MDMS
Mdoloris Medical Systems

The Analgesia Nociception Index technology

MD/QUA/EN52.ANI (EN)

When Innovation beats Pain.


When Innovat
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ion Beats Pain.

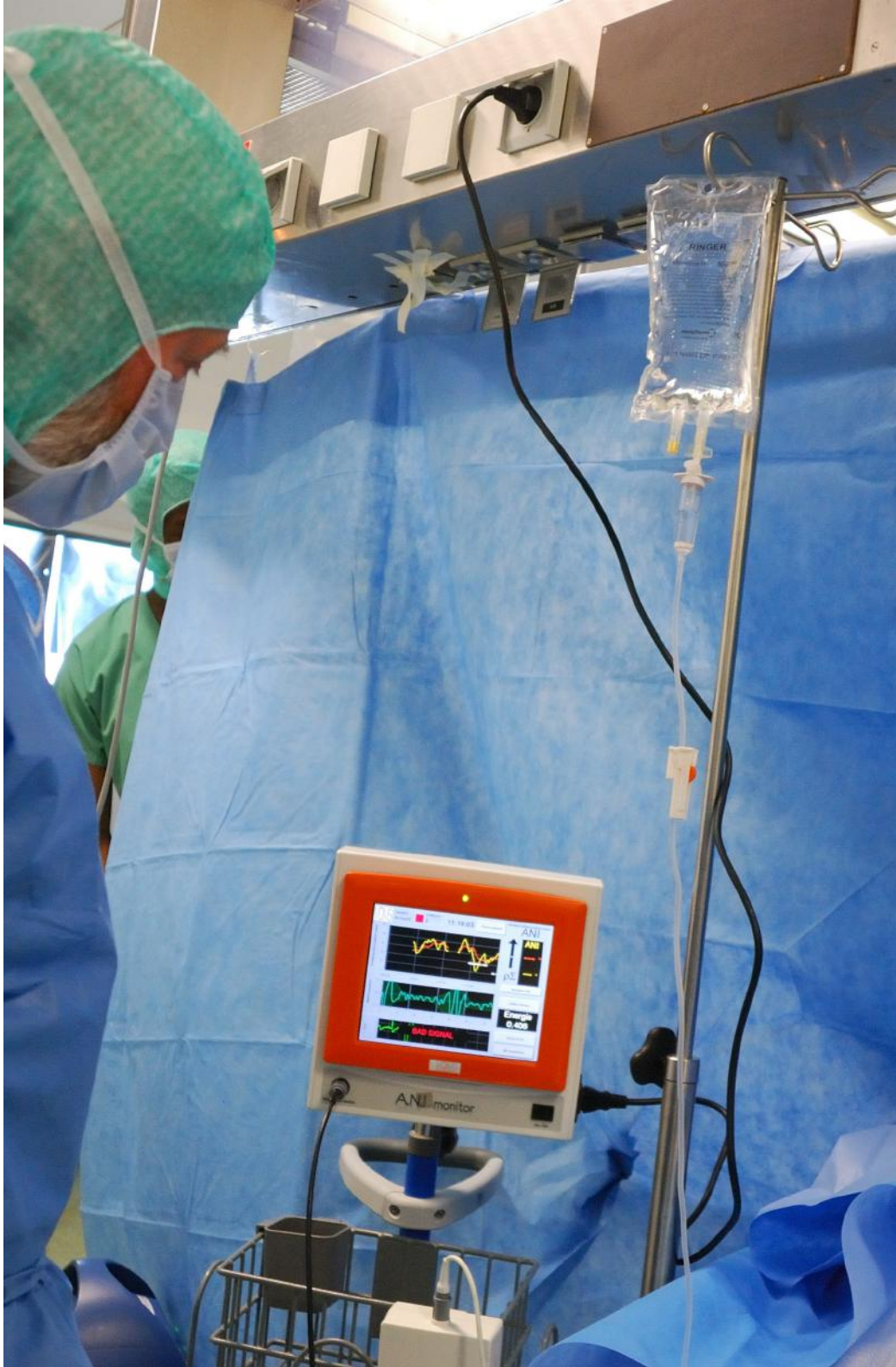
"Finding an objective pain monitoring is an increasing need during the perioperative time. Measuring the parasympathetic tone can help clinicians to deal with it."

Which SIGNAL should be analysed to measure PAIN?

Numerous studies show that the analysis of Respiratory Sinus Arrhythmia allows us to open a window into the autonomic nervous system (ANS), which is influenced by nociception. Mdoloris Medical Systems (MDMS) develops, manufactures and markets technologies which reflect variations in a patient's nociception/antinociception balance and which have been validated to date by an increasing number of scientific publications.

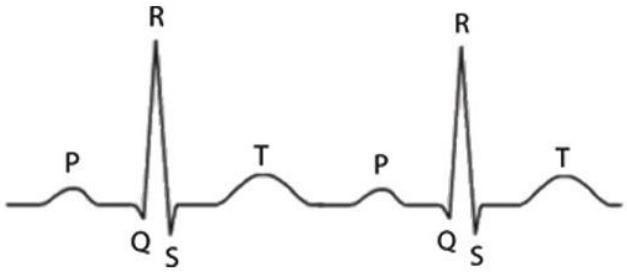
Physiological mechanisms related to nociception and to its removal are located at various subcortical levels of the brain. MDMS aims to provide doctors with a non-invasive and user-friendly monitoring system which offers a continuous and reliable index of nociception and antinociception treatments. MDMS monitors only require an electrocardiogram (ECG) as an entry point.

Analgesia Nociception Index (ANI®) technology is unique in using the sympathovagal balance in order to measure nociception and antinociception. In addition to being a nociception monitoring system, ANI® technology also monitors the parasympathetic tone, which provides information about the patient's comfort, i.e. the appearance of pain or stress.



The ECG analysis

The calculation of the Analgesia Nociception Index relies on obtaining the series of R-R time intervals in order to measure the influence of breathing on the heart rate: Each inspiratory cycle is associated with a short decrease in parasympathetic tone, which results in a brief shortening of R-R intervals. The clinical value of heart rate variability (HRV) analysis first appeared in 1965 when Hon and Lee noticed that fetal distress was preceded by a change in R-R intervals before an alteration in heart rhythm. Around 1970, Ewing and coll. developed simple tests using variations of R-R intervals on short periods to detect dysautonomia in diabetic patients. In 1977, Wolf and coll. showed that a reduction in heart rate variability after a myocardial infarction was associated with a lower survival rate. In 1981, Akselrod and coll. used spectral analysis of the R-R series to quantify cardiovascular control.

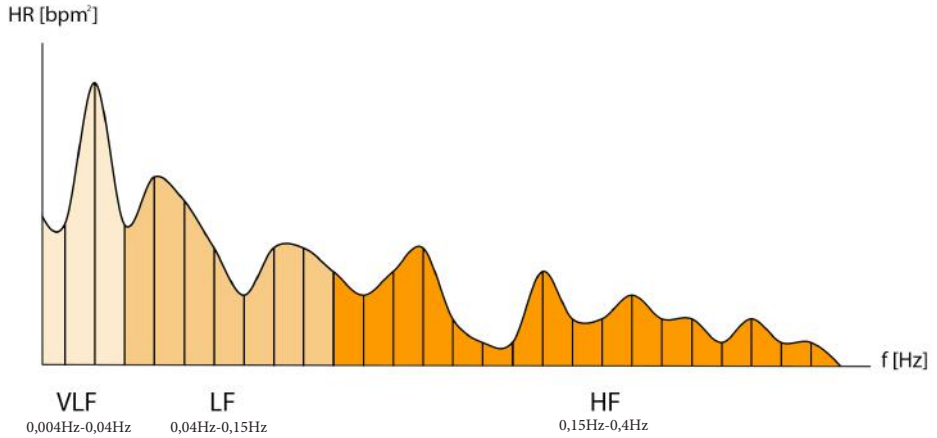


From ECG to ANI®

"Short term" fluctuations in heart rate variability reflect the state of the sympathetic and parasympathetic systems.

Instant modulation in heart rate caused by the opposite effects of sympathetic and parasympathetic nervous systems can be measured using spectral analysis: The high frequency (HF) element [0.15 – 0.4 Hz] is only related to parasympathetic activity, while the low frequency (LF) content [0.04 – 0.15 Hz] is mainly influenced by both sympathetic and parasympathetic activities. Thermoregulation and baroreflex influence the LF and very low frequencies (VLF) [0.004 – 0.04 Hz].

Respiratory movement represents an important part of HF heart rate modulation, whose effects on heart rhythm are described as "Respiratory Sinus Arrhythmia": The heart rate increases slightly with each inspiratory cycle because of a brief decrease in parasympathetic activity.



Spectral Analysis of the autonomic nervous system

Detection of the R wave on the ECG signal allows us to precisely measure the time between two consecutive heart beats (R-R interval), expressed in milliseconds. The resulting RR series are filtered in real-time thanks to a detection algorithm which prevents potential artifacts (e.g. extrasystoles) interfering with the analysis of the RR series.

Each RR series is then re-sampled at 8 Hz and isolated in a temporary window of 64 seconds. The average heart rate over that period is subtracted from the RR series as follows: the average value M of R-R intervals in each 64 second window is subtracted from each sample: RRi = (RRi – M). The RR series (RRi), is then considered as a 512 point vector, normalized using its vector norm S.

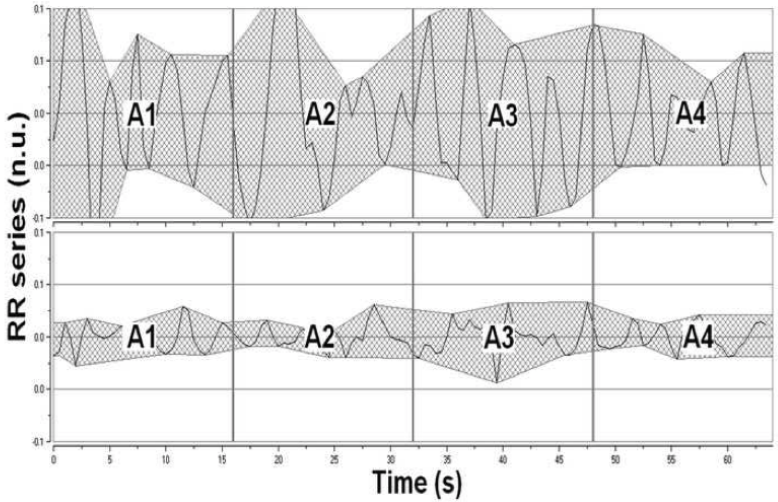
Many studies have shown that pain and/or anxiety induce sympathetic activation which can be measured by HRV analysis as an increase in the LF spectral content (sympathetic and parasympathetic) and a decrease in the HF spectral content (parasympathetic). Therefore, filtering the RR series between 0.15 and 0.4 Hz only contains the parasympathetic influence, mainly mediated by Respiratory Sinus Arrhythmia.

The ANI then measures different surfaces in the RR series: The automatic detection of maximum and minimum levels, the delimitation of the upper and lower envelopes and the calculation of the four sub-surfaces A1, A2, A3 and A4, each lasting 16 seconds, measured between the lower and the upper envelopes in the RR series.

AUCmin (Area Under the Curve minimum) is defined as the smallest value between the four A1, A2, A3 and A4 surfaces. The Analgesia Nociception Index® (ANI®) is then calculated as follows:

$$ANI = 100 * [\alpha * AUCmin + \beta] / 12,8$$

where $\alpha = 5,1$ and $\beta = 1,2$ have been determined in order to maintain the coherence between the visual effect of the influence of respiration on the RR series and the ANI® index.



Respiratory pattern on the ANI Monitor

Why use the ANI®?

The monitor can be used with unconscious as well as conscious patients. With unconscious patients under general anaesthesia, the ANI range [50-70] relates to adequate analgesia, which means that opioid antinociception is adequate and that the parasympathetic activity is mildly predominant over sympathetic activity.

When the ANI value falls below 50, if nociception persists, the occurrence of a hemodynamic response within the following 10 minutes is very likely (80% probability when the curve is under 40 and 100% probability when the curve is under 30). Anaesthetists can use this information in order to avoid a hemodynamic response and increase opioid analgesia. *

In cases where the ANI value rises above 70, opioid overdose is likely. Practitioners can therefore avoid using additional opioid analgesia and avoid the side effects of an opioid overdose such as:

- **longer time of recovery**
- **nausea, vomitting in PACU**
- **bradycardia**
- **respiratory failures**
- **post operative hyperalgesia****
- **dizziness**
- **constipation**
- **delirium*****
- **hypotension**
- **hallucinations******
- **stimulates cancer progression *******

* Boselli et al, Minerva Anestesiologica, 2014
** Fletcher et al; BJA, 2014
*** Krenk et al, BJA, 2012
****The Joint Commission, Issue 49, August 8,2012
***** Nguyen et al, BJA, 2014

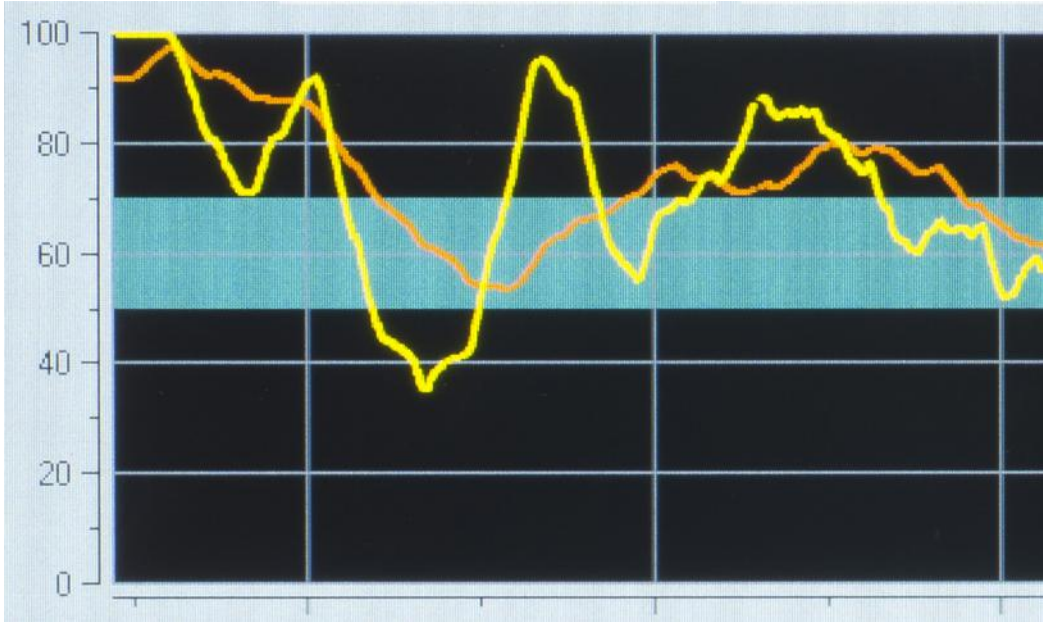
How to interpret the ANI?

Under general anaesthesia, three main ANI ranges have been identified: The 50-70 range, the <50 range and the >70 range. We recommend using the ANIm (the value and the orange curve) as follows:

- The >70 range corresponds to either an opioid overdose or to a time when nociception is clearly reduced.

-The [50-70] range is the most important. It corresponds to adequate opioid analgesia. The goal is to maintain the orange curve in this range during surgery.

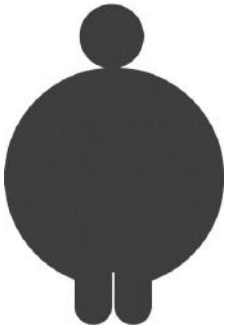
-The <50 range corresponds to an excess of nociception. This range indicates that opioid analgesia can be increased if nociception persists.



Screenshot of the ANIm and ANIi window of the ANI Monitor

For WHO?

Elderly people, very sensitive to opioids overdose, to bradycardia risk and to hypotension



Obese patients, whose distribution volumes are modified compared to others. Most of clinicians who are using the ANI® have reduced the opioids doses from 30% to 60% compared to the initial doses delivered to these patients

Children

Drug addict patients

Non communicating patients or bedridden

Long time surgery >3h, to make sure that the opiod titration is personnalized, avoiding the side effects of over and under dosage.

LIMITS of use

Drugs or any situation which interferes with the parasympathetic reflex loop:

- Apnea (interrupts the loop between bronchial stretch receptors and vagus nerve nucleus)

- Atropine (anticholinergic whose blocking action on the sinus node makes it improper to measure the vagus nerve influence). The ANI® is not interpretable during around 20 minutes after injection depending on the pharmacocinetic effect. However, as long as the energy value is within normal range [0,05-2,5], ANI® is interpretable.

- Ephedrine (indirect sympathetic stimulation); the ANI® is not interpretable during around 10 minutes after injection, except if the energy value is within normal range.

- A sinusal rhythm is needed (e.g. cardiac arrhythmia by atrial fibrillation of more than 9 minutes is a limit)

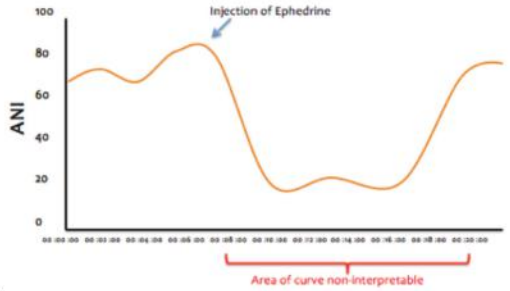
- Extracorporeal circulation

- Catecholamines: the ANI® is only interpretable when the Energy parameter is within the range of [0,05-2,5]

Examples of INTERACTIONS

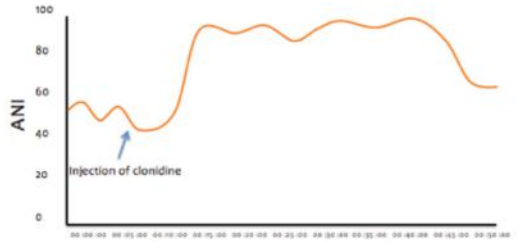
Injection of Ephedrine:

As a result of the sympathomimetic effect of ephedrine, the ANI falls drastically and stays low as far as the molecule is active (around 10 minutes). The Energy drops below 0,05 meaning that the ANI is not interpretable during this period.



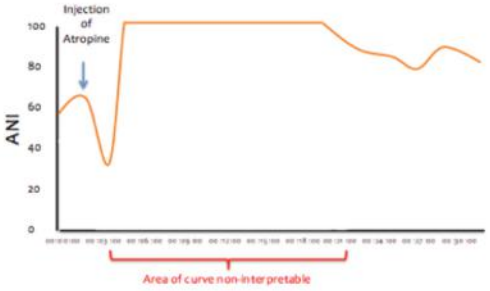
Alpha-2-agonists (eg Clonidine):

The Alpha 2 agonists are sympatholytics drugs which can increase the ANI values (for example in the case of clonidine). However, the cinetic fluctuations of the ANI® are still relevant.



Atropine injection:

Atropine acts as a parasympatholytic, which leads to a fall of the ANI but unlike ephedrine, the curve will cap at 100 because of a mathematical artifact.

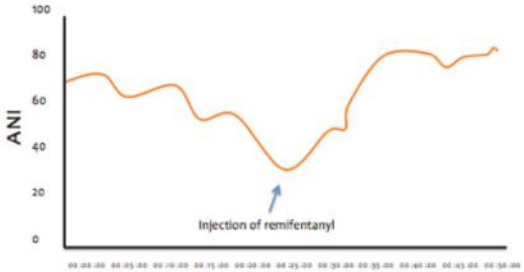


Intubation:

As intubation is performed during apnea, the Heart Rate Variability disappears.

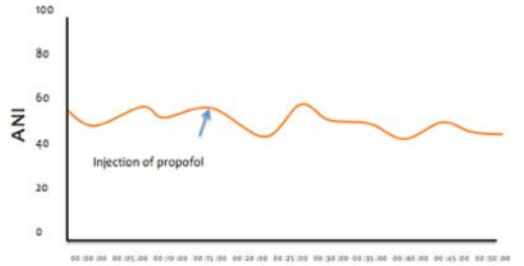
Remifentanil, sufentanil, ... :

Injecting opioids leads to an increase of the ANI curves by a modification of the nociception/antinociception balance. Differences in the ANI's behavior mainly depend on the context and on the half life of each molecule.



Propofol, sevoflurane, desflurane, isoflurane:

Anesthetic agents have no impact on ANI values.



Beta blockers:

Beta blockers have no impact on the ANI values because it does not interfere with the heart rate variability but with the heart rate variation.

Ketamine injection at anti-NMDA dose:

Ketamine at anti-NMDA dosage in order to prevent postoperative hyperalgesia have no impact on the ANI.

Clinical studies with ANI in conscious and anesthetized patients

	Design of the study	n	Results	Conclusion	References
Awake patients	During labor ANI and NRS during and between uterine contractions	45	Negative linear relationship between ANI and NRS (p=-0.18)	Good correlation between ANI and NRS during labor	Le Guen M et al., Int J Obstet Anesth, 2012.
	ANI and NRS in PACU after general anesthesia, ANI performance for the pain detection (NRS > 3) in PACU	200	Negative linear relationship between ANI and NRS (r^2=0.41) Good pain detection performance in PACU (AUC ROC=0.86) ANI ≤57 Se =78% and Sp=80%	Good correlation between ANI and NRS during immediate postoperative pain	Boselli E et al., Br J Anaesth, 2013.
	ANI and NRS in PACU after general anesthesia with sevoflurane and fentanyl, ANI performance for the pain detection (NRS ≥ 6) in PACU	120	Weak negative linear relationship between ANI and NRS (p=-0.075)	The use of sevoflurane and/or fentanyl could interfere with the ANI interpretation	Ledowski T et al., Br J Anaesth, 2013.
	ANI variations and VAS scores during physical therapy procedure, 24 and 48 hours	12	Decrease of ANI when VAS > 30. Good pain detection (AUC ROC=0.76, ANI Se=76%, SP=78%)	ANI can be used for pain management during physical therapy	De jonckheere J et al., Conf Proc IEEE Eng Med Biol Soc, 2014.
	ANI variations during the projection of a violent film, comparisons between controls and anorexia nervosa patients	24	Decrease of ANI during the projection, with a delay anorexia nervosa patients	ANI is decreased after an unpleasant emotion	Rommel et al. Psychiatry Res, 2015.

	Design of the study	n	Results	Conclusion	References
Anesthetized patients	Pediatric (8 ± 5 years old) ANI variations after tetanic stimulation (50 mA, 50 ms, 5s) with desflurane and different concentrations of remifentanil (0.04 to 0.2 µg/kg/min)	12	Decrease of ANI after tetanic stimulation, more important with the lowest remifentanil concentration	ANI is decreased after tetanic stimulation during pediatric surgery and seems more sensitive than the skin conductance	Sabourdin N et al., Paediatr Anaesth, 2013.
	Pediatric (2 – 16 years old) Locoregional anesthesia before surgery and sevoflurane only, ANI performance for the detection of a locoregional anesthesia failure (increase HR ≥ 10 % 2 min after incision)	58	ANI performance for the detection of locoregional anesthesia failure: AUC ROC=0.75 (0.61 - 0.88) ANI ≤ 51, Se=79% and Sp=62%	ANI is able to detect locoregional anesthesia failure	Migeon A et al., Paediatr Anaesth, 2013.
	Intravenous anesthesia with propofol and remifentanil ANI variations after tetanic stimulation (50 mA, 60 Hz, 30 s) at different targets of remifentanil (0., 2 and 4 ng/mL)	25	Decrease of ANI after tetanic stimulation	ANI is efficient for the detection of pain response during surgery under general anesthesia	Gruenewald M et al., Br J Anaesth,2013

	Design of the study	n	Results	Conclusion	References
Anesthetized patients	General anesthesia under sevoflurane and remifentanil ANI variations after tetanic stimulation (50 mA, 60 Hz, 30 s) at different targets of remifentanil (0, 2 and 4 ng/mL),	24	delta ANI significantly indicated patient's movement after tetanic stimulation (Se=77% and Sp=84%)	ANI is efficient for the detection of pain response during surgery under general anesthesia	Gruenewald M et al., Minerva Anestesiol, 2014.
	Intravenous anesthesia with propofol and remifentanil Abdominal laparoscopic surgery ANI variations at different times and after tetanic stimulation (80 mA, 100 Hz, 5 s)	15	Decrease of ANI during different nociceptive stimuli.	ANI is able to detect painful stimulations under general anesthesia	Jeanne M et al., J Comput, 2012.
	Intravenous anesthesia with propofol and sufentanil bolus Knee arthroplasty ANI performance for the detection of peroperative hemodymanic reactivity (increase > 20% HR and/or BP in 5 min)	27	Good performance for the hemodynamic reactivity (AUC ROC=0.92) ANI ≤ 63 Se=80% and SP=88%	A drop of ANI values predicts a hemodynamic response lead by pain	Jeanne M et al., Clin J Pain, 2014.
	TIVA propofol and remifentanil Laryngoscopy suspension procedures ANI performance for the prediction of hemodynamic reactivity and sedation.	50	Good performance for the hemodynamic reactivity (AUC ROC=0.88) ANI ≤ 55, Se=88% and Sp=83%	The prediction of hemodynamic reactivity is slightly reduced by the use of sevoflurane and/or fentanyl	Boselli et al. Minerva Anestesiol, 2015.
	General anesthesia with sevoflurane and fentanyl General or orthopedic surgery ANI variations at different times PK for the prediction of increase HR and Systolic BP >10%	30	Decrease of ANI after nociceptive stimulation Increase of ANI after fentanyl administration Modest prediction probability for increase HR (PK=0.61), increase BP (PK=0.59)	The prediction of hemodynamic reactivity is slightly reduced by the use of sevoflurane and/or fentanyl	Ledowski T et al., Acta Anaesthesiol Scand, 2013.
	General anesthesia with halogen and remifentanil ORL surgery or inferior limb orthopedic surgery ANI performance before extubation for the prediction of immediate postoperative pain (NRS >3)	200	Negative linear relationship ANI before extubation and NRS in PACU (r^2=0.33) Good ANI performance for the prediction of NRS > 3 (AUC ROC=0.89) ANI ≤ 50, Se=86%, Sp=86%	ANI values at the end of the surgery are able to predict postoperative pain	Boselli E et al., Paris:SFAR, 2014.
	General anesthesia with sevoflurane and fentanyl Abdominal hysterectomy procedures Effect of 0.5 mg/kg ketamine administration on ANI	20	No modifications of ANI 5 min after ketamine administration	Ketamine administration does not interfere with ANI response during surgery	Bollag L et al., J Clin Monit Comput, 2014.
	Experimental study on anesthetized piglets Continuous administration of beta-blockers (Esmolol ®, 0.3mL/20kg/min) after induction of septic shock	10	Decrease of HR No variations of ANI values	ANI values are not influenced by beat-blockers administration	Boselli E et al., Abstract from SFAR Congress, 2014.

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