ANALGESIA NOCICEPTION INDEX ONLINE COMPUTATION AND PRELIMINARY CLINICAL TEST DURING CHOLECYSTECTOMY UNDER REMIFENTANIL-PROPOFOL ANAESTHESIA

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Introduction : during general anaesthesia (GA), the reactions of the autonomous nervous system (ANS) to nociceptive stress are dampened by opioid administration, but opioid overdose can impair hemodynamic status and might induce post operative hyperalgesia. The search for the minimal efficient dose of opioid has become an objective of modern anaesthesia. Up to now, there is no validated, routinely used analgesia monitor. Clinical parameters such as Heart Rate (HR) and Arterial Blood Pressure (ABP) are used to assess the need for opioid, but neither are sensitive or specific of pain and analgesia. Several studies have shown that Heart Rate Variability (HRV) analysis gives information related to the ANS activity [1-2]. The strong influence of anaesthetic drugs over the ANS led some authors to test whether HRV could be used as an anaesthesia global depth measure [3-4], but to our knowledge, none has described a measure of the pain / analgesia balance during GA. HRV is mediated primarily by changing levels of parasympathetic and sympathetic outflow from the central nervous system to the sinoatrial node of the heart. In adults, growing evidence highlights that a high frequency power decrease (0.15 - 0.5 Hz) during unpleasant stimuli or emotions is related with a drop of vagal tone [5]. During surgical procedures in adult patients, HRV is correlated with the balance between the nociceptive stimulus and the level of analgesia [6]. We have previously described and evaluated a pain / analgesia balance measurement algorithm using HRV analysis [7].

In this paper, we present the development of a new monitoring system (PhysioDoloris) based on the previously described technology, giving an original Analgesia Nociception Index (ANI) for nociception / analgesia balance online assessment during GA.

Method
ECG acquisition and ANI computation: the whole online ANI computation process relies on a real time ECG analysis. The 250 Hz digitized ECG is used for R wave detection, automatic filtering [8] and computation of the RR series. The raw RR series is mean centred and resampled at 8 Hz, normalised and then band pass filtered between [0.15–0.50Hz]. When parasympathetic tone is present, each respiratory cycle influences the RR_{HF} series and causes a brief decrease in heart period (figure 1, upper panel). In case of parasympathetic tone decrease, the influence of each respiratory cycle is dampened (figure 1, lower panel) [7].
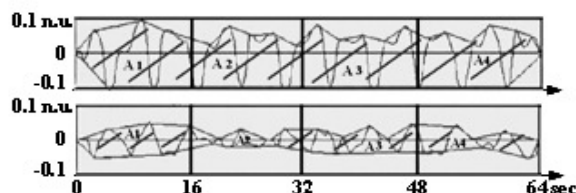

Fig. 1: normalized and filtered RR series in two different states of analgesia/nociception balance during general anaesthesia. A1, A2, A3 and A4 are the areas measuring the respiratory influence in the RR series; upper panel: adequate analgesia; lower panel: light analgesia leading to an increase of HR and ABP.

The relative parasympathetic tone is assessed by computing the area under the normalised RR_{HF} series curve as shown in figure 1 : 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. We defined AUCmin = min(A1,A2,A3,A4). ANI is then computed in order to express the fraction of the total window surface occupied by respiratory influenced RR_{HF} series, which leads to a measure between 0 and 100 : _ANI = 100 * [α*AUCmin+β] / 12.8_
The constant α = 5.1 and β = 1.2 have been determined in order to keep coherent the qualitative visual effect of respiratory influence on RR_{HF} series and the quantitative measurement of ANI.

Preliminary clinical test : after institutional approval, a prototype has been evaluated in a prospective, non interventional clinical trial on patients planned to undergo general anaesthesia for urgent laparoscopic cholecystectomy. All patients gave written informed consent. Anaesthetic protocol comprised propofol and remifentanil delivered by a target controlled device (Orchestra® Base Primea, Fresenius Kabi, France). The surgical and anaesthetic procedures were not altered by inclusion in the study; medical staff was blind to the monitor. After induction of GA, myorelaxation and tracheal intubation, the patient was ventilated in a volume controlled mode. Propofol target was lowered to 2 µg/ml[-1] and afterwards adapted in order to maintain the Bispectral index in the predefined range of [40-60]. Remifentanil target was lowered at 2 ng.ml^{-1} and afterwards adapted in case of hemodynamic reactivity

(HemodReact) defined as a 20% increase in heart rate or systolic blood pressure. ANI, hemodynamic and anaesthetic data were recorded during anaesthesia at predefined time points : (1) after induction of anaesthesia with volume controlled ventilation ; (2) during surgery ; (3) in case of HemodReact ; (4) after end of surgery but still under anaesthesia with volume controlled ventilation. Friedman test for multiple comparisons and Wilcoxon test for paired comparisons were used. A p value of less than 0.0125 was considered significant. Results are presented as median (interquartile).

Results : nine patients were included, aged 32(7) years. Eight patients presented a HemodReact period during anaesthesia. Bispectral index remained stable in the predefined range at 43(10). Systolic blood pressure was significantly higher at HemodReact time points as expected from the study design. ANI was significantly lower during HemodReact time points (table 1), but also during surgery (i.e. before HemodReact) as compared with measurements after induction and after end of surgery. Propofol and remifentanil targets did not vary significantly during these predefined time points.

	Fried-man test	(1) After Induc-tion	(2) During Surgery	(3) Hemod React	(4) After End of Surgery
HR (bpm)	NS	65(9)	65(16)	72(7)	58(21)
SBP (mmHg)	<0.01	95(20)	113(24)	130(8) *	124(25)
BIS	NS	34(12)	31(11)	41(10)	49(16)
ANI (%)	<0.01	88(17)	50(9) *+	40(13) *+	97(22)
prop Ce (μg.ml^{-1})	NS	3.0(0.6)	3.0(0.9)	3.0(0.5)	2.2(1.1)
remi Ce (ng.ml^{-1})	NS	4.0(2.1)	3.6(0.7)	4.3(1.1)	3.0(0.8)

Table 1. Data presented as median (interquartile).
*p<0.01 vs After Induction(Wilcoxon test) +p<0.01 vs After end of surgery(Wilcoxon test)

Discussion : these preliminary clinical results show that ANI seems to be related with the surgical context of the patient: parasympathetic tone was highest when nociception was absent as recorded after induction (1) and after end of surgery (4). Parasympathetic tone decreased when nociception increased during surgery (2), and further decreased (although not significantly) in case of HemodReact (3). A greater number of inclusions is needed to measure the predictive positive values of an ANI decrease. Limitations to ANI measurement are essentially non sinus rythms, non ventilated periods such as during intubation and electric noise produced by the electric knife.

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