variability analysis, Autonomic Nervous System.**

I. Introduction

GENERAL anesthesia can be divided into a hypnotic component linked with cortical activity and an under-cortical activity linked with the analgesia / nociception balance. The hypnotic component can be monitored in clinical usual practice using EEG monitors such as the bi-spectral index (BIS®, Aspect Medical Systems) and the spectral entropy (M-ENTROPY ; GE Healthcare). Nowadays, several indexes allow the analgesia / nociception balance evaluation (*ANI*; METRODOLORIS, *SPI*; GE Healthcare, *Algiscan*; IDmed. And several studies showed that such indexes can be of precious help regarding analgesic drug administration [1, 2]. During general anesthesia, the over or under determination of the analgesic administration constitutes a risk for the anesthetized patients. Analgesic drugs decrease the autonomic nervous system (ANS) reactivity to the nociceptive stress linked to the surgical procedure, but their overdose can lead to undesirable peri operative cardiovascular effects like arterial hypotension, and would be at the origin of post operative hyperalgesia [3]. On the other hand, an insufficient analgesic dose can also be at the origin of several undesirable effects like arterial hypertension, patient movements or awaking. That is the reason why the research of the minimal and sufficient analgesic dose during general anesthesia constitutes a global objective of modern anesthesia.

Heart Rate Variability (HRV) analysis allows to give information on ANS cardiac control. Several studies have shown that the HRV high frequency (HF) variations between 0.15 Hz-0.4 Hz are exclusively influenced by the parasympathetic component of the ANS. On the other hand, low frequency (0.04 Hz-0.15 Hz) changes are mediated by both parasympathetic and sympathetic [4, 5]. In adult, pain, stress, anxiety or fear result in a decrease of the heart rate HF content [6, 7, 8]. On adult patient under general anesthesia, HRV allows to evaluate the balance ratio between the level of analgesia and the importance of the nociceptive stimulus [9].

We have developed an original HRV index using the ECG signal for continuously measure the ANS activity and its reaction to anesthesia medication as well as to nociceptive stimuli [10] ; the Analgesia Nociception Index (ANI). The ANI ability for the analgesia / nociception balance evaluation has been established during a large number of clinical validations [9, 11, 12, 13] which showed that the index was able to detect noxious stimulus with increase sensitivity and specificity than usual clinical parameters (Arterial Blood Pressure and Heart Rate). Furthermore, we showed that, in case of insufficient analgesia, ANI decreases 10 minutes before the occurrence of hemodynamic impairment [13, 14].

Thanks to these preliminary clinical studies, we showed the helpfulness of ANI for analgesic drugs delivery. Several clinical studies are in progress to evaluate the monitor benefits in terms of improvement of the quality and safety of anesthesia, reduction of adverse cardiovascular events and reduction of delivered analgesic drugs.

Following these observations, we hypothesized that such an index could be used as a tool to regulate the infusion rate of analgesic drugs syringe pump. We therefore developed a device for automated analgesic drugs administration based on the ANI evolution during surgical procedures under general anesthesia.

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II. Methods and Materials

A – ANI computation

The ECG is digitized at a sampling rate of 250 Hz. ECG R waves are then detected in order to build the RR intervals series defined as the time evolution of the time intervals between two R waves. RR series is analyzed using an original non linear filtering algorithm [15] in order to detect and replace each disturbed RR sample. Filtered RR series are then re-sampled at 8 Hz using a linear interpolation. RR series is then mean centered and normalized into a 64 seconds moving window. Since the method is based on the analysis of HF changes, the RR series is band pass filtered between [0.15-0.4 Hz]. The band pass filtering is realized using a numerical filter based on the 4 coefficients Daubechies wavelet. Fig. 1 shows an example of the normalized, mean centered and band pass filtered RR series (black curve).

As shown in Fig. 1, local maxima and minima are detected and the upper and lower envelopes are plotted by connecting the local minima together and the local maxima as well (red curves). The 64 sec moving window is then divided into four sub-windows of 16 sec. The areas between the lower and upper envelopes are then measured in the four sub-windows. We defined AUCmin as the smallest of these sub-areas.

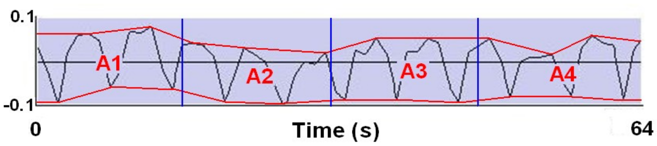

Fig. 1: normalized, mean centered and band pass filtered RR series.

ANI is then computed in order to obtain a value between 0 and 100:

$$ANI = 100 * [a*AUCmin+b] / 12.8 \qquad (1)$$

Where a = 5.1 and b = 1.2 have been empirically determined in a data set of more than 100 anesthetized patients in order to obtain a good correlation between the visual pattern of the parasympathetic influence on RR series and the quantitative measurement of ANI.

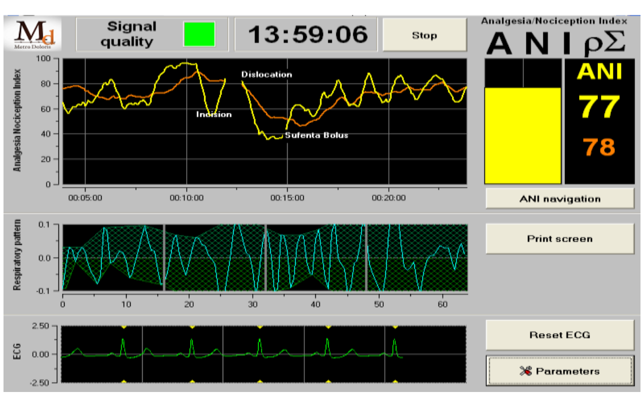

Fig. 2: Physiodoloris monitor user interface. Lower scope: ECG signal. Middle scope: normalized, mean centered and band pass filtered RR series. Upper scope: ANI trend curves.

This parameter is available through the Physiodoloris® monitor [16] commercialised by MetroDoloris® (Lille, France). The monitor user interface (Fig. 2) allows visualizing in real time the instantaneous and averaged values of the ANI index (respectively ANI_i in yellow and ANI_a in orange). The different index values are also available in real time through the classical RS-232 monitor serial port.

B – Decision rules for analgesic drugs administration

Since 2008, the Physiodoloris® monitor is used in the orthopedic surgery unit of the Lille University hospital. During these 4 years, we observed and recorded ANI evolutions and reactions on more than 2000 patients during orthopedic surgical procedure under general anesthesia. Thanks to this experience, we determinate several decision rules based on ANI_i and ANI_a analysis in order to help anesthesiologists in the ANI guided anesthesia understanding. In order to regulate analgesic drug administration, we determinate two kind of action:

- ***Infusion flow Changes:*** Increase or decrease the syringe pump infusion rate.
- ***Bolus:*** Infusion rate fast increase during 10 s. Infusion rate returns to its previous value after these 10s.

Each action is followed by a refractory period which shut down the regulation algorithm for several seconds.

Several regulation variables and constants are defined.

<u>*Variables used for regulation:*</u>

- ***ANI_i :*** instantaneous ANI.
- ***ANI_a :*** average ANI.
- ***S_i:*** ANI_i slope (computed on 30 s).
- ***S_a:*** ANI_a slope (computed on 30 s).
- ***InF:*** Syringe pump infusion Flow (in µg/Kg/min).

<u>*Constants used for regulation (set by the user):*</u>

- ***ANI_{max}:*** representing the ANI max value.
- ***ANI_{min}:*** representing the ANI min value.
- ***S_aT:*** representing the S_a threshold
- ***S_iT:*** representing the S_i threshold
- ***InI:*** Infusion Rate increment (in µg/Kg/min).
- ***InF_{min}:*** Minimum infusion rate (in µg/Kg/min).
- ***Inf_{max}:*** Maximum infusion rate (in µg/Kg/min).
- ***BolusI:*** Infusion Flow bolus increment (in µg/Kg/min).
- ***RefP**:* Refractory period (in s)

ANI_{mean} is computed as

$$ANI_{mean} = ANI_{min}+(ANI_{max}-ANI_{min})/2 \qquad (2)$$

The defined rules are established in order to treat both acute pain and global analgesia level changes.

<u>*Acute pain treatment:*</u>

$$\textbf{If}(ANI_i< ANI_{min})\textbf{and}(S_i<-S_iT)\textbf{then}\ \text{Bolus} \qquad (3)$$

Bolus corresponds to an Infusion rate increase of BolusI µg/Kg/min during 10 s. Infusion rate returns to its previous baseline after these 10s.

Each Bolus is followed by a 3*RefP s refractory period.

Analgesia level changes:

- **$ANI_a < ANI_{min}$:**

In this area, we considered that the analgesia is insufficient. This event is treated by increasing the infusion pump rate.

$$\textbf{If}(InF<InFmax)\textbf{and}(S_a<SaT)\textbf{ then } InF = InF+InI \quad (4)$$

- **$ANI_{min} < ANIa < ANI_{max}$:**

In this area, we consider that the patient is comfortable. However, in order to anticipate, we consider the ANI_a slope (S_a) changes in order to regulate the infusion rate.

$$\textbf{If}(ANI_a<ANI_{mean})\textbf{and}(S_a<-S_aT)\textbf{and}(InF+InI<InF_{max})\textbf{ then } InF = InF+ InI \quad (5)$$

$$\textbf{If}(ANI_a> ANI_{mean})\textbf{and } (S_a>S_aT)\textbf{and}(InF- InI>InF_{min})\textbf{ then } InF = InF- InI \quad (6)$$

- **ANIa>75 :**

In certain condition, we can consider that if ANI is too high, ANS doesn't respond to noxious stimuli. This effect could be explained by an ANS morphine overdose which would require an infusion flow decrease.

$$\textbf{If}(S_a>0)\textbf{and}(InF- InI>InF_{min})\textbf{then } InF = InF- InI \quad (7)$$

Each infusion rate change is followed by a RefP s refractory period.

In order to avoid arterial hypotension (SBP<80), we added two rules on systolic blood pressure (SBP).

$$\textbf{If } SBP<90 \textbf{ then } InF = InFmin \quad (8)$$

$$\textbf{If } SBP<80 \textbf{ then } InF = 0 \quad (9)$$

In the case of SBP<80, the regulation algorithm is shut down until SBP recovers a value over 85 mmHg. Rules (8) and (9) have the highest level of priority.

C – Algorithm implementation

In a technical point of view, the system consist on a software ("controller") implemented on a classical personal computer allowing to adapt in real time the syringe pump infusion rate according to ANI_i and ANI_a evolutions. ANI_i and ANI_a values are obtained from the Physiodoloris monitor communication interface and SBP is obtained from the Anesthesia monitor (Datex Ohmeda AS-5, GE Healthcare). The syringe pump (Alaris GH, Cardinal health) and the two monitor are linked to the computer through a Keyspan® 4-port serial to USB adapter. Technical scheme of the system is described on Fig. 3.

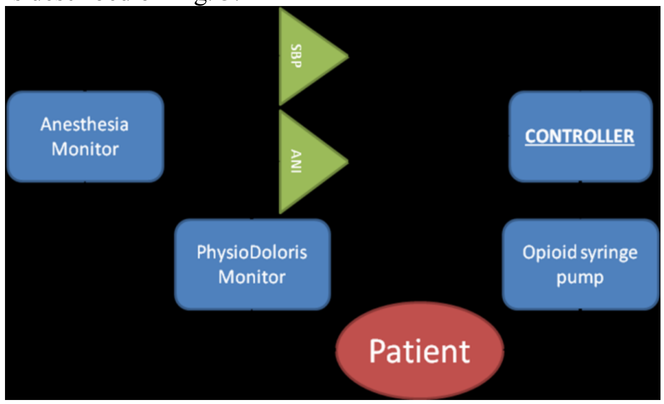

Fig. 3: Automated analgesic drug delivery system technical scheme: Controller collects ANIi, ANIa and SBP through RS-232 interfaces and computes S_i and S_a. Variables are then submitted to rules equations (3) to (9) in order to determinate the infusion flow in µg/Kg/min. According to the patient weight, the controller then computes the infusion rate in ml/h in order to send the rate change command to the syringe pump.

The software also allows users to enter patient characteristic (age, size, weight, ASA) and constants values used for regulation. Thanks to the interactive aspect of the controller, all the predefined constants can be adapted and manually changed during the regulation. Finally, a specific software interface (Fig. 4) allows users to follow the variables evolution, the syringe pump status and the regulation results. Direct syringe pump commands are also available in order to allow the anesthesiologists to manually adapt the syringe pump infusion flow or to shut down the automatic regulation.

Fig. 4: software interface. The right panel shows the regulation variables and the syringe pump resulting infusion rate (in gray). The left panel allow manual control of the syringe pump.

III. Results

The system has been pre-tested on 4 patients planed to undergo general anesthesia for a total hip replacement. Anesthetic protocol comprised Sevoflurane (hypnotic drug) and Remifentanil (analgesic drug) delivered following our decision rules. The Remifentanil concentration was 25µg/ml.

Constants used for regulation has been defined as follow:

- ***ANI_{max}=75***
- ***ANI_{min}=50***
- ***S_aT=7***
- ***S_iT=25***
- ***InI=0.01 µg/kg/min***
- ***InF_{min}=0.05 µg/kg/min***
- ***Inf_{max}=0.6 µg/kg/min***
- ***BolusI= 0.04 µg/kg/min***
- ***RefP=10 s***

Blood pressure was measured every 2.5 minutes.

ANI based regulation showed good results regarding ANI and SBP stability. Indeed, none of the 4 evaluated patients have presented any hypo (<80 mmHg) or hypertensive (>140 mmHg) episodes after the induction of anesthesia and ANI_a has been correctly maintain between the predefined thresholds. Anesthesia duration was about 133±27 minutes with a remifentanil total dose about 1.286±0.111 mg which constitutes a low dose for such a surgery. Fig. 5 shows an example of the regulation result.

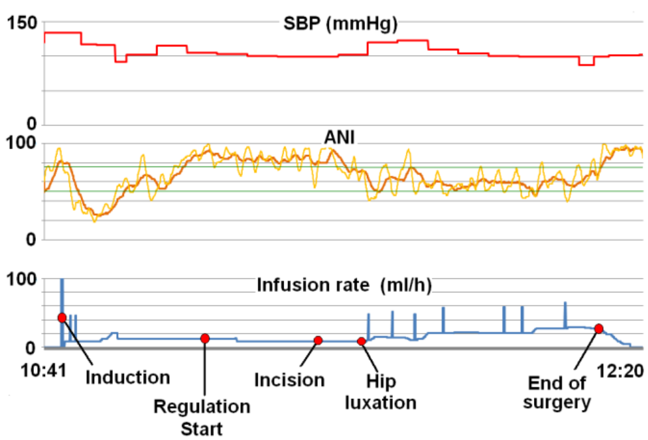

Fig. 5: Automated remifentanil delivery result example.

IV. Conclusion

In this paper, we described a system for automated analgesic drugs delivery guided by ANI. ANI is an index related to the ANS vagal tone. Its ability for the analgesia / nociception balance evaluation has been established during a large number of clinical validations showing the helpfulness of ANI for analgesic drugs delivery. We therefore developed an automatic analgesic drugs administration system based on several decisions rules established regarding our own experience of the use of ANI during surgical procedures under general anesthesia.

Even if preliminary tests on 4 patients under remifentanil showed good preliminary results, the number of tested patients is really low and investigations are still in progress in order to correctly assess the system performances in terms of regulation. A comparative clinical trial needs to be performed in order to evaluate the system potential benefits regarding usual remifentanil administration.

Finally, we suggest that using this system on a large set of patients would allow to determinate the best regulation constants values for each analgesic drug allowing to obtain a set of efficient analgesia regulation models.

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