

Could Analgesia Nociception Index (ANI) reflect a symptom other than pain in intensive care units?

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▶ **To cite this version:**

Chloé Raimbert. Could Analgesia Nociception Index (ANI) reflect a symptom other than pain in intensive care units?. Human health and pathology. 2021. dumas-03446327

HAL Id: dumas-03446327

https://dumas.ccsd.cnrs.fr/dumas-03446327

Submitted on 24 Nov 2021

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THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement
Par
Chloé RAIMBERT

le Lundi 20 Septembre 2021

TITRE
COULD ANALGESIA NOCICEPTION INDEX (ANI) REFLECT A SYMPTOM OTHER THAN PAIN IN INTENSIVE CARE UNITS?

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Au président du jury, le Professeur Samir JABER

Merci de me faire l'honneur de présider mon jury pour ce jour important et de m'accueillir dans votre service pendant mes 2 ans d'assistanat.

A mon directeur de thèse, le Professeur Gérald CHANQUES,

Merci de nous avoir guidé Lili et moi dans ce travail et d'avoir partagé votre passion pour le bien être des patients, pour la recherche et surtout l'art. Ce fut un honneur de travailler avec vous sur ce projet.

Au Docteur Audrey DE JONG,

Merci de faire partie de mon jury de thèse, de m'avoir tant appris et transmis ta joie de vivre.

Aux personnes qui ont contribué à la réalisation de cette thèse,

A Océane GARNIER,

Merci de t'être autant investi sur notre projet. C'est une très belle rencontre sur le plan professionnel et amical.

Au Professeur Nicolas MOLINARI et Mme Sandrine AKOUETE,

Merci pour votre aide très précieuse pour les statistiques de cette thèse.

A Lili, mon duo de choc pour cette thèse,

Merci d'avoir réalisé ce travail avec moi, d'avoir toujours été au rendez-vous avec le sourire que ce soit pour travailler ou autour d'un verre avec Océane, nous formons une sacrée équipe.

A ceux qui ont participé à ma formation,

Merci à tous les anesthésies réanimateurs ou autres spécialités qui ont pris le temps de me former pendant ces quatre années. Il est impossible de tous vous citer, mais bravo

à l'équipe du CHU de Montpellier et de Nîmes de nous offrir une si bonne formation pendant notre internat.

Merci à tous mes Co-internes d'anesthésie réanimation de la promo 2017,
Chloé la blonde, Yaya, Lulu, Eve, Adri, PB, Toto, Flo, Marine, Ambre, Cléa, Dim, Ben, Hugo, Joris, Pauline, Nicolas, Thomas, Boris, principalement pour avoir partagé la meilleure SFAR de tous les temps dans l'aquarium de Paris.
Et ceux que j'ai rencontré à travers les stages : Chachou, Popo, Caillaboux, Geo, Bourdon, Thomas, Cyp, Ludo, Rimka...

A ceux qui m'ont supporté depuis de nombreuses années maintenant,
Merci à ma famille, à mes parents, à ma sœur et mes grands-parents, Mumu et Domi, Vero et Jean Yves de m'avoir soutenue et poussée pour que je puisse en arriver là aujourd'hui, et de traverser la France pour pouvoir être là à mes côtés pour ce jour important.

Merci à mes copines de Poitiers, Amandine, Clémentine, Lucie et Marilou, ma team de gonz avec qui j'ai tout partagé depuis 10 ans, les meilleurs et les pires moments, les rires et les pleurs, qui habitent au 4 coins de la France (presque du monde selon les mois) et qui arrivent toujours à être présentes, comme aujourd'hui. Merci pour tout.

Merci à Lulu et Thomas, mes jeunes mariés pref' en lune de miel pour ma thèse.

A mes copines rencontrées à Montpellier, Chach ma nouvelle voisine, Chlo la blonde avec qui je ne fais plus qu'un en stage et Manax que j'ai redécouverte ici, et maintenant la queen J, merci pour tous les souvenirs, les virées shoppings et les soirées gonz.

A toute notre team, Chach, Chlo, Manax, Clem, Cons, Jéjé, Melik, Maxou, Richie, Yaya et toute la team de Toulouse, merci pour tous ces week-end de retrouvailles, de festivals et de villa seventies (et de rando...).

A Clément, mon Clem (le meilleur pour la fin), merci de me supporter depuis 7 ans et de me rendre heureuse.

INTRODUCTION

Over the last decades, great efforts have been made to better manage comfort and welfare in critically-ill patients (1).

Suffering and psychological disorders are linked to admissions in intensive care units (ICU) (2–5). Reasons are multiple: anxiety-inducing environment and pathologies, painful procedure of care (6), absence of a day-night cycle, noises, light … These disorders may be associated with short and long-term repercussions in our patients (7). Primarily neuro-psychological disorders include nightmares, reviviscence, and also a real post-traumatic stress syndrome, that will delay the return to social and professional normal life (8).

The development of new strategies to promote comfort while improving cognitive abilities are topical (9). Current guidelines recommend reducing the depth and duration of deep sedation, in order to screen and manage cognitive dysfunction (10).To achieve this double goal (promoting comfort in one hand while avoiding deep sedation in the other hand), research efforts are recommended to develop non-pharmacological analgesic and relaxing techniques that are, by nature, not associated with drug adverse events, especially delirium (10). Several studies have already shown the benefit of using non-pharmacological techniques in intensive care, such as hypnosis (11), music therapy (12,13), massage, cold therapy and relaxation techniques.

Recommended assessment of patient's stressful symptoms is currently based on clinical tools (10). Such tools remain subjective by nature, depending on nurses' education and training, and/or the patient's ability to use tools (14,15). To deal with these issues, several electrophysiological tools have been developed to measure the stress response related to pain in patients unable to report their suffering, for example, in patients who are deeply anesthetized in the operating room, or sedated in the ICU. One of the most studied electrophysiological tools is the Analgesia Nociception Index (ANI). ANI is a mathematical assessment of Heart Rate Variability (HRV), derived from the patient's Electro-Cardio-Graphic (ECG) monitoring. HRV is a physiological response induced by the breathing cycles, driven by the parasympathetic tone and thus, linked to the parasympathetic/sympathetic balance.

ANI provides a number from 0 to 100 through spectral analysis, which is an estimation of the balance between parasympathetic and sympathetic outflows: 100 indicates a high parasympathetic modulation (low stress level = low risk of pain), while 0 indicates an extremely low parasympathetic modulation (high stress level = high risk of pain) (16,17). ANI has shown promising results in patients under general anesthesia during surgery (18), just after surgery in the recovery room (19), as well as in the ICU setting (6,16,20).

However, ANI might not be specific of pain but could rather be a marker of the adrenergic response, as reported in a study enrolling healthy volunteers undergoing non painful but fearful procedures (21). Consequently, it remains interesting to study whether ANI may be more specific to another component of stress and suffering than pain, such as general discomfort, anxiety, dyspnea, lack of rest, or thirst, among the most frequently stressful symptoms reported by patients hospitalized in ICU (22).

The present study is an ancillary, exploratory study of an interventional study designed to evaluate the benefit of different relaxation methods in ICU patients who self-reported their intensity of different stressful symptoms before and after the relaxation sessions, and for who ANI was also continuously monitored. The hypothesis of this ancillary exploratory study was that ANI could be influenced by suffering symptoms other than pain in ICU patients. The primary endpoint was to measure the correlation between ANI and the intensity of overall discomfort and of the five most frequently reported stressful symptoms in ICU: pain, anxiety, dyspnea, thirst and lack of rest. Secondary endpoints were to measure the correlation between the variation of ANI and the variation of each symptom, and to measure the statistical performance of ANI to detect any symptom of at least moderate intensity.

MATERIALS AND METHODS

Ethics approval

The primary study is an interventional randomized cross-over trial aimed at measuring the effect of several relaxation techniques on ICU patients' suffering symptoms. It was approved by an ethics committee [*Comité de Protection des Personnes Sud-Méditerranée-1* (ID-RCB:2016-A00748-43)] according to French law (23), and registered on Clinical Trials NCT04017299.

Patient population

This trial took place in the medical-surgical ICU of the University Hospital of Saint Eloi, Montpellier, France, from July 2019 to December 2019.

All consecutive patients over 18-years admitted to the ICU were eligible if they were non delirious (rated as negative following the Confusion Assessment Method (CAM) for the ICU (24,25), alert according to the Richmond Agitation Sedation Scale (RASS) ≥ 0 (26–28), and with current organ dysfunctions defined by a Sequential Organ Failure Assessment (SOFA) score ≥ 3 (29).

The exclusion criteria were: patient transferred from another ICU, dying patients, patients needing hygiene precautions limiting the access to the headset, patients undergoing psychotic treatment or with previous cognitive impairment, patients hospitalized for brain injury, and according to French law (23): pregnant or breastfeeding women, patients under tutelage or curatorship, patients not registered with the national social security system, or who refused to participate.

Conduct of the primary interventional study and description of the multimedia relaxation tools

Patients were screened daily for eligibility by investigators, and included in the study after written consent. Patients underwent four relaxation sessions consecutively, after randomization of the session order using a cross over design. The randomization was made by the statistic department, and provided via envelopes available for the ICU investigators. The four relaxation sessions are described as follows:

- STANDARD: a relaxation and distraction period of 15 minutes during which a standard usual distraction was chosen by the patient (e.g. television, radio, books…). The bedroom's door was kept closed, and any nursing and medical procedures were prevented during the session.
- MUSIC CARE© (Paris, France): a 15 minutes relaxation session of psychomusical intervention (music therapy) using the MUSIC CARE© device, consisting of U-shaped music score provided through a high-quality audio headset, the style of music being chosen by the patient from the range offered by the software.

- DEEPSEN® VR system (Saint-Didier-au-Mont-d'Or, France): a 15 minutes relaxation session of Virtual Reality (VR), immersing the patient into a series of filmed sequences, using an "all-in-one" headset created by the company. The patient is able to choose the film among four kinds of videos (Norway, mountain countryside, India and Camargue, a quiet seaside in South of France, near Montpellier) using real motion picture, two types of voice (male and female).
- HEALTY MIND® VR system (Paris, France)**:** a 15 minutes relaxation session of VR, immersing the patient into an artificial world created from computer-generated images using a software linked to the Occulus Rift® helmet and a headset. The patient is able to choose four kinds of environments (beach, mountain, snow and Japan) using synthetic motion pictures, breathing exercises and advanced psychological/relaxation principles such as cardiac coherence.

Data handling

After enrollment in the study, a relaxation technique was proposed to the patient at the time of the day that she or he prefers. At baseline, before starting the session, the following vital parameters were recorded from the patient's bedside monitoring: heart rate, blood pressure, respiratory rate and ANI. Only instant-ANI was recorded because it had previously been reported that instant-ANI was more accurate than mean-ANI in ICU patients (20). Then, the patient was asked to report her or his symptoms' intensity using a large visual Numeric Rating Scale (NRS) ranging from 0 to 10 (0 = no discomfort at all; 10 = the most uncomfortable possible symptom) (30). Overall discomfort as well as the five current stressful symptoms were assessed: pain, anxiety, thirst, dyspnea and lack of rest. All parameters were recorded again just after the end of each relaxation session.

Statistical analysis (ancillary study)

1) Study hypothesis

The hypothesis of the present ancillary exploratory study, derived from the primary interventional trial, was that ANI could be influenced by suffering symptoms other than pain in ICU patients. All measurements performed before and after all relaxation sessions were taken into account for the exploratory analysis.

2) Primary endpoint: correlation between ANI and NRS for each of the 6 stressful symptoms reported by the patients (overall discomfort, pain, anxiety, thirst, dyspnea and lack of rest). The non-parametric Spearman's correlation coefficient was calculated to measure the correlation between ANI and NRS. To test the hypothesis of the study, correlation coefficients were compared between each other for each of the 6 symptoms, following the method by Hotelling - William (31).

3) Secondary endpoints:

- correlation between ANI's variation and NRS' variation (Spearman's coefficient).
- ANI's statistical performance to detect a stressful symptom of at least moderate intensity: Receiving Operator Characteristics (ROC) curves were constructed based on the definition of a moderate to severe stressful symptom as a NRS ≥ 4, based on previous studies on pain in ICU patients (30,32) and experts' opinion regarding the management of stressful symptoms in ICU patients (22).

4) Number of patients needed to be enrolled

The number of patients needed to be enrolled was n=60 in the primary interventional trial. As the present ancillary study was exploratory, all patients who were enrolled in the primary study were taken into account for analysis.

5) Presentation of data

Quantitative data are shown as medians and 25th-75th percentiles. For descriptive data regarding the impact of relaxation session on ANI and NRS, the difference between the median value recorded before and after each kind of relaxation session was tested by the Student's t test or the Wilcoxon's U test depending on the distribution of the variable. For all statistical tests, a p value of 0.05 was considered statistically significant. Data were analyzed by independent statisticians using the SAS Enterprise Guide version 9.4 (SAS Institute, Cary, NC).

RESULTS

1) Description of the population

Among the 277 patients admitted to the ICU during the study period, 237 were eligible and 60 were enrolled in the primary trial**. Figure 1** shows the study flow chart. Patients' demographic and medical characteristics were summarized in **Table 1.** The median age was 62 [51-69], and there were a majority of men (67%). The main reasons of admission were liver transplantation (30 %) and other abdominal and or thoracic surgical interventions (28%), respiratory failure (10%), hemorrhagic shock (8%) and septic shock (7%). The median Simplify Acute Physiological Score II (SAPS II) score was 36 [13-82]. Seventy five percent of patient were treated with analgesics, and twenty seven percent with anxiolytics.

During the study, patients were assessed up to eight times, i.e. before and after each of the 4 relaxation sessions: Standard relaxation, Music Care©, Healthy Mind® VR, and Deepsen® VR, accounting for up to 428 assessments of patient's symptoms **(Fig 1).** The number of evaluations is lower after relaxation sessions because of a few cases of early relaxation interruptions. ANI recording could be obtained in 406/428 (95%) assessments. **Table 2** shows the measurement of symptom's intensity (NRS), ANI and other vital parameters, according to the type of relaxation session.

Briefly, ANI was significantly higher after music therapy and virtual reality (suggesting a lower physiological stress after these relaxation sessions), while suffering from lack of rest was significantly lower. Anxiety was significantly lower after virtual reality, and overall discomfort was significantly lower after Healthy Mind® VR only (univariate analysis).

2) Correlation between ANI and the intensity of Overall discomfort, Pain, Anxiety, Thirst, Dyspnea and Lack of rest (primary endpoint).

The correlation between ANI and NRS for each of the 6 symptoms studied (all sessions combined) is shown in **Table 3**. The correlation with ANI was low or very low for each symptom (Spearman's r between -0,01 and -0,13) but statistically significant for overall discomfort (r= -0,13 ; p= 0,007), pain (r= -0,13 ; p= 0,006), anxiety (r= -0,12 ; p= 0,02), and lack of rest (r= -0,11; p = 0,03).

There was a statistically significant difference between the correlation for pain and the correlation for thirst (p= 0.007), and for dyspnea (p= 0.02). There was no significant difference between the correlation for pain and the correlation for overall discomfort (p= 0.97), anxiety (p= 0.75), and suffering from lack of rest (p= 0.67).

3) **Correlation between the variation of ANI, and the variation of the intensity of Overall discomfort, Pain, Anxiety, Thirst, Dyspnea and Lack of rest after relaxation (secondary endpoint).**

The correlation between ANI variation and the variation of each symptom was between 0,02 and -0,25, statistically significant for overall discomfort (r= - 0,25; p= 0,0004) and lack of rest (r= -0,14; p = 0,05). These results are shown in **Table 3.**

4) **ANI performance to detect a stressful symptom (secondary endpoint)**

The ROC curves **(Fig 2)** constructed to report the ANI's performance to detect a stressful symptom as defined by a NRS $\geq$ 4 was close to the central line with Areas Under the Curve (AUC) ranging from 0,58 (95% CI : 0,53 to 0,64) for overall discomfort to 0,50 (95%CI : 0,44 to 0,56) for dyspnea.

DISCUSSION

The main result of this study is that ANI is statistically significantly correlated with pain but also with diverse stressful symptoms reported by ICU patients: overall discomfort, anxiety and lack of rest. The highest correlation was measured with pain, and this correlation was statistically significantly different from the correlation with dyspnea and thirst. However, the correlation with pain was not significantly different from the correlation with overall discomfort, anxiety and lack of rest.

ANI is probably able to measure the general physiological response of stress which is by nature not only specific of pain. ANI was used principally in intensive care and in perioperative anesthesia to evaluate pain, it has never been studied for the management of another symptom. This study is the first one, that evaluated if ANI could be a marker of other symptoms than pain in the ICU setting.

In non medical setting, ANI was assessed in 20 healthy volunteers, reporting a significant decrease in ANI values (suggesting a significant higher physiological stress response), after nociceptive stimuli including a placebo stimulation or even the information of the stimulation alone without any effective stimulation (21). This suggests that even the only impact of fear could modify the ANI. In the same way, Heart Rate Variation (HRV) technology was used to assess the stress response developed by acute care physicians during simulated training of critical intubations (33). HRV was also studied in the context of depression and anxiety in young peoples and found lower HRV in this case compared to control (34). In all, the present study suggests that when ANI reports a low value in ICU patients, any source of discomfort or suffering should be considered, and not only pain, contrary to what ANI is used for usually today in ICU and perioperative anesthesia care. It is paramount to understand that the name of the technology (“Analgesia and Nociception” Index) would make a confusion regarding its use for pain management only, while ANI is rather a marker of general stress response. Similar results have been found in a pediatric study, where HRV was well correlated with two clinical scoring system evaluating postoperative discomfort and pain (35) .

In our study, the correlation coefficients between ANI and the 6 symptoms were low. Similar results have been found in a previous study (20) measuring the correlation between ANI and the Behavioral Pains Scale (BPS). In that study (20), the validity of ANI to measure pain during painful care procedures was demonstrated by discriminant validation method (i.e. significant changes of ANI were demonstrated before and after nociceptive stimulation) (36). This suggests that the correlation between ANI and symptom measurement is not the best appropriate method to assess the validity of ANI. In the present study, ANI changed also significantly before and after relaxation, along with changes in the intensity of stressful symptoms reported by the patients. Even if the correlation between ANI and the symptoms is not the best appropriate method to assess the validity of ANI, it was chosen in the present study in order to compare the association between ANI and each symptom, with an exploratory objective. It should be also note that the ROC curves reported also a low performance of ANI to detect significant stressful symptoms including pain in the present study, contrary to a previous study (37).

This could be explained by the fact that in the original studies performed to measure the association of ANI with pain, the stimulations that were used were much more nociceptive, and variations were therefore much more marked than in the present study. The median NRS before relaxation was less than 4 meaning that patients suffered from light to moderate pain only. Median ANI values were between 62 and 77 before relaxation suggesting that patients had light or moderate physiological stress, as values above 43 are usually reported in the literature to be not associated with suffering (37).

There are several strengths and limitations in the present study. Strengths include the prospective recording of parameters by a research team dedicated to the primary trial. Parameters were chosen based on validation studies (22,27,37,38), international guidelines (26,38) or experts' opinion (22,39). Assessed symptoms were chosen because they were the stressful symptoms the most frequently reported by ICU patients (22). The exploratory analysis of the impact of a symptom on ANI was performed by independent senior statistical methodologists. Finally, this exploratory analysis is the first study investigating the link between ANI and diverse stressful symptoms other than pain in ICU patients.

Regarding the study limits, first, the correlation between ANI and symptoms, including pain, as well as the ROC curves, were small, more than previously reported in studies investigating pain specifically. The primary study was not designed to validate the capability of ANI to assess these symptoms, but as a surrogate and objective marker of the physiological stress response associated with patient's suffering and diverse relaxation techniques. Also, the present study could not assess all factors impacting on ANI for the same reason than the primary study was not calibrated for this endpoint. Finally, if the paramedical or medical team were asked not to enter the room during the relaxation sessions and to prevent monitor's alarms, so that the patients could take full advantage of the relaxation, this was done as far as possible but impossible to realize in 100% of sessions because of the critical nature of patients' illness. ANI values could be impacted by stressful stimulations that were not reported by the measurement of selected symptoms.

CONCLUSION

This ancillary exploratory study suggests that Analgesia Nociception Index (ANI) is not only an electrophysiological assessment of pain as its name would suggest. ANI is probably more a surrogate marker of overall discomfort and other stressful symptoms, especially anxiety and lack of rest. Discomfort is a parameter that is humanely fundamental to take into account in the overall management of critically ill patients, but it is difficult to analyze objectively, as the present study reports low to very low correlation between ANI and symptoms. However, ANI is a tool that can help managing patient's overall suffering, especially patients unable to communicate. The present study suggests than all sources of stress and suffering should be considered when ANI is used in ICU, and not only pain.

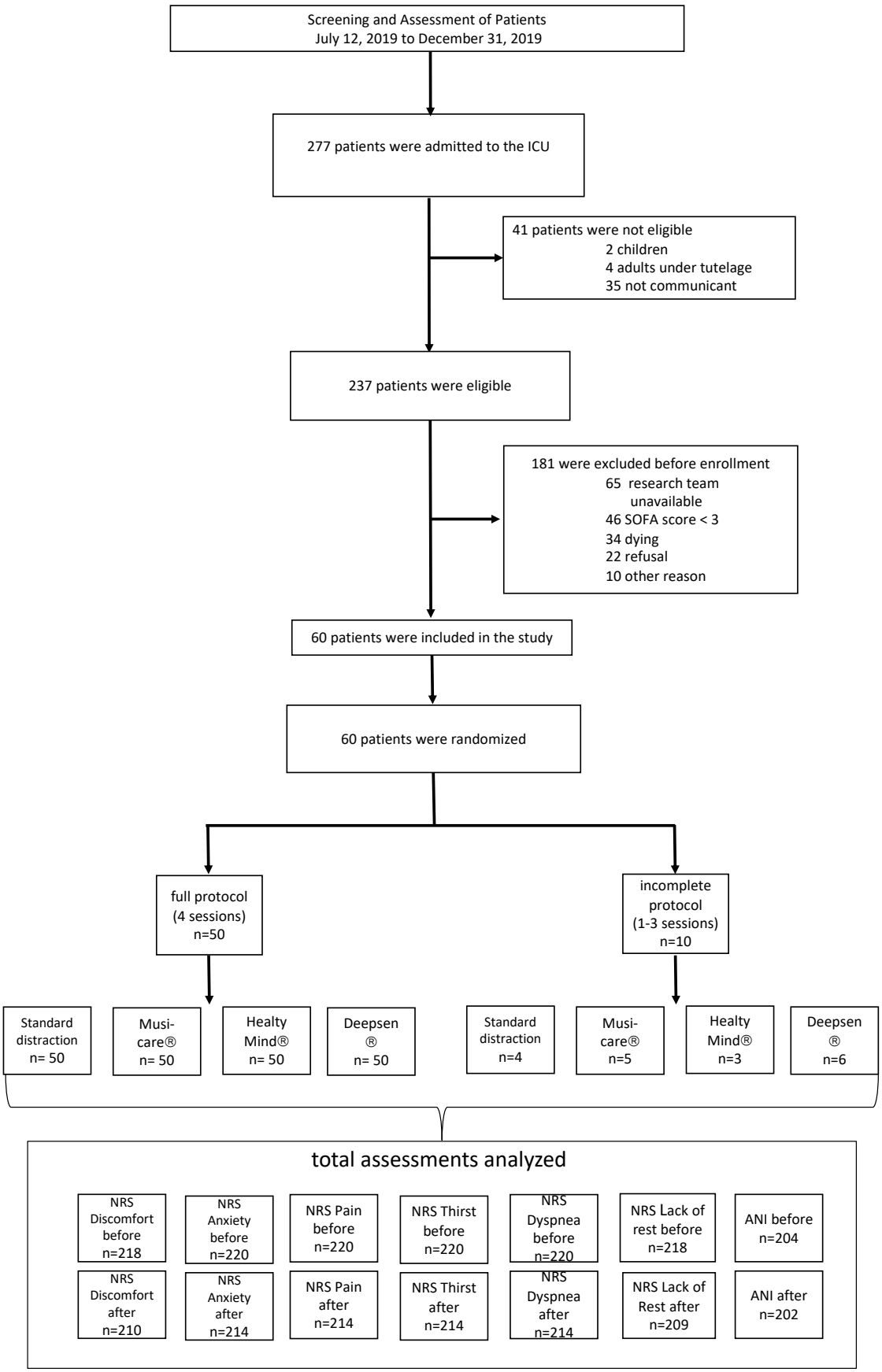


Fig 1 Study Flow Chart.
N are different in total assessments analyzed because of uncomplete sessions

Table 1 - Demographic and medicals characteristics

Medical history and characteristics upon admission to ICU	
Age (yr)	62 [51-69]
Sex (F/M)	20/40
BMI ($kg.m^{-2}$)	27 [22-30]
SAPS II score	36 [28-44]
SOFA score	6 [4-8]
Reason for admission to the ICU	
Liver transplant, n(%)	18 (30%)
Post operative, n(%)	17 (28%)
ARDS, n (%)	6 (10%)
Hemorragic choc, n(%)	5 (8%)
Septic choc, n(%)	4 (7%)
Others, n(%)	10 (17%)
Characteristics upon enrolment into the study	
RASS level	0 [0-0]
CAM-ICU negative, n(%)	60 (100%)
Length of stay in ICU before enrolment (days)	2,7 [1,1-3,6]
Invasive mechanical ventilation before enrolment, n(%)	36 (60%)
Time between extubation and enrolment (hours)	25 [14-42]
Sedation before enrolment, n(%)	36 (60%)
Number of catheters	4 [2-5]
Medical characteristics of patients on the first relaxation session	
Mecanical ventilation, n(%)	1 (2%)
Non invasive ventilation, n(%)	2 (3%)
Hight flow nasal oxygen therapy, n(%)	18 (30%)
Dialysis, n(%)	2 (3%)
Vasopressors, n(%)	7 (12%)
Sedation at enrollment, n(%)	0 (0%)
Analgesic administration at enrollment, n(%)	45 (75%)
Acetaminophen, n(%)	19 (32%)
Nefopam, n(%)	38 (63%)
Tramadol, n(%)	32 (53%)
Opioid, n(%)	2 (3%)
Peridural analgesia, n(%)	3 (5%)
Anxiolytic administration at enrollment, n(%)	16 (27%)

Table 1 Patient and medical characteristics of the 60 patients included for analysis. Continuous data are expressed in median [25th-75th percentiles].

BMI: Body Mass Index; SAPS II: simplified acute physiology score II; SOFA: Sequential Organ Failure Assessment score; RASS: Richmond Agitation-Sedation Scale; CAM-ICU: Confusion Assessment Method for the ICU; ARDS: Acute Respiratory distress syndrome

Table 2

Symptoms and vital parameters depending on the type of distractions

	Type of relaxative techniques							
	STANDARD		MUSIC CARE®		VR DEEPSEN®		VR HEALTY MIND®	
Symptoms								
NRS Overall Discomfort								
BEFORE	4	[2;6]	4	[2;6]	5	[2;6]	4	[2;6]
AFTER	4	[2;5]	2,5	[1;5]	4	[1,5;5]	2	[0;5]
p		*0,27*		*0,06*		*0,21*		***0,02***
NRS Pain								
BEFORE	2	[0;5]	2	[0;5]	3	[0;5]	2,5	[0;5]
AFTER	2	[0;5]	1	[0;5]	2	[0;4]	1	[0;4]
p		*0,7*		*0,45*		*0,3*		*0,12*
NRS Anxiety								
BEFORE	2,5	[0;5]	3	[0;5]	3	[0;5]	3	[0;5]
AFTER	2	[0;4]	2	[0;5]	1	[0;4]	1,7	[0;4]
p		*0,52*		*0,32*		***0,03***		***0,05***
NRS Thirst								
BEFORE	6	[1;9]	6	[1;8]	5	[1;8]	4	[0;7]
AFTER	6	[0;8]	5	[1;8]	4	[0;8]	4	[0;6]
p		*0,68*		*0,53*		*0,38*		*0,93*
NRS Dyspnea								
BEFORE	1,5	[0;5]	2	[0;5,5]	2	[0;5]	2	[0;4]
AFTER	1	[0;4]	1	[0;4]	2	[0;5]	0,5	[0;4]
p		*0,89*		*0,13*		*0,44*		*0,5*
NRS Lack of rest								
BEFORE	4	[2;6]	5	[2;7]	5	[3;8]	5	[3;8]
AFTER	4	[1;6]	4	[0;5]	2	[1;5]	3,5	[2;5]
p		*0,49*		***0,05***		***< 0,01***		***0,02***
Vital parameters								
ANI								
BEFORE	62	[48;85]	66	[56;82]	72	[53;80]	67	[51;80]
AFTER	69	[51;82]	82	[65;93]	80	[70;98]	91	[70;98]
p		*0,45*		***< 0,01***		***< 0,01***		***< 0,01***
Heart Rate (/min)								
BEFORE	89	[81;102]	88	[80;102]	87	[78;99]	88	[77;100]
AFTER	92	[79;102]	85	[81;101]	84	[74;98]	92	[80;97]
p		*0,88*		*0,68*		*0,51*		*0,69*
Respiratory Rate (/min)								
BEFORE	21	[18;24]	20	[17;26]	20	[17;25]	21	[16;27]
AFTER	22	[18;27]	19	[15;24]	21	[17;26]	20	[16;24]
p		*0,74*		*0,34*		*0,81*		*0,14*
Systolic blood Pressure (mmHg)								
BEFORE	134	[120;144]	128	[117;154]	136	[121;151]	134	[118;146]
AFTER	133	[119;146]	127	[113;143]	137	[120;151]	131	[115;148]
p		*0,99*		*0,51*		*0,86*		*0,82*
Diastolic Blood Pressure (mmHg)								
BEFORE	72	[65;82]	71	[62;82]	70	[62;81]	73	[65;82]
AFTER	72	[64;79]	66	[61;77]	75	[61;84]	71	[62;81]
p		*0,52*		*0,18*		*0,38*		*0,65*

Table 2 The values correspond to a rating from 1 to 10 on a numerical scale, were 0 is the best and 10 the worst intensity, and are expressed in median [25th-75th percentiles]. The p value was calculated via Mann Whitney test for non-parametric values and via Student test for parametric values.

Table 3

Correlation ANI - NRS of Overall Discomfort, Pain, Anxiety, Thirst, Dyspnea and Lack of Rest

	ANI/NRS Overall Discomfort	ANI/ NRS Pain	ANI/ NRS Anxiety	ANI/ NRS Thrist	ANI /NRS Dyspnea	ANI / NRS Lack of Rest
Correlation between ANI (before/after) and NRS (before/after) on all sessions						
Nb	398	404	404	404	404	397
r = Spearman's Correlation Coefficient	-0,13	-0,13	-0,12	0,07	-0,01	-0,11
p	***0,007***	***0,006***	***0,02***	*0,13*	*0,78*	*0,03*
Correlation between ANIi variation and NRS variation on all sessions						
Nb	193	198	198	198	198	191
r = Spearman's Correlation Coefficient	-0,25	-0,11	-0,06	0,02	-0,09	-0,14
p	***0,0004***	*0,13*	*0,43*	*0,74*	*0,18*	***0,05***
Correlation between ANI variation and NRS variation with Healthy Mind VR						
Nb	51	52	52	52	52	52
r = Spearman's Correlation Coefficient	-0,31	0,07	-0,13	-0,05	-0 ,06	-0,11
p	***0,02***	*0,59*	*0,33*	*0,7*	*0,67*	*0,42*

ANI: Analgesia Nociception Index ; NRS: Numerating Rate Scale; VR: Virtual Reality

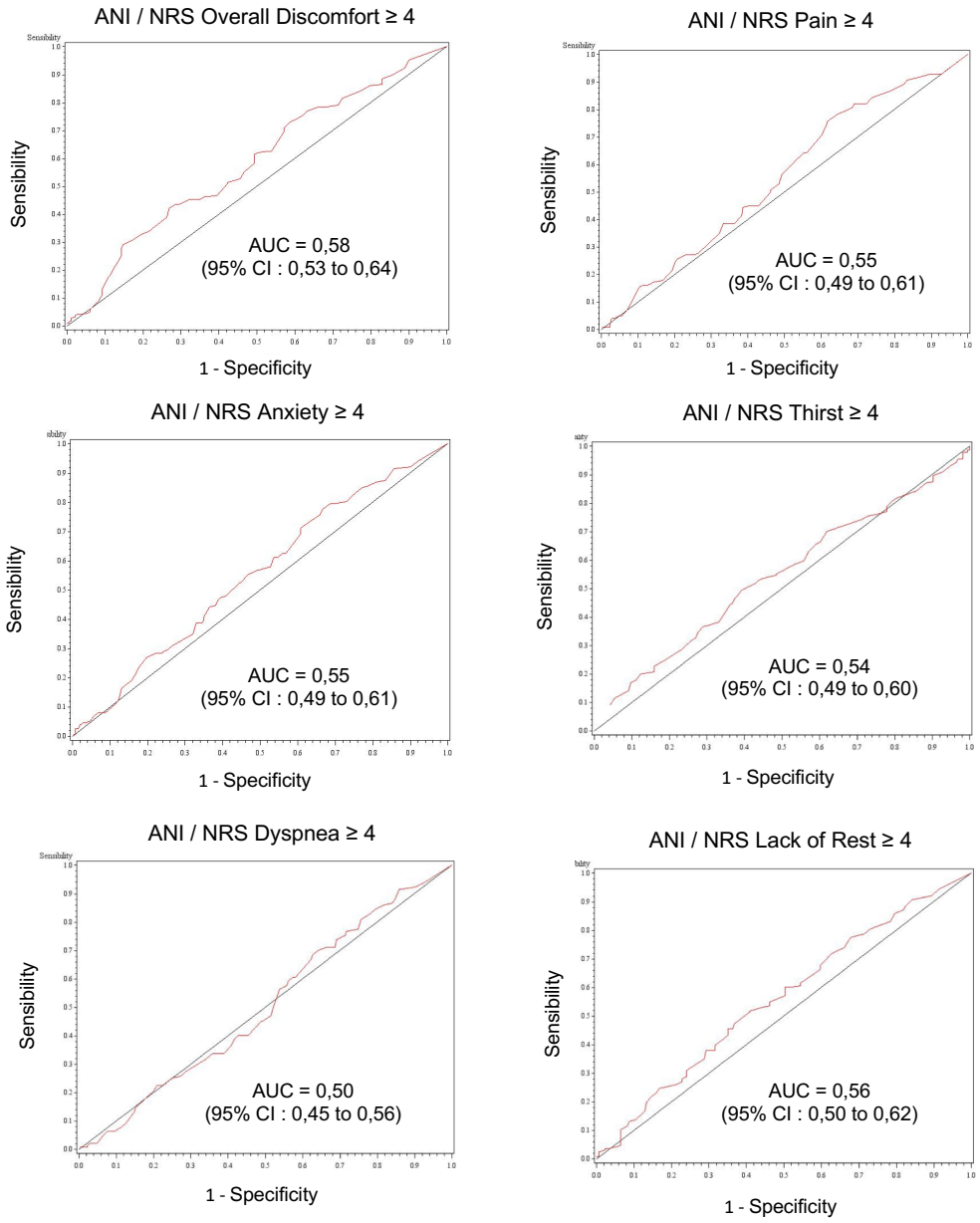


Fig 2 Reveiver Operating Characteristics (ROC) curves for ANI associated with Overall Discomfort, Pain, Anxiety, Thirst, Dyspnea and Lack of Rest defined by a NRS ≥4.
ANI, Analgesia Nociception Index; NRS, Numerating Rate Scale; AUC, Area under the Curve

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SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

ABSTRACT

Introduction: The management of the comfort of patients in intensive care is fundamental because of the invasive nature of the care and the criticism of the situation which is associated with many states of post-traumatic stress in surviving patients. The Analgesia Nociception Index (ANI) is a tool currently used to monitor pain, ranging from 0 (predominant sympathetic tone, maximum pain) to 100 (predominant parasympathetic tone, no pain). In this ancillary study of an interventional study evaluating different relaxation techniques, we explore the association between ANI and different symptoms of suffering, with the hypothesis that ANI is not a specific measure of pain.

Methods: Discomfort, pain, anxiety, dyspnea, thirst and lack of rest, which are the main symptoms associated with suffering in intensive care, were measured as well as ANI before and after 4 periods of randomized 15-minutes relaxation: standard relaxation, Music Care© music therapy, Deepsen® virtual reality (VR) headset (real images) or Healthy Mind® (synthetic images). The primary outcome was the correlation between ANI values and the 0-10 numerical scales measured by the Spearman coefficient.

Results: 404 evaluations were analyzed in 60 patients. ANI was significantly correlated with pain ($r = -0.13$; $p = 0.006$), discomfort ($r = -0.13$; $p = 0.007$), anxiety ($r = -0.12$; $p = 0.02$) and lack of rest ($r = -0.11$; $p = 0.03$), but not thirst or dyspnea. There was a significant difference between the ANI / pain correlation and the ANI / thirst and dyspnea correlation, but the difference was not significant between the ANI / pain correlation and the ANI / discomfort, anxiety and lack of rest correlation ($p > 0.7$; Hotelling - William method)

Conclusion: ANI is not only as the name suggests a marker of pain and nociception, but rather a marker of more general suffering, including other symptoms of stress.

RESUME

Introduction : La prise en charge du confort des patients en réanimation est fondamentale au vu du caractère invasif des soins et de la criticité de la situation qui est associée à de nombreux états de stress post traumatique. L'Analgesia Nociception Index (ANI) est un outil utilisé pour monitorer la douleur, s'échelonnant de de 0 (tonus sympathique prédominant, douleur maximale) à 100 (tonus parasympathique prédominant, absence de douleur). Dans cette étude ancillaire d'une étude interventionnelle évaluant différentes techniques de relaxation, nous explorons l'association entre l'ANI et différents symptômes de souffrance, dans l'hypothèse que l''ANI ne soit pas une mesure spécifique de la douleur.

Méthodes : L'inconfort, la douleur, l'anxiété, la dyspnée, la soif et le manque de repos, qui sont les principaux symptômes associés à la souffrance en réanimation, ont été mesurés de même que l'ANI avant et après des 4 périodes de relaxation de 15 min ordonnées de manière randomisée : relaxation standard, musicothérapie Music Care©, casque de réalité virtuelle (VR) Deepsen® (images réelles) ou Healthy Mind® (images synthétique). Le critère de jugement principal était la corrélation entre les valeurs d'ANI et les échelles numériques 0-10 mesurée par le coefficient de Spearman.

Résultats : 406 évaluations ont été analysées chez 60 patients. L'ANI était corrélée significativement à la douleur (r= -0,13 ; p= 0,006), l'inconfort (r= -0,13 ; p= 0,007), l'anxiété (r= -0,12 ; p= 0,02) et au manque de repos (r= -0,11 ; p = 0,03), mais pas à la soif ni à la dyspnée. Il existait une différence significative entre la corrélation ANI/douleur et la corrélation ANI/soif et dyspnée, mais la différence n'était pas significative entre la corrélation ANI/douleur et la corrélation ANI/inconfort, anxiété et manque de repos (p> 0.7 ; méthode de Hotelling - William)

Conclusion : L'ANI n'est pas seulement comme son nom l'indique un marqueur de la douleur et de nociception, mais plutôt un marqueur de souffrance plus globale, incluant d'autres symptômes de stress comme l'inconfort général, l'anxiété, et le manque de repos. En cas de valeur basse mesurée avec l'ANI, tout source potentielle de stress et de souffrance doivent être recherchée et pas seulement la douleur.

Mots Clés (8) : Analgesia-Nociception-Index, Réponse physiologique de stress, Douleur, Anxiété, Réanimation Thérapeutiques non pharmacologiques, Musicothérapie, Réalité virtuelle