



MEASURE THE ANS
TITRATE ANALGESICS
IMPROVE POSTOPERATIVE PAIN

ANI and NIPE in OR

Analgesia
Nociception Index

New born Infant
Parasympathetic Evaluation

The problem

Pain is the conscious perception of nociception

Nociception (from Latin nocere 'to harm or hurt') is the process of the sensory nervous system response to certain harmful or potentially harmful stimuli. In nociception, intense chemical (chili powder in the eyes), mechanical (cutting, crushing.), or thermal (heat and cold) stimulation of sensory nerve cells, called nociceptors, produces a signal that travels along a chain of nerve fibres via the spinal cord to the brain.

Nociception triggers a variety of physiological changes and usually results in a subjective experience of pain (in the conscious patient). Therefore in unconscious patients there is nociception and autonomic reflex rather than pain.

The physiological changes that occur in the autonomic nervous system (ANS), following a nociceptive stimulation, are due to the activation of the sympathetic nervous system. With increased sympathetic activity the production of stress hormones (catecholamines and cytokines) increase which is a major cause of physiological stress.

A change in the anaesthesia paradigm

In 1960, Dr. Gray changed his previous Pain, Narcosis and Neuromuscular Blockade concept by substituting pain with areflexia (1).

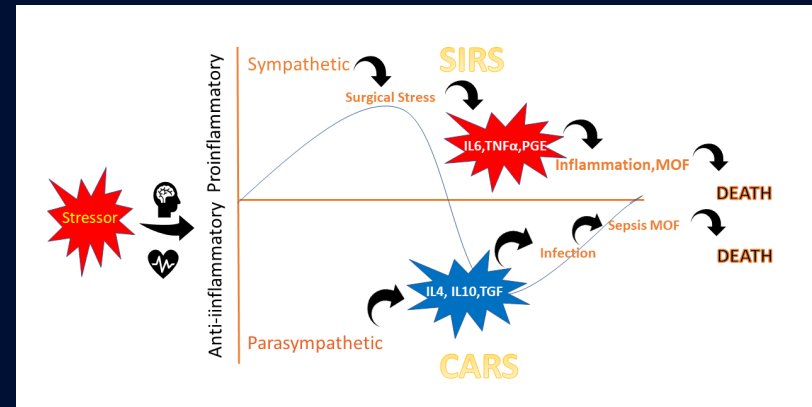


Dr Eger defined anesthesia as Amnesia and Arreflexia (2), including muscle activity into the reflexes. Dr Egan affirmed that the use of opioids and other analgesics in general anesthesia is

to control the autonomic reflex to nociception (3).

Control Surgical Stress

It is the ANS response that causes the stress and immunity system activation, increasing inflammation and affecting outcomes (4) morbidity and mortality [5], and this response is what should be kept under control.



(1) Gray C. A reassessment of the signs and levels of anaesthesia. Ir J Med Sci. 1960 Nov;419:499-508. (2) Eger EI 2nd, Koblin DD, Harris RA, Kendig JJ, Pohorille A, Halsey MJ, Trudell JR. Hypothesis: inhaled anesthetics produce immobility and amnesia by different mechanisms at different sites. Anesth Analg. 1997 Apr;84(4):915-8. (3) Egan TD. Are opioids indispensable for general anaesthesia? Br J Anaesth. 2019 Jun;122(6):e127-e135. doi:10.1016/j.bja.2019.02.018. Epub 2019 Mar 28. (4) Moore EE1, Moore FA, Harken AH, Johnson JL, Ciesla D, Banerjee A. The two-event construct of postinjury multiple organ failure. Shock. 2005 Dec;24 Suppl 1:71-4. (5) Tiansheng Sun, Xiaowei Wang, Zhi Liu, Xiaobing Chen, Jianzheng Zhang Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction in elderly hip fracture patients. Injury, Int. J. Care Injured 42 (2011) 707-713

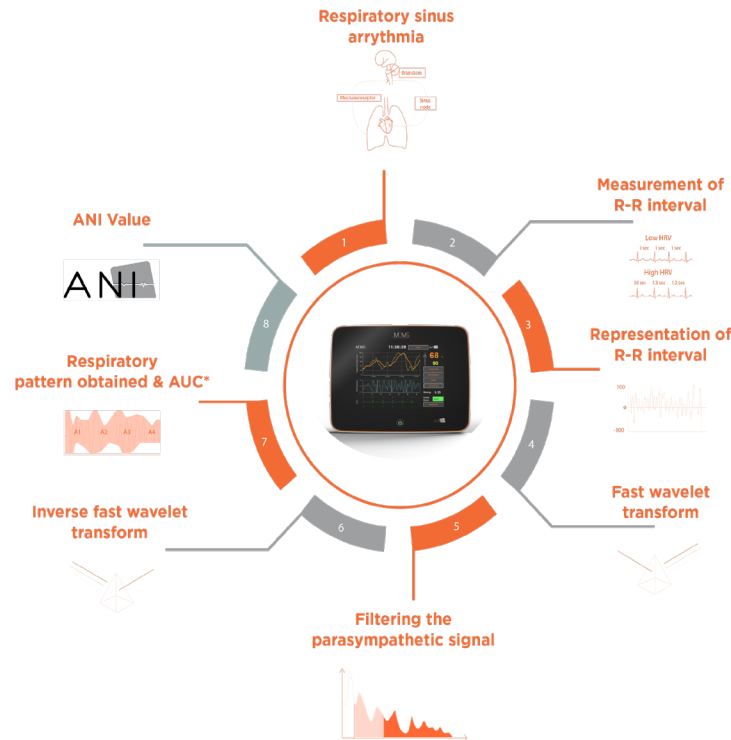
In order to control surgical stress analgesics, often opioids, are administered, but overdosing and infra-dosing can cause side effects such as: longer recovery times (12), PONV (13), urine retention (14), shivering (15), thromboembolism (16), pulmonary complications (17), bradycardia (18), hypotension (19), ileum (14), respiratory failures (14), post-op hyperalgesia (15), delirium (16) (17), POCD (18), cancer progression (18) and chronic pain (19). By using ANI and NIPE monitors MDoloris offers insights into the sympathetic/parasympathetic balance allowing titration of analgesics (24) and the ability to IMPROVE OUTCOMES. (21,23,25)

(12) de Boer HD, Detriche O, Forget P. Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. *Best Pract Res Clin Anaesthesiol.* 2017 Dec;31(4):499-504. doi: 10.1016/j.bpa.2017.07.002. Epub 2017 Jul 8. (13) Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth.* 1997 May;78(5):606-17. (14) Joshi GP, Warner DS, Twersky RS, Fleisher LA. A comparison of the remifentanyl and fentanyl adverse effect profile in a multicenter phase IV study. *J Clin Anesth.* 2002 Nov;14(7):494-9. (15) Imam MZ KA, Ghassabian S, Smith MT. Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. *Neuropharmacology* 2018; 131: 238-55. (16) Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia *Lancet.* 2019 Apr 13;393(10180):1558-1568. doi: 10.1016/S0140-6736(19)30430-1. (17) Relationship Between Pain and Opioid Analgesics on the Development of Delirium Following Hip Fracture *Journal of Gerontology: MEDICAL SCIENCES The Gerontological Society of America* 2003, Vol. 58A, No. 1, 76-81 (18) The Comparative Risk of Delirium with Different Opioids: A Systematic Review *Drugs Aging.* 2017; 34(6): 437-443. Published online 2017 Apr 12. (19) Iwasaki M, Edmondson M, Sakamoto A, Ma D. Anesthesia, surgical stress, and «long-term» outcomes. *Acta Anaesthesiol Taiwan.* 2015 Sep;53(3):99-104. doi: 10.1016/j.aat.2015.07.002. Epub 2015 Jul 30. (20) Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; 393: 1537-46.

Our Solution

ANI Measures the Autonomic Nervous System Response to nociception

Time between heart beat to heart beat changes due to ventilation. This phenomenon is known as heart rate variability and is controlled by the ANS. Heart rate variability reflects the activity of the sympathetic and parasympathetic nervous systems (6). The nucleus accumbens and nucleus ambiguus, in the brain, make the heart beat slower during expiration due to vagal activation and faster in inspiration because of sympathetic innervation (7). MDoloris Medical Systems has developed a technology based on heart rate variability analysis; The NIPE from 26 weeks gestational age to 2 years, and the ANI from 2 years and above, to measure the activity of the ANS and to control surgical stress. The ANI and NIPE express the relative parasympathetic activity of the patient. The total energy of the ANS is shown in the screen



*AUC : calculation of area under the curve of the respiratory pattern



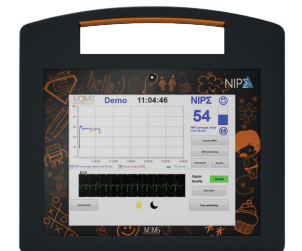
ANI MOC-9 Module



ANI monitor V2



ANI-MR Module



NIPE Monitor V1

of the monitor. During general anesthesia an ANI/NIPE range between 50-70 relates to adequate analgesia (11,21), meaning that antinociception is adequate and that parasympathetic activity is mildly predominant over sympathetic activity. If ANI/NIPE value falls below 50 the occurrence of a hemodynamic response within the following 10 minutes is very likely (8). This information can be used to predict and avoid a hemodynamic response by increasing analgesia.

(6) European Heart Journal (1996) 17,354-381 Guidelines Heart rate variability Standards of measurement, physiological interpretation, and clinical use Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (Membership of the Task Force listed in the Appendix) (7) Jeanne M, Logier R, De Jonckheere J, Tavernier B. Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia. *IEEE Proceedings* 2009. doi: 10.1109/IEMBS.2009.5332598. (8) Jeanne M, Delecroix M, De Jonckheere J, Kerbedj A, Logier R, Tavernier B. Variations of the Analgesia Nociception Index during propofol anesthesia for total knee Replacement. *Clin J Pain* 2014 Dec; 30(12):1084-8. doi: 10.1097/AJP.000000000000083.

Interpretation of ANI

100

Possibility to decrease opioids administration without any risks

70

Optimal range; Adequate analgesia

50

Probability of a hemodynamic reaction in the next few minutes, possibility to anticipate analgesic's needs

0

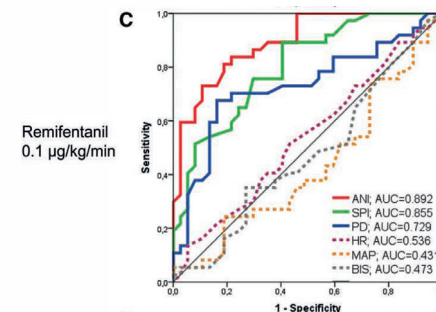
nb : the energy must be between 0,05 and 2,5 for an interpretable ANI.



The result

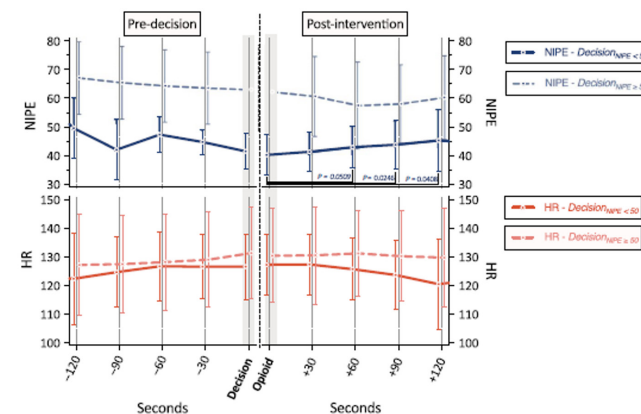
Analgesics are titrated based on heart rate and blood pressure. Funcke et al., demonstrated that ANI is more sensible and specific than haemodynamics to detect nociception in adults (9) and children (10). NIPE is able to show the effect of the analgesic provided and detect nociception better than heart rate (11). ANI/NIPE has been recommended with a B level by The Society for Pediatric Anesthesia in their recommendations for the use of opioids in children during the preoperative period (11).

Detect nociception in adults



Picture modified from Funcke et al. (9)

Detect nociception in pediatrics



Picture modified from Weber et al. (11)

(9) Funcke S, et al. Validation of Innovative Techniques for Monitoring Nociception during General Anesthesia: A Clinical Study Using Tetanic and Intracutaneous Electrical Stimulation. *Anesthesiology*. 2017 Aug;127(2):272-283. doi: 10.1097/ALN.0000000000001670. (10) Sabourdin N, Arnaout M, Louvet N, Guye M-L, Piana F & Constant I, Pain monitoring in anesthetized children: first assessment of skin conductance and Analgesia Nociception Index at different infusion rates of remifentanyl. *Pediatric Anesthesia* 2013 Feb; 23(2):149-55. doi: 10.1111/pan.12071 (11) 2019- Frank Weber , Hilde G. Roeleveld , Noortje J.E. Geerts , Annejet T. Warmenhoven , Rosalie Schröder, Thomas G. de Leeuw The heart rate variability derived Newborn Infant Parasympathetic Evaluation (NIPE™) Index in paediatric surgical patients from 0-2 years under sevoflurane anaesthesia - a prospective observational pilot study *Paediatr Anaesth*. 2019 Feb 21. doi: 10.1111/pan.13613. (11') P Cravero et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Paediatr Anaesth* 2019 Jun;29(6):547-571 DOI: 10.1111/pan.13639



The main benefits of using ANI technology



Refine opioids titration (23)



Predictivity of hemodynamic reactivity (8)



Helpful to diagnose the etiology of a hemodynamic event (26)



Predict post-extubation pain (27)



Reduce post operative pain (21)



Reduce length of stay in outpatient surgery units (25)



Testimonials



“I use daily the ANI monitor during my opioid-free anesthesia to titrate the non-opioid analgesic drugs. It allows me to reduce the dexmedetomidine and lidocaine dosages, which results in a faster and better awakening process of the patient as hemodynamics do not always reflect the surgical stress of the patient.”

Dr. Jan Paul J Mulier MD

**Department of Anaesthesiology & Intensive care,
AZ Sint-Jan Brugge KULeuven & UGent**



“NIPE is an excellent intraoperative tool for pediatric anesthesiologists who assist neonates and infants. NIPE device allow us not only to confirm the efficacy of regional blocks but also titrate analgesic drugs like opiates, dexmedetomidine while tailoring hypnotic agents, achieving a very early and comfortable extubation in these very young patients.”

Dr. Francisco Reinoso Barbero

**Chief of Anaesthesia of Paediatric department
Hospital la Paz, Madrid**



“At the heart of Enhanced Recovery After Surgery (ERAS) programs is the reduction in surgical stress. Whilst there are many approaches to this (such as minimally invasive surgery) a key area is excellent pain control. The ANI monitor allows objective intraoperative assessment of analgesia, permitting titrated pain control, optimizing patient analgesia and comfort, and thus minimizing the stress response.”

Dr. Bill Fawcett

Professor of Anesthesia, Consultant anesthesia/pain medicine, Guildford

Improve outcomes: Published evidences:



Intraoperative «Analgesia Nociception Index» - Guided Fentanyl Administration During Sevoflurane Anesthesia in Lumbar Discectomy and Laminectomy: A Randomized Clinical Trial

Henry D Upton¹, Guy L Ludbrook, Andrew Wing, Jamie W Sleigh

1,3 less NRS in PACU
64% lower PACU tot fentanyl
82% lower nausea / 23% shivering



Evaluation of the variability of ani values in digestive surgery

Nguyen Quoc Kinh, Trinh Ke Diep, Emmanuel Boselli, Luu Quang Thuy

Decreased pain in PACU
Less Opioid dosage during surgery
50% lower nausea / vomiting 75%
Lower respiratory failure



Analgesia nociception index (ani) monitoring in patients with thoracic paravertebral block: a randomized controlled study

Nurseda Dunder¹, Alparslan Kus², Yavuz Gurkan², Kamil Tokar³, Mine Solak²

34% less remifentanyl dosage during surgery
Haemodynamic stabilization
ANI helps guiding analgesia



A targeted remifentanyl administration protocol based on the analgesia nociception index during vascular surgery

Georges Daccache¹, Edouard Caspersen², Michel Pegoix², Kelly Monthé-Sagan², Ludovic Berger³, Dominique Fletcher⁴, Jean-Luc Hanouz²

Low remifentanyl dosage during surgery
Lower need of analgesia in PACU
Lower post operative pain
Can be safely used in diabetics and betablocked patients
Lower haemodynamic events
(11% vs 40% historically)

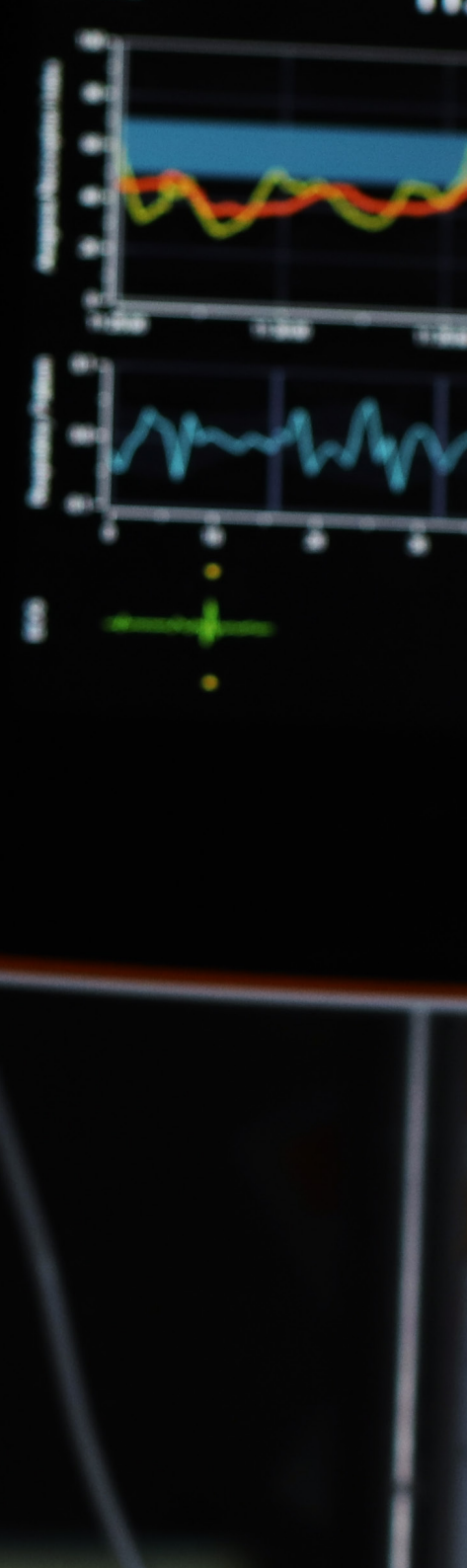


Usefulness of ANI (analgesia nociception index) monitoring for outpatient saphenectomy surgery outcomes: an observation study

Adolfo Ramos-Luengo¹, Adela Gardeta Pallarés², Fernando Asensio Merino²

11% reduction in length of stay in outpatient surgery

(21) Henry D. Upton, MBBS, BMedSc (Hons), Guy L. Ludbrook, MBBS, FANZCA, PhD, Andrew Wing, BMBS (Hons), BSc (Hons), FANZCA, and Jamie W. Sleigh, MD Intraoperative "Analgesia Nociception Index"- Guided Fentanyl Administration During Sevoflurane Anesthesia in Lumbar Discectomy and Laminectomy: A Randomized Clinical Trial Anesthesia & Analgesia July 2017 doi: 10.1213/ANE.0000000000001984. (22) Trịnh Kế Diệp, Nguyễn Quốc Kinh. ĐÁNH GIÁ SỰ THAY ĐỔI CỦA TRỊ SỐ ANI TRONG PHẪU THUẬT TIỂU HÓA. Preliminary data, Ahead of publication (23) Nurseda Dunder, Alparslan Kus, Yavuz Gurkan, Kamil Tokar, Mine Solak. Analgesia nociception index (ani) monitoring in patients with thoracic paravertebral block: a randomized controlled study. J Clin Monit Comput DOI 10.1007/s10877-017-0036-9. (24) Daccache G, Caspersen E, Pegoix M, Monthé-Sagan K, Berger L, Fletcher D, Hanouz JL. A targeted remifentanyl administration protocol based on the analgesia nociception index during vascular surgery. Anaesth Crit Care Pain Med. 2017 Aug;36(4):229-232. (25) Ramos-Luengo A, Gardeta Pallarés A, Asensio Merino F. Usefulness of ANI (analgesia nociception index) monitoring for outpatient saphenectomy surgery outcomes: an observational study. J Clin Monit Comput. 2020 Feb 28. doi: 10.1007/s10877-020-00491-1. (26) Logjer R, De Jonckheere J, Delecroix M, Keribedj A, Jeanne M, Jounwaz R, Tavernier B. Heart Rate Variability analysis for arterial hypertension etiological diagnosis during surgical procedures under tourniquet. IEEE Proceedings 2011. doi:10.1109/IEMBS.2011. (27) Boselli E, Bouvet L, Bégou G, Dabouz R, Davidson J, Davidov J-Y, Rahali N, Zadani A, Allaouchiche B. Prediction of immediate postoperative pain using the Analgesia Nociception Index: a prospective observational study. Br J Anaesth. 2014 Apr;112(4):715-21. doi:10.1093/bja/aet407. (28) Yi D, Wei B, Zhang L, Guo X. Analgesia nociception index guides remifentanyl administration during general anesthesia in posterior lumbar spinal surgery. Basic & Clinical Medicine ; (12): 1341-1345, 2015.





53

55

average 0.29

control
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ANI Monitor V2, ANI MOC-9, NIPE Monitor V1 and the ANI-MR are class IIa medical device, manufactured by MDoloris Medical Systems. CE evaluation was performed by Bureau Veritas Italy (1370) for the ANI Monitor V2, NIPE Monitor V1 and the ANI MOC-9. CE evaluation was performed by BSI (2797) for the ANI-MR. © 2021 MDoloris Medical Systems. All rights reserved. MD/QUA/EN14.3 v.04