ANESTHESIOLOGY

Nociception-guided *versus* Standard Care during Remifentanil–Propofol Anesthesia

A Randomized Controlled Trial

Fleur S. Meijer, M.D., Chris H. Martini, M.D., Ph.D., Suzanne Broens, M.D., Martijn Boon, M.D., Marieke Niesters, M.D., Ph.D., Leon Aarts, M.D., Ph.D., Erik Olofsen, Ph.D., Monique van Velzen, Ph.D., Albert Dahan, M.D., Ph.D.

ANESTHESIOLOGY 2019; 130:745–55

ABSTRACT

Background: The multidimensional index of nociception, the nociception level, outperforms blood pressure and heart rate in detection of nociceptive events during anesthesia. We hypothesized that nociception level–guided analgesia reduces opioid consumption and suboptimal anesthesia events such as low blood pressure and use of vasoactive medication.

Methods: In this single-blinded randomized study, 80 American Society of Anesthesiologists class I–III adult patients of either sex, scheduled for major abdominal procedures under remifentanil/propofol anesthesia by target-controlled infusion, were included. During the procedure nociception level, noninvasive blood pressure, and heart rate were monitored. Patients were randomized to receive standard clinical care or nociception level–guided analgesia. In the nociception level–guided group, remifentanil concentration was reduced when index values were less than 10 or increased when values were above 25 for at least 1 min, in steps of 0.5 to 1.0 ng/ml. Propofol was titrated to bispectral index values between 45 and 55. The primary outcomes of the study were remifentanil and propofol consumption and inadequate anesthesia events.

Results: Compared with standard care, remifentanil administration was reduced in nociception level–guided patients from (mean ± SD) 0.119 ± 0.033 to 0.086 ± 0.032 μg · kg^{-1} · min^{-1} (mean difference, 0.039 μg · kg^{-1} · min^{-1}; 95% CI, 0.025–0.052 μg · kg^{-1} · min^{-1}; $P < 0.001$). Among nociception level–guided patients, 2 of 40 (5%) experienced a hypotensive event (mean arterial pressure values less than 55 mm Hg) *versus* 11 of 40 (28%) patients in the control group (relative risk, 0.271; 95% CI, 0.08–0.77; $P = 0.006$). In the nociception level–guided group, 16 of 40 (40%) patients received vasoactive medication *versus* 25 of 40 (63%) patients in the standard care group (relative risk, 0.64; 95% CI, 0.40–0.99; $P = 0.044$).

Conclusions: Nociception level-guided analgesia during major abdominal surgery resulted in 30% less remifentanil consumption.

(ANESTHESIOLOGY 2019; 130:745–55)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The nociception level index (Medasense Biometrics Ltd., Ramat Gan, Israel), is a reliable measure of moderate to intense noxious stimulation during anesthesia and surgery

What This Article Tells Us That Is New

- In a randomized trial in patients having major abdominal surgery, compared to standard practice, nociception level-guided analgesia resulted in 30% less intraoperative remifentanil consumption

Multiple factors have improved the quality of anesthesia over the last decades, including the adoption of state-of-the art monitoring during surgery.[1] One type of monitor that is currently not part of standard clinical care is nociception monitoring. Nociception is defined as the neural process of encoding and processing noxious stimuli (noxious stimuli are actually or potentially tissue damaging events), causing behavioral, autonomic, and hormonal responses in conscious and unconscious individuals.[2] There are currently several nociception monitors available that differ in various elements, such as the number of variables implemented in the algorithm (ranging from just one variable to a series of variables), the source of the variables (derived from hemodynamic or electroencephalographic measurements), and evidently the applied algorithm that results in a practical index of nociception.[3] We recently showed that a novel monitor, the nociception level index (Medasense Biometrics Ltd., Ramat Gan, Israel), is a reliable measure of moderate to intense noxious stimulation during anesthesia and surgery.[4] The nociception level is a multiparameter monitor that combines information from the finger photoplethysmogram amplitude, skin conductance, skin conductance fluctuation, heart rate, heart rate variability, and their time derivatives into one index ranging from 0 (absence of noxious stimulation) to 100 (severe noxious stimulation).[5] The nociception level outperforms individual hemodynamic variables and bispectral index (BIS) in ability to distinguish between noxious and nonnoxious

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. The study was presented at the 38th anesthesia research conference at Leiden University Medical Center, Leiden, The Netherlands, on June 16, 2018, and at the American Society of Anesthesiologists annual meeting in San Francisco, California, October 13, 2018, Abstract No. BOC02 (Best of Abstracts: Clinical Science session).

Submitted for publication April 15, 2018. Accepted for publication December 31, 2018. From the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

<zdoi;10.1097/ALN.0000000000002634>

stimuli.[4] In an independent study, Edry *et al.*[6] presented similar results and further showed that the nociception level outperformed the pulse plethysmographic amplitude and the surgical pleth index in discriminating noxious from nonnoxious stimuli.

A meta-analysis (published in 2017) of randomized clinical trials showed that the use of nociception monitors (*i.e.*, monitors specially developed to detect moderate to severe nociceptive events during surgery) is associated with a reduction of movement events during anesthesia but not with other relevant endpoints such as a reduction in opioid consumption or a reduction of inadequate anesthesia events as measured by hemodynamic indices.[3] Still some more recent and well-designed studies did find advantage of nociception monitoring during anesthesia over standard clinical care, such as Upton *et al.*,[7] who showed that fentanyl-administration guided by the analgesia nociceptive index during sevoflurane anesthesia for lumbar discectomy and laminectomy results in reduced fentanyl use during surgery combined with decreased pain scores in the postanesthesia care unit. Sabourdin *et al.*[8] showed that pupillometry-guided remifentanil administration in gynecologic surgery reduced intraoperative remifentanil consumption and postoperative morphine requirements.

There are currently no clinical outcome studies to assess whether the nociception level index impacts general anesthesia care during surgery, and consequently outcome studies using the nociception level index were not included in the aforementioned meta-analysis. We therefore designed a randomized controlled trial to assess the ability of nociception level monitoring to modify anesthesia care during elective major abdominal surgery. In this first study, we focused on opioid consumption during anesthesia and the occurrence of suboptimal or inadequate anesthesia events. We hypothesized that nociception level monitoring combines reduced opioid administration with a reduction in the number of inadequate anesthesia events during surgery.

Materials and Methods

Ethics

The Investigational Review Board of Leiden University Medical Center (Commissie Medische Ethiek, Leiden, The Netherlands) approved the protocol in September 2016. The study was registered at trialregister.nl (identifier NTR6500) in February 2017, after which patients were recruited from March 2017 to December 2017. There were no amendments to the study protocol. All patients received written information about the protocol, had ample time to decide on their participation, and gave oral and written informed consent before enrollment into the study.

Patients

American Society of Anesthesiologists (ASA) class I–III patients (aged 18 to 80 yr) of either sex, scheduled for elective major abdominal surgical, urologic, or gynecologic procedures under general anesthesia without epidural analgesia, were recruited to participate in the study. Exclusion criteria included inability to give informed consent, planned spinal or epidural anesthesia, all forms of regional anesthesia including wound infiltration, nonelective procedures, pregnancy or lactation, body mass index more than 35 kg/m^2, perceived difficult intubation, planned rapid sequence intubation, use of β-adrenergic receptor antagonists, baseline mean arterial pressure (MAP) less than 60 mm Hg or more than 120 mm Hg, baseline heart rate less than 45 min^{-1} or more than 90 min^{-1}, the presence of acute preoperative pain, use of chronic opioid and nonopioid pain medication, peripheral or central nervous system disorder (including chronic pain), use of illicit drugs in the 30 days before surgery, use of psychoactive drugs, or severe medical conditions (untreated or persistent peripheral or central cardiovascular disease; metabolic syndromes, including diabetes, severe pulmonary disease; significant hepatic disease with increased bilirubin, international normalized ratio, or low albumin).

Study Design

The study had a single-blinded, randomized, parallel group, superiority design and was performed in a single tertiary center. Patients were randomized to receive nociception level–guided analgesia or standard clinical care using a computer-generated randomization list by a research nurse not involved in the study. The randomization list was not available to the investigators. Patients were allocated to treatment just before the surgical procedure by the research nurse, after which the anesthesia team was informed of the patient's randomization assignment. Patients were not informed on their group assignment and could not discern to what group they were allocated.

Clinical Care in Both Treatment Groups. Upon arrival in the operating room, the patients received an intravenous access line and were connected to standard monitors (3-lead continuous electrocardiogram, blood pressure by arm cuff, pulse oximetry by finger probe, neuromuscular monitoring by TOF-Cuff (RGB Medical Devices, Spain), and BIS monitoring using the BIS forehead sensor). Additionally, all patients were connected to the nociception level monitor (PMD-200, Medasense Biometrics Ltd., Israel) *via* a finger probe that contains sensors to measure the different components of the nociception level. The sensor was positioned on the middle finger of the hand contralateral to the blood pressure cuff. In case of nociception level–guided analgesia, the value of nociception level was visible and used to steer analgesia during surgery. In case of standard clinical care, the nociception level index was collected but not visible for clinical decision making.

None of the patients received premedication. Anesthesia was delivered by target-controlled infusion in which the target was a preset plasma concentration of propofol and

remifentanil. To this end, two separate infusion pumps (Orchestra Base Primea, Fresenius Kabi, Zeist, The Netherlands), one programed with the remifentanil pharmacokinetic data set of Minto *et al.*[9] and one programed with the propofol pharmacokinetic data set of Marsh *et al.*[10] were used. For induction, the target plasma concentrations depended on the patient's age. In patients younger than 65 yr the target for remifentanil was set at 4 ng/ml for remifentanil and 4 μg/ml for propofol; in patients 65 yr of age or older the target for remifentanil was set at 2.5 ng/ml and 2.5 μg/ml for propofol. After consciousness was lost (as detected by BIS values below 60, absence of eyelash reflex, and no response to verbal stimulation), rocuronium 0.6 mg/kg was administered and the trachea of the patient was intubated when the TOF-cuff measured zero twitches. The ventilator settings were such that end-tidal PCO_2 was kept at 4.5 ± 0.4 vol.% (34 ± 3 mm Hg). After intubation the target propofol concentration was adjusted in steps of 0.5 μg/mL to ensure a steady state in the value of the BIS at 50 ± 5. The train-of-four target was 1 ± 1; additional rocuronium could be administered as deemed necessary. The remifentanil target concentration was set to zero 5 to 10 min before the end of surgery. At the end of surgery, all patients with train-of-four ratios less than 0.9 were reversed with sugammadex 2 mg/kg and extubated when the train-of-four ratio exceeded 0.9, the patient was breathing and awake. If the train-of-four ratio was 0.9 or greater no reversal agent was administered. In both treatment groups, fluid administration was standardized to 5 to 6 ml/min. Additional fluids could be administered in case of moderate to severe blood loss.

Each patient received preemptive treatment for postoperative pain: acetaminophen 1 g 30 min before surgery and intravenous morphine 0.15 to 0.20 mg/kg, 45 to 60 min before the end of surgery. In the postanesthesia care unit (PACU) additional intravenous morphine doses could be given. These morphine doses were based on the postoperative pain scores (pain scores were obtained using an 11-point numerical rating scale from 0 [*no pain*] to 10 [*most severe pain imaginable*]): in case of pain scores greater than 4 morphine bolus doses of 1 or 2 mg could be given at 5-min intervals until pain was reduced below a numerical rating scale of 4.

Standard Clinical Care Group. When hemodynamic changes outside of the normal range were observed, our standard clinical care was as follows. In case of high blood pressure (systolic blood pressure greater than 140 mm Hg) or tachycardia (heart rate greater than 90 min^{-1}), the remifentanil infusion is increased; in case of concurrent high BIS values (greater than 55), the propofol infusion is increased. In case of low blood pressure (mean arterial pressure less than 60 mm Hg), initially, the remifentanil infusion is lowered (lowest target plasma concentration that was allowed is 1 ng/ml), and in case of concurrent low BIS values (less than 45) the propofol infusion is lowered as well. Next, vasoconstrictors may be given (a continuous infusion of norepinephrine, or bolus doses of ephedrine or phenylephrine). Only when blood pressure remains low additional crystalloids are given. Adaptations in remifentanil target-controlled infusion are performed in steps of 0.5 to 1.0 ng/ml. There are no restrictions in the timing of the changes in remifentanil or propofol targets. Finally, in case of bradycardia (heart rate less than 30 min^{-1}), atropine may be given. All of these adaptations (such as the magnitude of remifentanil/propofol changes in target concentration, the dose of vasoactive medication, the amount of fluids given) are at the discretion of the attending anesthesiologist.

Nociception Level–guided Analgesia Group. In the nociception level–guided group the remifentanil target was adjusted to maintain a nociception level value between 10 and 25. In case the nociception level decreased less than 10 for more than 60 s, remifentanil target-controlled infusion levels were lowered in steps of 0.5 ng/ml, whereas in case of a values greater than 25 for more than 60 s, remifentanil target-controlled infusion levels were increased in steps of 0.5 (nociception level increase remained less than 45) or 1.0 ng/mL (nociception level increase greater than 45). A nociception level cutoff value of 20 yields specificity and sensitivity values of 80% and 73%, respectively, for discrimination between nonpainful and painful stimuli.[4] A somewhat wider nociception level window was applied for a less rigid and possible unstable use of the nociception level. After the target-controlled infusion value was changed, 5 min were allowed before a next change was made. The lowest remifentanil target permitted was 1 ng/ml. If the target remifentanil concentration of 1 ng/mL was reached (at nociception level values less than 10) and the patient was hypotensive, vasoactive medication (ephedrine, phenylephrine, norepinephrine, atropine) could be administered. Atropine was administered when heart rate decreased less than 30 min^{-1}. Because the nociception level may be sensitive to such medication, nociception level values were then not used for at least 5 min to guide analgesia, with the exception of norepinephrine as this drug was given as continuous infusion.

The Nociception Monitor

The nociception level has been described previously.[4–6] In brief, the nociception level is a composite score derived from a set of physiologic variables (*i.e.*, peripheral effectors of the autonomous nervous system): heart rate, heart rate variability, amplitude of the photoplethysmogram, skin conductance, skin conductance variability, and the time derivatives of these variables. High nociception level levels can be explained by higher sympathetic activity. The nociception level ranges from 0 to 100, which correlates with reference clinical scores of nociception based on estimated opioid concentration and nociceptive stimulus strengths as determined in previous studies.[4–6] The device received EU

and Health Canada certification but still has not received U.S. Food and Drug Administration clearance.

Data Collection

Data were derived from three sources: (1) the nociception level monitor, (2) the BIS monitor, (3) and the electronic medical record database (Healthcare Information X-change, Chipsoft, The Netherlands). All monitors were time-aligned before induction of anesthesia. Various events occurring during anesthesia were annotated in the nociception level monitor such as drug administration (including targets and doses) and surgical and anesthesia events (*e.g.*, loss of consciousness, intubation, incision, end of surgery, eye opening, start and end of anesthesia; end of anesthesia is defined by spontaneous ventilation after extubation). Hemodynamic parameters (MAP, heart rate) were collected from the electronic medical record. In case of evident occurrences of artefacts in blood pressure or heart rate that were observed during the case, a note in the case record form was made and the data were excluded from the analysis. Finally, in the PACU, we queried the patients for indications of memory of surgery/awareness (using the Brice questionnaire)[11] and obtained pain scores at 30-min intervals.

Primary and Secondary Study Endpoints

The study had the following primary endpoints: remifentanil and propofol use during anesthesia and inadequate anesthesia events. Per protocol, inadequate anesthesia events were defined by[12]: (1) use of vasoactive medication (ephedrine, phenylephrine, norepinephrine, atropine); (2) hypotension: MAP less than 55 mm Hg (severe hypotension) or MAP less than 60 mm Hg (moderate hypotension); (3) hypertension: occurrence of systolic blood pressure greater than 140 mm Hg; (4) bradycardia: heart rate less than 45 min^{-1}; and (5) occurrence of tachycardia: heart rate greater than 90 min^{-1}.

Secondary endpoints were (1) time from reversal of relaxant to extubation; (2) occurrence of awareness; (3) pain scores in the PACU; (4) morphine use in the PACU; and (5) level of sedation in the PACU. Sedation was measured according to the Leiden Observers' Assessment of Alertness and sedation score, a 7-point scale ranging from normal alertness (score = 0) to unrousable to painful stimuli (score = 6).[13]

Statistical Analysis

Because this study is the first to assess nociception level–guided analgesia, we remained unknown on effect sizes and SDs. Using the results from a study on a different nociceptive tool,[13] we assumed that remifentanil use is 0.21 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the standard clinical care group and 0.14 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in nociception level–guided group, a SD of 0.08, 1-beta = 0.9 and alpha = 0.05, 37 patients were required per group. For practical purposes, we used 40 patients per group.

Primary endpoints remifentanil and propofol consumption were analyzed by independent two-tailed *t* tests; inadequate anesthesia events were analyzed by χ^2 test with relative risks calculated from the 2 × 2 contingency tables. Secondary endpoints were analyzed by independent two-tailed *t* test or Mann–Whitney *U* test depending on the type of data and data distribution. The analyses were restricted to data related to the primary and secondary endpoints. Data are presented as mean ± SD, median and interquartile range, or frequency; *P* values less than 0.05 were considered significant. Data analysis was performed using GraphPad Prism version 7.00 for macOS (GraphPad Software, United States).

Results

A total of 150 patients were approached for participation in the study. Forty-two patients either refused participation or were not randomized because their surgery was rescheduled for logistic reasons. Twenty-eight subjects were recruited to train the research team in the use of the nociception level; these data were discarded. Following training, eighty subjects (40 in each group) were randomized and completed the study. Patient characteristics (age, sex, body mass index, ASA classification, baseline hemodynamics) are given in table 1. The age distribution was similar between groups with 16 patients aged 65 yr or older in both treatment arms. Surgery types were similar between nociception level–guided and standard clinical care groups: urology (48%), abdominal surgery (39%), and gynecology (14%). Surgical procedure and anesthesia times were similar between treatment groups (data not shown). The average nociception level, blood pressure, heart rate, and BIS values observed during the course of anesthesia are given in figure 1. All study patients completed the trial without any harms or adverse events, and there we no missing data.

Table 1. Baseline Patient Characteristics and Surgeries in the Nociception Level-guided and Standard Clinical Care Groups

	Nociception Level–guided Analgesia	Standard Clinical Care
n	40	40
M/F, n	20/20	24/16
Age, yr	59 (22–79)	59 (20–81)
Weight, kg	80 ± 16	81 ± 15
Height, cm	174 ± 9	176 ± 9
BMI, $kg.m^{-2}$	26 ± 4	26 ± 3
Heart rate, mn^{-1}*	75 ± 10	77 ± 15
MAP, mm Hg*	103 ± 12	99 ± 10
ASA class 1/2/3, *n*	10/28/2	11/26/3
ASA class 1/2/3, %	25/70/5	27/65/8
Urology, n (%)	19 (47)	19 (47)
General surgery, n (%)	15 (38)	16 (40)
Gynecology, n (%)	6 (15)	5 (13)

All values are represented as mean ± SD, median (interquartile range), or numbers (n). ASA, American Society of Anesthesiologists; BMI, body mass index; F, female; M, male; and MAP, mean arterial pressure.

*Values obtained at patient screening in the preoperative clinic.

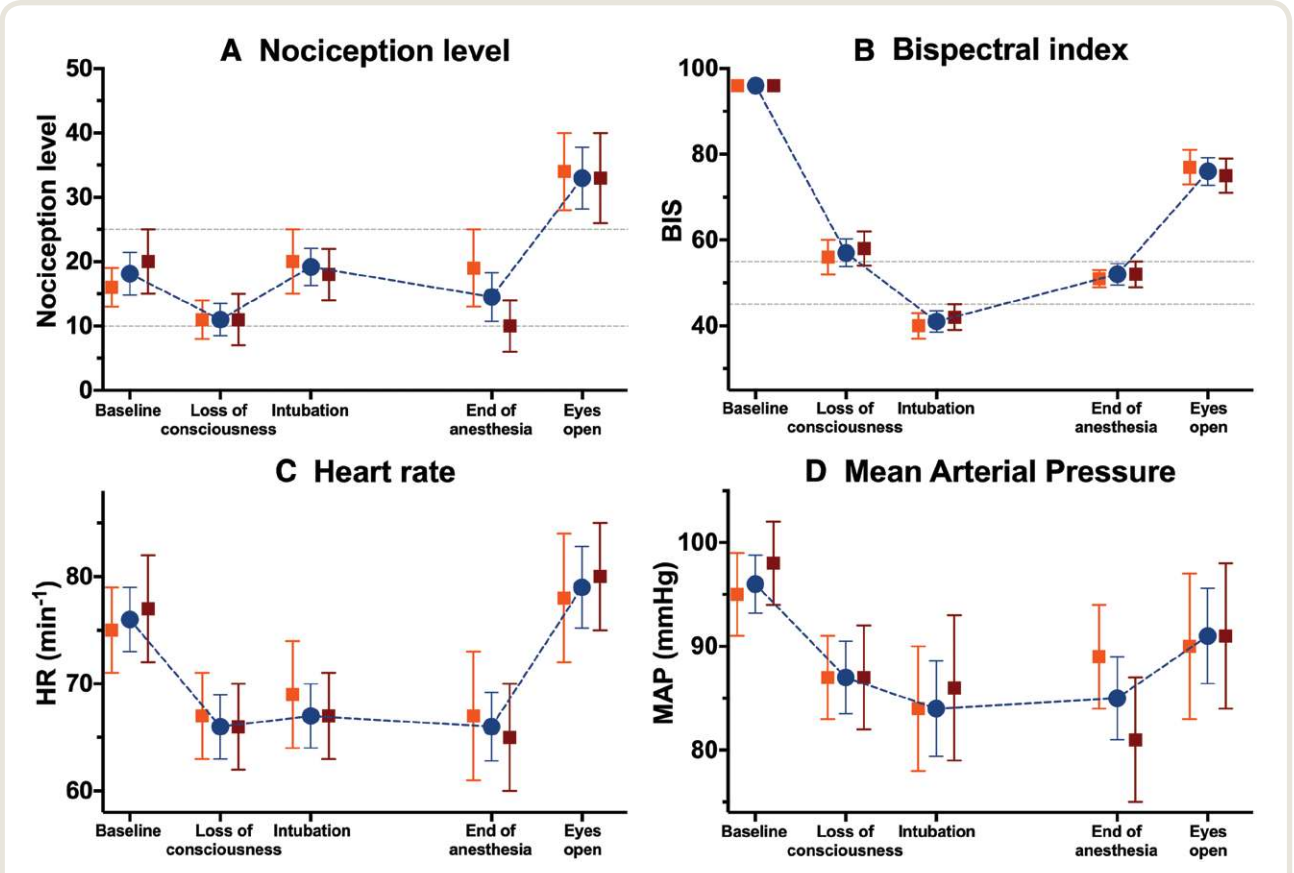


Fig. 1. Average nociception level (index; *A*), bispectral index (*B*), heart rate (HR; *C*), and mean arterial pressure (MAP; *D*) values observed at baseline (awake), loss of consciousness, intubation, end of anesthesia, and eyes open. Data are given for the total population (*blue symbols*), nociception level–guided (*orange squares*), and standard clinical care (*dark red squares*). Comparisons shown are for the total population. Values are mean ± 95% CI.

Remifentanil and Propofol Consumption

To control for patient weight and duration of surgery, we report the anesthesia drug doses as dose · kg^{-1} · min^{-1} of anesthesia time. The intraoperative remifentanil administration was less in the nociception level–guided group compared with standard clinical care by 28%: nociception level–guided 0.086 ± 0.032 μg · kg^{-1} · min^{-1} (mean ± SD) *versus* standard clinical care 0.119 ± 0.033 μg · kg^{-1} · min^{-1} (mean difference 0.039 μg · kg^{-1} · min^{-1} with 95% CI 0.025 to 0.052 μg · kg^{-1} · min^{-1}, unpaired *t* test $P < 0.001$; fig. 2, panels A and B). Propofol administration did not differ between treatments: nociception level–guided 0.105 ± 0.022 mg · kg^{-1} · min^{-1} *versus* standard clinical care 0.107 ± 0.025 mg · kg^{-1} · min^{-1}, mean difference 0.003 mg · kg^{-1} · min^{-1} with 95% CI −0.012 to 0.017 mg · kg^{-1} · min^{-1}, $P = 0.715$).

Inadequate Anesthesia Events

Vasoactive Medication. In the standard clinical care group, 25 of 40 (63%) patients received either one vasoactive (n = 16 of 40, 40%) or at least two vasoactive (n = 9 of 40, 23%) drugs (norepinephrine, ephedrine, phenylephrine, or atropine). In contrast, in the nociception level–guided group 16 of 40 (40%) received vasoactive medication, of which just 3 of 40 (8%) received more than one drug. In comparison to standard care, the relative risk of receiving at least one vasoactive drug was 0.64, 95% CI, 0.40–0.99, $P = 0.044$ (table 2).

Blood Pressure. Two of 40 (2 of 40, 5%) patients in the nociception level–guided group experienced a single hypotensive event with MAP values less than 55 mm Hg, whereas 11 of 40 patients (28%) in the standard clinical care group experienced at least one such an event (relative risk, 0.271; 95% CI, 0.08–0.77; $P = 0.006$). Nine of 40 patients (23%) in the nociception level–guided and 17 of 40 (43%) in the standard clinical care group experience a MAP less than 60 mm Hg event (relative risk, 0.53; 95% CI, 0.27–1.02; $P = 0.055$). See figure 3 for the distribution of the duration of these hypotensive events. There were no differences in hypertensive events between treatment groups. Sixteen of 40 (nociception level; 40%) and 12 of 40 (standard clinical care; 30%) patients experienced episodes with systolic blood pressure greater than 140 mm Hg (relative risk, 1.33;

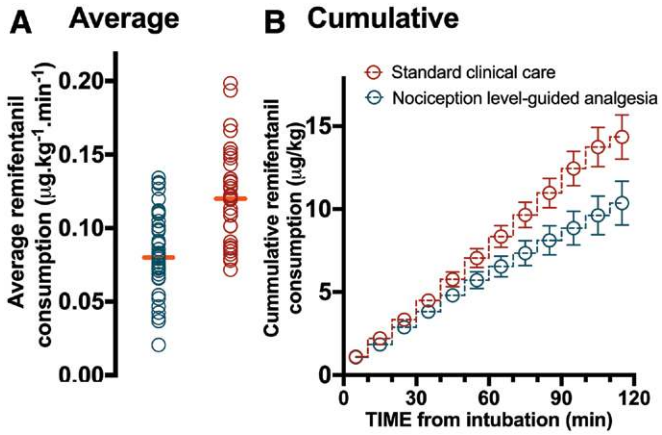


Fig. 2. (*A*) Individual remifentanil doses (in µg · kg^{-1} · min^{-1}) and mean values (*orange bars*) in the two treatment groups ($P < 0.001$). (*B*) Cumulative remifentanil consumption (µg/kg) during the first 2 h of anesthesia. *Red symbols*, standard clinical care; *dark green symbols*, nociception level–guided analgesia.

Table 2. Vasoactive Medication

	Nociception Level–guided		Standard Clinical Care		
	Dose	n (%)	Dose	n (%)	*P* Value
Ephedrine, mg	10 ± 5	6 (15)	9 ± 5	13 (33)	
Phenylephrine, µg	275 ± 133	6 (15)	200 ± 140	12 (30)	
Atropine, mg			0.8 ± 0.4	2 (5)	
Norepinephrine, µg	130 ± 55	7 (18)	166 ± 59	6 (15)	
Number of patients receiving at least one drug		16 (40)		25 (63)	0.044*

Values are mean ± SD.
*Relative risk, 0.64; 95% CI, 0.40–0.99.

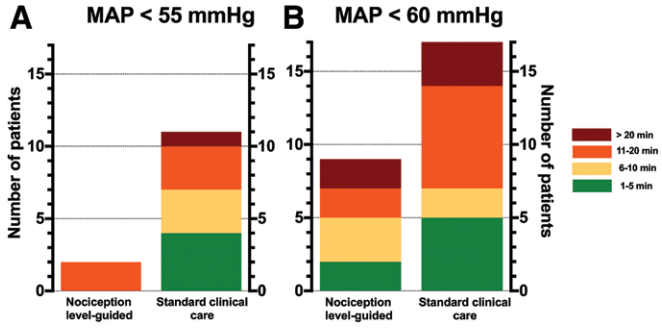


Fig. 3. Number of patients and duration of hypotensive events in standard clinical practice and nociception level–guided patients with a mean arterial pressure (MAP) cutoff of 55 mm Hg (*A*; $P = 0.006$) and 60 mm Hg (*B*; $P = 0.055$).

95% CI, 0.74–2.46; $P = 0.348$). No patients in the nociception level–guided group had both hypotensive (MAP less than 55 mm Hg) and hypertensive (systolic blood pressure greater than 140 mm Hg) events against 4 of 40 patients (10%) in the standard clinical care group (relative risk, 0; 95% CI, 0–0.91; $P = 0.040$).

Heart Rate. None of the patients that received nociception level–guided analgesia experienced a heart rate below 45 min^{-1} against 5 of 40 (13%) in the standard clinical care group (relative risk, 0; 95% CI, 0–0.73; $P = 0.021$). In the nociception level–guided group, 7 of 40 (18%) patients *versus* 6 of 40 (15%) patients in the standard clinical care patients had a heart rate greater than 90 (relative risk, 1.17; 95% CI, 0.45–3.07; $P = 0.762$).

Secondary Endpoints

The median time between reversal of the relaxant to extubation differed between treatment groups: nociception level–guided group (n = 25) 7 min with interquartile range 4 to 10 min *versus* standard clinical care-group (n = 31) 9 min with interquartile range 7 to 13.5 min (difference between medians, −2 min; 95% CI, −5–0 min; $P = 0.027$). In both groups there were no patients who reported awareness during anesthesia. Intraoperative morphine doses were 0.19 ± 0.04 mg/kg and 0.18 ± 0.04 mg/kg in nociception level–guided and standard clinical care groups, respectively (mean difference, 0.01 mg/kg; 95% CI, −0.01–0.03 mg/kg; $P = 0.237$), as defined in the protocol. See table 3 for observations made in the PACU. There were no differences in pain scores, opioid treatment for pain, and sedation scores.

Nociception Level Events

Nociception Level Less Than 10. All subjects had at least one event during anesthesia with nociception level values less than 10.

Nociception Level Greater Than 25. Thirty-three (83%) and 35 (88%) patients in standard clinical care and nociception level–guided groups, respectively, experienced a nociception level–value greater than 25 during anesthesia. The frequency and time spent at high nociception level values differed between treatment groups: nociception level values greater than 25 occurred at least 10 times in 9 (23%) standard clinical care patients *versus* 2 nociception level–guided patients (5%); nociception level values greater than 45 and greater than 60 occurred in 17 (nociception level–guided; 43%) *versus* 14 patients (standard clinical care; 35%), and 5 (nociception level–guided; 13%) *versus* 2 patients (standard clinical care; 5%), respectively. In none of the patients a nociception level value above 70 occurred. Figure 4 gives the distribution of nociception level values for the first 2 h of anesthesia (fire plots of the 5-s output of the nociception level device).

Finally, the amount of crystalloids (normal saline or Ringer's lactate solution) was similar between treatments. The median (interquartile range) volume given in nociception level–guided group was 850 (613 to 1,200) ml *versus* in the standard clinical care group 1,000 (638 to 1,125) ml. The median (interquartile range) PACU stay did not differ between groups: 53 (36 to 72) min and 61 (44 to 78) min in the nociception level and standard clinical care groups, respectively.

Discussion

The main observations from our randomized clinical trial are that nociception level monitoring is associated with 30% reduction in the use of remifentanil combined. These results indicate that nociception level monitoring during anesthesia has certain advantages in terms of opioid consumption. We did not find any differences in propofol requirements during anesthesia or differences in early postoperative outcome measures such as postoperative pain or opioid consumption in the PACU.

Opioid Consumption

We calculated that the difference in remifentanil dose resulted in a 33% lower target plasma remifentanil concentration: average remifentanil target plasma concentration during nociception level–guided anesthesia 2.4 ng/ml *versus* 3.6 ng/ml during standard clinical care. These are clinically relevant differences. Apparently, because of the use of the monitor the anesthesiologist is more attentive and proactive in keeping the nociception level between threshold values according to protocol, whereas in the standard clinical care

Table 3. Observations Made in the Postanesthesia Care Unit

	Nociception Level–guided [n]	Standard Clinical Care [n]	Mean Difference or Median Difference (95% CI)	*P* Value
Morphine consumption, mg/kg	0.06 ± 0.06 [40]	0.06 ± 0.06 [40]	0.01 (–0.02 to 0.03)	0.661
Maximum pain score	6 (4–7) [40]	5 (3–7) [40]	1 (–1 to 1)	0.590
Pain upon arrival in PACU	5 (2–6) [40]	2.5 (0–6) [40]	2.5 (0–2)	0.242
Pain after 30 min	5 (4–6) [35]	4.5 (3–6) [36]	0 (–1 to 1)	0.761
Pain after 60 min	4 (3–5) [14]	4 (3–5.5) [15]	0 (–1 to 1)	0.926
Sedation score (0–6) upon arrival in PACU	2 (1–2) [40]	1 (0.25–2) [40]	1 (0–1)	0.075

All values are represented as mean ± SD (morphine consumption) or median (interquartile range). Pain scores are verbal rating scores ranging from 0 (*no pain*) to 10 (*most severe pain imaginable*). The sedation score is the Leiden Observers' Assessment of arousal/sedation.[13] PACU, postanesthesia care unit.

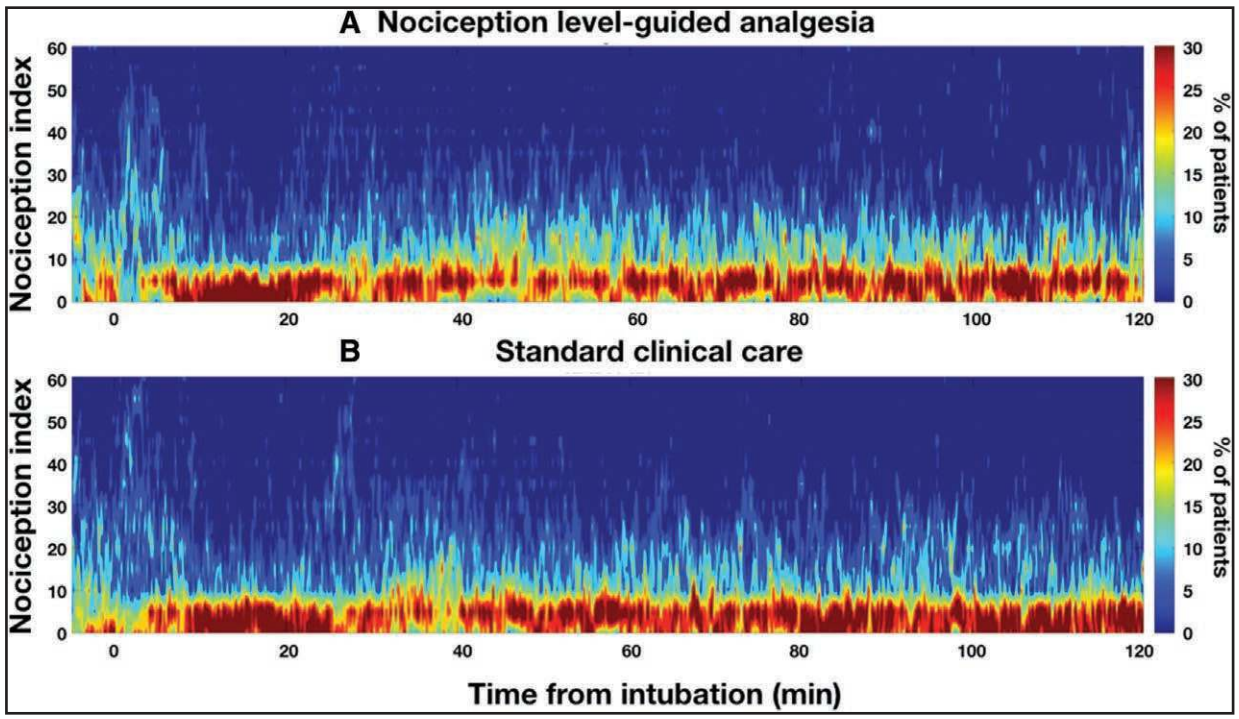


Fig. 4. Distribution of nociception level values during nociception level–guided analgesia (*A*) and during standard clinical care (*B*). The colors represent the percentage of patients ranging from dark blue (0%) to dark red (30%); see legend bars. The data are the 5-s outputs of the nociception level device. The data are aligned at intubation ($t = 0$ min). In the nociception level–guided group more patients fall in the designated limits of nociception level 10 to 25 as apparent by more light blue to yellow color; the equal amounts of dark blue and dark red are the manifestation of no difference between groups in nociception level values less than 10 and greater than 25.

group the approach to adjust the target-controlled infusion level might have been less aggressive because of the lack of continuous monitoring of nociceptive events. Five percent of patients in the nociception level–monitored group experienced a hypotensive event with MAP values less than 55 mm Hg whereas 28% in the standard clinical care group experienced at least one such event (relative risk, 0.271; 95% CI, 0.08–0.77; $P = 0.006$). According to our *post hoc* type-1 error correction (see item 9 in Study Limitations), further studies with larger sample sizes are needed to address whether nociception monitoring results in improved hemodynamic stability. Severe hypotension is not uncommon, and even short durations are associated with poor outcomes such as acute kidney and myocardial injury.[14] During their stay in our clinic none of our patients developed any major complications. Still, we did not follow our patients beyond their hospital stay and hence remain uninformed on possible long-term complications.

Secondary Endpoints

We relate the observed 2-min difference in time between rocuronium reversal and extubation between the two treatment groups to the lower plasma remifentanil concentration in nociception level–guided patients and consequently an earlier onset of spontaneous respiration. As we previously showed, breathing activity is initiated when remifentanil plasma concentrations drop to about 2 ng/ml.[15,16] We observed no differences in pain scores and morphine consumption in the PACU (table 3). This could be related to the inability of the nociception level to impact postoperative events when using short-acting opioids or to the use of preemptive morphine treatment. Because the rapid drop in remifentanil plasma concentration may be associated with high pain levels, we administered 0.15 to 0.2 mg/kg morphine to all of our patients, irrespective of treatment group, 40 to 60 min before the end of surgery. This may have obfuscated any effect of the lower remifentanil dosing in the nociception level–guided patient population on postoperative pain scores. These findings are in agreement with the majority of studies using nociception monitoring during anesthesia that show no difference in postoperative pain scores despite reduced opioid administration during surgery (but not all, see articles by Upton *et al.* and Sabourdin *et al.*)[7,8,12,17–20] In one study in children,[21] the use of the surgical pleth index during fentanyl/sevoflurane anesthesia was associated with increased postoperative pain scores and an increase in the proportion of patients with high emergence agitation scores, whereas the use of fentanyl during anesthesia was reduced by

about 75%. However, this study might not have been optimal to demonstrate clinical benefits of the nociception monitor as the procedures were short (adenotonsillectomies) and the opioid used was fentanyl with a relatively long duration of action. Irrespective, these as well as our observations point directly to the need to be cautious in the extreme lowering of opioid administration and the need for a predefined lowest permitted opioid target during anesthesia as well as relaxed lower monitor thresholds as otherwise there may be insufficient opioid carryover effect from anesthesia to recovery.

Nociception Level Thresholds

We based the lower nociception level threshold (*i.e.*, the nociception level value below which remifentanil infusion was lowered) on the results of our previous study in which we observed that low nociception level values (less than 10) were associated with absence of nociception.[4] It is important to realize that low nociception level values (less than 10) may occur under three circumstances: (1) in the presence of noxious stimuli when patients are treated with high doses of opioids; (2) in the absence of noxious stimuli in patients treated with (relatively) high dose opioids; or (3) in the absence of noxious stimuli with low dose analgesic treatment. In the latter case a sudden noxious (surgical) stimulus applied by the surgeon will cause a nociception level increase above the upper threshold (*i.e.*, nociception level greater than 25) because these patients then lack appropriate analgesics coverage. Hence, we advise to dose the analgesic medication not purely based on the nociception level thresholds but also on the anticipated nociceptive input.

Study Limitations

The study has several limitations. (1) In common with all studies on the influence of nociception monitor-guided anesthesia on various anesthesia endpoints, our study was single blinded. This may have influenced the outcome due to an implementation or performance bias. (2) We cannot exclude a learning effect in our study. Possibly the knowledge gained when treating nociception level–guided patients may have been used in some way when giving anesthesia to the standard clinical care group. Whether this offsets a possible implementation bias is not known. (3) We relied on intermittent blood pressure measurements to guide anesthesia in the standard clinical care group. It may well be that a continuous blood pressure signal from an arterial line may have improved our ability to guide anesthesia with more rapid response to nociceptive input.[4,6] We are unaware of any studies comparing nociception monitors with continuous blood pressure monitoring in their ability to adequately and promptly detect nociceptive stimuli. (4) As discussed earlier, there is no agreement on the use of specific thresholds in nociception monitoring. Some of our results will evidently alter when different (wider) thresholds are applied. (5) We excluded patients using β-adrenergic receptor antagonists. This exclusion is somewhat arbitrary and based on the idea that such medication may alter the performance of the nociception level. However, current clinical use of the nociception level index in our hospital does not support this assumption and shows that the nociception level behaves similarly in patients using β-adrenergic receptor antagonists. Still, this needs to be confirmed under controlled conditions.[22] (6) We were cautious in using the nociception level to guide anesthesia following administration of vasoconstrictors or atropine (with the exception of norepinephrine) because these drugs may influence the performance of the nociception level monitor. It is our experience that just a short window (up to 5 min) is needed before nociception level–guidance may be continued. (7) Standard clinical care differs across medical centers. Our standard clinical care (target-controlled infusion propofol/target-controlled infusion remifentanil/low threshold use of norepinephrine) makes generalizability of our results challenging. We will next study whether similar results are obtained with the more common anesthesia practice of anesthesia with intermittent sufentanil administration and sevoflurane maintenance. (8) We argue that only when the nociception level monitor is used as part of standard clinical care we can eventually assess its true added value with respect to long-term outcome measures.

Finally (9), we did not apply preplanned type-1 error control, which is a major limitation given the multiple endpoints (remifentanil/propofol consumption and five inadequate anesthesia events). We therefore performed *post hoc* Bonferroni corrections. After correction the level of significance was set at $P < 0.05/2 = 0.025$ for drug consumption and $P < 0.05/2$ for inadequate anesthesia events. A second correction for remifentanil and propofol consumption was applied ($P < 0.025/2 = 0.0125$) and for single inadequate anesthesia events ($P < 0.025/5 = 0.005$). This resulted in a significant difference between treatments after correction for remifentanil consumption ($P < 0.001$). Severe hypotensive events ($P = 0.006$) just failed to reach the level of significance.

Conclusions

We studied the influence of nociception-guided anesthesia using the nociception level monitor and observed that, compared with standard clinical care, nociception level guidance resulted in about 30% less remifentanil use during anesthesia. Nociception level monitoring had no effect on postoperative pain scores or postoperative opioid requirements.

Acknowledgments

The authors thank medical students (Leiden University Medical Center) Yvonne Kuo, B.Sc., and Gracia van Wieren, M.D., for their help with the experiments.

Research Support

This investigator-initiated trial was supported by institutional and departmental funds. Medasense Biometrics Ltd.

(Ramat Gan, Israel) provided the hardware devices used in the study.

Competing Interests

Dr. Dahan is chairman of the Institutional Review Board of Leiden University Medical Center, Leiden, The Netherlands, but was not involved in the review or approval of this protocol, and has received speaker fees from Medasense Biometrics Ltd. (Ramat Gan, Israel). The remaining authors declare no competing interests.

Reproducible Science

Full protocol available at: a.dahan@lumc.nl. Raw data available at: a.dahan@lumc.nl.

Correspondence

Address correspondence to Dr. Dahan: Department of Anesthesiology, Leiden University Medical Center, H5-22, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. a.dahan@lumc.nl.

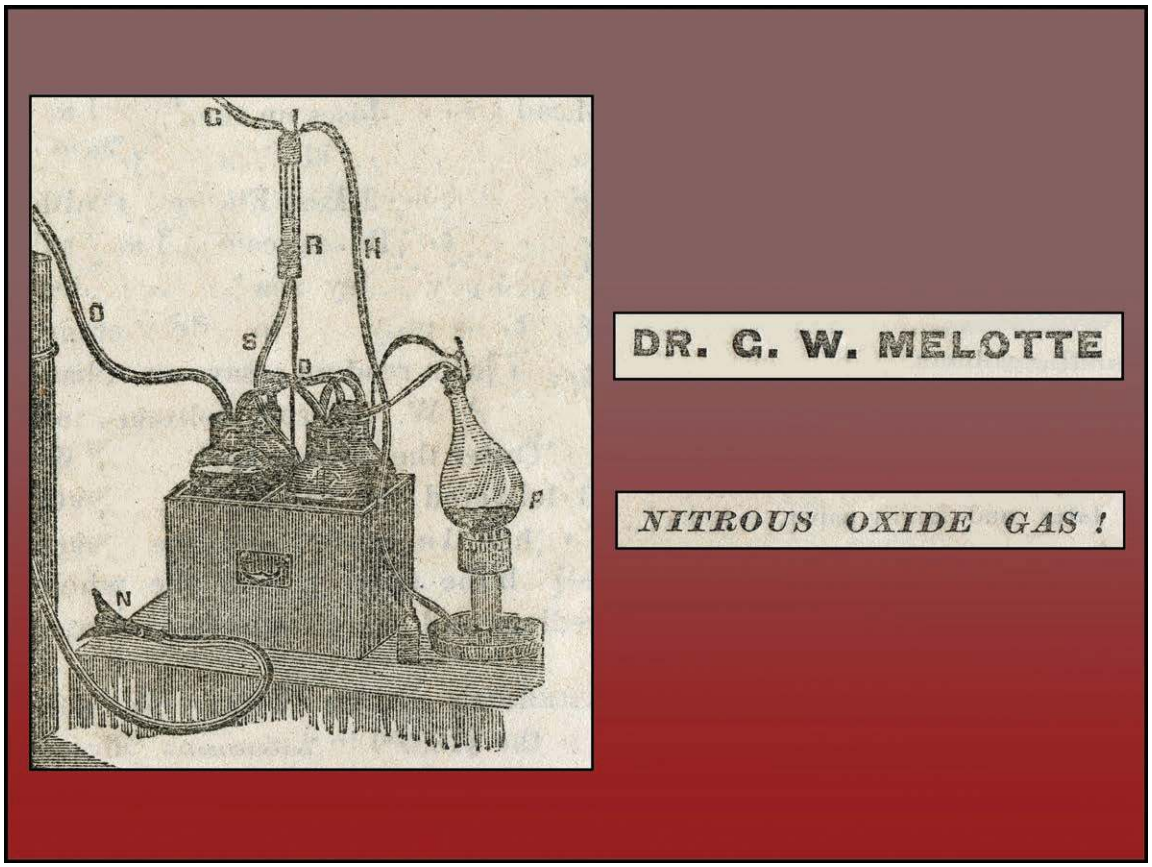
References

1. Connor CW, Conley CM: Commonly used monitoring techniques, Clinical Anesthesia, 8th edition. Edited by Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, Ortega R, Sharar SR, Holt NF. Philadelphia, Wolters Kluwer, 2017, pp 706–30
2. Loeser JD, Treede RD: The Kyoto protocol of IASP Basic Pain Terminology. Pain 2008; 137:473–7
3. Gruenewald M, Dempfle A: Analgesia/nociception monitoring for opioid guidance: Meta-analysis of randomized clinical trials. Minerva Anestesiol 2017; 83:200–13
4. Martini CH, Boon M, Broens SJ, Hekkelman EF, Oudhoff LA, Buddeke AW, Dahan A: Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia. Anesthesiology 2015; 123:524–34
5. Ben-Israel N, Kliger M, Zuckerman G, Katz Y, Edry R: Monitoring the nociception level: A multi-parameter approach. J Clin Monit Comput 2013; 27:659–68
6. Edry R, Recea V, Dikust Y, Sessler DI: Preliminary intraoperative validation of the nociception level index: A noninvasive nociception monitor. Anesthesiology 2016; 125:193–203
7. Upton HD, Ludbrook GL, Wing A, Sleigh JW: Intraoperative "Analgesia Nociception Index"-guided fentanyl administration during sevoflurane anesthesia in lumbar discectomy and laminectomy: A randomized clinical trial. Anesth Analg 2017; 125:81–90
8. Sabourdin N, Barrois J, Louvet N, Rigouzzo A, Guye ML, Dadure C, Constant I: Pupillometry-guided intraoperative remifentanil administration *versus* standard practice influences opioid use: A randomized study. Anesthesiology 2017; 127:284–92
9. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86:10–23
10. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991; 67:41–8
11. Brice DD, Hetherington RR, Utting JE: A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 1970; 42:535–42
12. Chen X, Thee C, Gruenewald M, Wnent J, Illies C, Hoecker J, Hanss R, Steinfath M, Bein B: Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: A pilot study. Anesthesiology 2010; 112:1175–83
13. van den Elsen M, Sarton E, Teppema L, Berkenbosch A, Dahan A: Influence of 0.1 minimum alveolar concentration of sevoflurane, desflurane and isoflurane on dynamic ventilatory response to hypercapnia in humans. Br J Anaesth 1998; 80:174–82
14. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
15. Olofsen E, Boom M, Nieuwenhuijs D, Sarton E, Teppema L, Aarts L, Dahan A: Modeling the non-steady state respiratory effects of remifentanil in awake and propofol-sedated healthy volunteers. Anesthesiology 2010; 112:1382–95
16. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A: Esketamine counters opioid-induced respiratory depression. Br J Anaesth 2018; 120:1117–27
17. Bergmann I, Göhner A, Crozier TA, Hesjedal B, Wiese CH, Popov AF, Bauer M, Hinz JM: Surgical pleth index-guided remifentanil administration reduces remifentanil and propofol consumption and shortens recovery times in outpatient anaesthesia. Br J Anaesth 2013; 110:622–8
18. Colombo R, Raimondi F, Rech R, Castelli A, Fossali T, Marchi A, Borghi B, Corona A, Guzzetti S: Surgical Pleth Index guided analgesia blunts the intraoperative sympathetic response to laparoscopic cholecystectomy. Minerva Anestesiol 2015; 81:837–45
19. Szental JA, Webb A, Weeraratne C, Campbell A, Sivakumar H, Leong S: Postoperative pain after

laparoscopic cholecystectomy is not reduced by intraoperative analgesia guided by analgesia nociception index (ANI®) monitoring: A randomized clinical trial. Br J Anaesth 2015; 114:640–5
20. Gruenewald M, Willms S, Broch O, Kott M, Steinfath M, Bein B: Sufentanil administration guided by surgical pleth index vs standard practice during sevoflurane anaesthesia: A randomized controlled pilot study. Br J Anaesth 2014; 112:898–905
21. Park JH, Lim BG, Kim H, Lee IO, Kong MH, Kim NS: Comparison of surgical pleth index-guided analgesia with conventional analgesia practices in children: A randomized controlled trial. Anesthesiology 2015; 122:1280–7
22. Edry R, Rechea V, Dikust V: NOL index performance with beta-blockers. European Society of Anaesthesiology (ESA) meeting, Geneva, 2017, Abstract 08AP05-12

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Melotte's Nitrous Oxide Ad…That Subtracted: More Than Vague about That Sprague!



An inventive dentist, Dr. George Washington Melotte (1836 to 1915) held eight United States patents, but he had no patentee rights to the nitrous oxide generator depicted (*left*) in his 1870 newspaper advertisement. Melotte had cropped out most of the gasometer from the diagram that originally accompanied the 1868 patent of A. W. Sprague. (Hopefully, Melotte was actually using a Sprague apparatus in his office in Ithaca, New York!) Thirty-seven years after not being challenged for "borrowing" Sprague's diagram, Melotte considered himself challenged by his own mailman. Only the mailbag saved the postal employee from what was deemed Melotte's "temporary insanity" while lunging with a ceremonial sword. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.