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RESEARCH REPORT

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The heart rate variability-derived Newborn Infant Parasympathetic Evaluation (NIPE™) Index in pediatric surgical patients from 0 to 2 years under sevoflurane anesthesia—A prospective observational pilot study

Frank Weber | Hilde G. Roeleveld | Noortje J. E. Geerts | Annejet T. Warmenhoven | Rosalie Schröder | Thomas G. de Leeuw

Department of Anaesthesia, Erasmus University Medical Center - Sophia Children's, Hospital, Rotterdam, The Netherlands

Correspondence
Dr Frank Weber, Department of Anaesthesia, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, The Netherlands.
Email: f.weber@erasmusmc.nl

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Abstract

Background: The heart rate variability-derived Newborn Infant Parasympathetic Evaluation (NIPE™) Index is a continuous noninvasive tool to assess pain and discomfort in infants <2 years. Initial studies focused on pain monitoring in the neonatal intensive care unit environment.

Aims: The aim of this study was to investigate the performance of the NIPE in infants under sevoflurane anesthesia. The primary objective of this study was to compare the NIPE and heart rate as tools to help recognize the need for additional opioid drugs. Secondary objectives were the course of the NIPE and heart rate around specific standardized noxious procedural mile-stones.

Methods: NIPE and heart rate values recorded during a 120 seconds interval before the anesthetist's decision to administer additional opioid due to the perceived insufficient antinociception and during a 120 seconds interval after drug administration were analyzed by means of a repeated measures ANOVA. The same analyses were performed for datasets around per protocol administration of morphine for postoperative analgesia, performance of a caudal block and surgical incision.

Results: In patients with a NIPE value <50, an additional opioid drug administration resulted in a rise of NIPE values, reaching a maximum increase of 5.1 (95% CI: 0.22-9.99) units 120 seconds after drug administration ($P = 0.041$). There was no evidence of a change in heart rate during these two 120 seconds periods. Per protocol administration of morphine, caudal block, and surgical incision did not result in changes of the NIPE, which was around 65 units on these occasions, and heart rate.

Conclusion: In infants anesthetized with sevoflurane, NIPE values <50 might be indicative of insufficient antinociception. The results of this observational pilot study might suggest that the NIPE could be a better measure of the nociception/antinociception balance than heart rate.

KEYWORDS
general anesthesia, infant, monitors, pain

1 | INTRODUCTION

The assessment of the nociception/antinociception balance in anesthetized patients is often performed by using surrogate parameters, such as heart rate and blood pressure, together with other clinical signs such as sweating or movement. These parameters are known to have low sensitivity and specificity in detecting inadequate antinociception, possibly resulting in under- or overdosing of opioid drugs.[1] The clinical impression of an anesthetist surely remains the most frequently applied heuristic approach to help decide whether or not an anesthetized patient needs additional opioids.

Several analgesia monitoring systems, aiming to achieve continuous, objective, and nondisruptive detection of analgesia or assessment of the nociception/antinociception balance have recently become commercially available. These devices use surrogate parameters of nociception, such as processed skin conductance, plethysmography, pupillometry, and heart rate variability (HRV) analysis.[2]

Recent studies performed in anesthetized children suggest that the heart rate variability analysis derived Analgesia Nociception Index (ANI™; Mdoloris Medical Systems, Loos, France) may provide a more sensitive assessment of the nociception/antinociception balance than hemodynamic parameters.[3-5] These pediatric studies are in accordance with the results of studies investigating the performance of the ANI in anesthetized adult patients.[6-8]

The ANI was developed for HRV analysis in adults and children older than 2 years. Neonates and infants (<2 years), due to immaturity of the autonomous nervous system and a higher baseline HR resulting in a lower possible variability, require a modified approach to HRV analysis. The Newborn Infant Parasympathetic Evaluation (NIPE, Mdoloris Medical Systems) Index, a modified version of the ANI, was developed for use in neonates (including premature infants) and infants up to 2 years of age.[9] While there is a growing body of evidence showing the ability of the ANI to provide valid information regarding the nociception/antinociception balance in anesthetized children, little is known about the performance of the NIPE in anesthetized neonates and infants.

The primary objective of this prospective observational pilot study in surgical neonates and infants under sevoflurane anesthesia, was to investigate the ability of the NIPE and heart rate to detect an insufficient antinociception. Major secondary objectives were the impact of per protocol opioid administration for postoperative analgesia, caudal analgesia, and the surgical incision on the course of the NIPE. Changes in NIPE values were compared to concomitant changes in heart rate for all analyses.

What is already known

- Processed heart rate variability is a sensitive measure of insufficient antinociception in anesthetized adult patients and children >2 years. Data regarding its performance in anesthetized neonates and infants are lacking.

What this article adds

- The heart rate variability-derived Newborn Infant Parasympathetic Evaluation (NIPE™) Index might be a more reliable measure of the nociception/antinociception balance in anesthetized infants than heart rate.

2 | MATERIALS AND METHODS

2.1 | Patient selection

This single center prospective observational pilot study was approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam, The Netherlands (MEC-2016-501; August 9, 2016) and was conducted in accordance with the Declaration of the World Medical Association. The written informed consent was obtained for all participating patients from their parents or legal representatives. The study was conducted in accordance with the STROBE guidelines[10] between March and June 2017.

Pediatric patients aged 0-2 years, scheduled for surgical or diagnostic procedures under sevoflurane anesthesia, performed at the Erasmus University Medical Center—Sophia Children's Hospital, Rotterdam, The Netherlands, were eligible for inclusion. According to departmental standards patients received intravenous paracetamol 20 mg/kg and diclofenac 1 mg/kg (only infants >6 months) during the procedure for postoperative analgesia. Depending on the surgical procedure patients furthermore received either a caudal block (ropivacaine 0.2%, 1-1.25 mL/kg) or iv morphine (0.1 mg/kg).

Due to technical requirements of the NIPE algorithm any cardiac rhythm other than sinus rhythm, presence of an internal cardiac pacemaker, high-frequency oscillation- or jet-ventilation during surgery, and chronic use of medication interfering with the cardiac rhythm were defined as primary exclusion criteria. Intraoperative need for clonidine, atropine or inotropes, and vasopressors resulted in secondary exclusion.

2.2 | The Newborn Infant Parasympathetic Evaluation Index

The heart rate variability-derived Newborn Infant Parasympathetic Evaluation Index (NIPE) is calculated by using the ECG signal

recorded by and extracted from the standard anesthesia patient monitoring system (Dräger Infinity®, Drägerwerk AG & Co. KGaA, Lübeck, Germany), without the need for additional ECG electrodes.

The basic principle of the NIPE is the real-time analysis of the parasympathetic (pS) activity of the autonomous nervous system using heart rate variability (HRV) analysis. HRV-signals >0.15 Hz are high pass filtered, enabling an automated HRV analysis of data representative of parasympathetic activity, expressing the physiological respiratory sinus arrhythmia.[9] This automated analysis results in a dimensionless numerical value, called the NIPE. The NIPE ranges from 0 to 100 and reflects relative pS activity, with high index values indicating a high level of pS activity and vice versa. According to the manufacturer, NIPE values <50 are indicative of either discomfort, stress, or pain.[11]

An in depth description of the NIPE methodology and the development of the algorithm has been published by Butruille et al.[9] The NIPE serves as a surrogate parameter of the nociception/antinociception balance in unconscious neonates and infants younger than 2 years, in conscious patients it also reflects comfort and psychological well-being or discomfort and psychological stress.

The NIPE-monitor calculates two types of NIPE indices: The $NIPE_m$ is computed as a mean value over 20 minutes, whereas the instantaneous $NIPE_i$ provides infromation regarding short-term HRV-analysis, displayed as the result of a 64 seconds moving window with an update frequency of 1 per second.[12] In this study, designed to investigate acute changes of the nociception/antinociception balance during surgery, we only used the $NIPE_i$; for simplicity's sake, in this paper we refer to it as the NIPE.

2.3 | Intraoperative collection of study data

NIPE- and heart rate data, recorded during the anesthetic, were downloaded from the NIPE-monitor as .txt-files. Data derived from our Dräger Infinity patient monitoring system were exported as .xls files. Only data recorded during the surgery were used for subsequent analysis.

The pediatric anesthetist in charge was blinded to the screen of the NIPE monitor and the conduct of the anesthetic was totally unrestricted. Each decision to give an opioid analgesic, for whatever reason, was announced to a researcher who recorded this decision and the subsequent drug administration.

2.4 | Statistical analysis

Analyses were performed using data timely related to predefined events. An event was defined as the intraoperative administration of opioid drugs, either due to the clinical judgement of insufficient antinociception or per-protocol administration for postoperative analgesia.

Repeated measures (RM) one-way ANOVA with subsequent Dunnett's multiple comparisons test was performed to investigate the course of NIPE and HR-values; for the primary objective of the study during a 120 seconds period both before the clinical judgement of insufficient antinociception and after subsequent opioid drug application. Additionally, a Wilcoxon matched-pairs signed rank test, comparing the lowest NIPE values (along with associated HR values) during the 120 seconds predecision period to the NIPE/HR values 120 seconds after opioid drug application was performed.

Both ANOVA and the Wilcoxon matched-pairs signed rank test were performed separately for cases when the NIPE was either <50 ($Decision_{NIPE\ <50}$) or ≥50 ($Decision_{NIPE\ \geq 50}$) at the time of decision to administer additional opioid analgesia.

For the secondary objectives, ANOVA was performed to investigate the impact of per-protocol application of morphine for postoperative analgesia the effect of caudal epidural analgesia and surgical incision on the NIPE.

Unfortunately, we had no scientifically sound data available on which we could have based a valid sample size calculation. We assumed that data from at least 50 patients should provide us with sufficient information to further develop our research efforts regarding monitoring of the nociception/antinociception balance in anesthetized infants. The duration of the project was set to 3 months, which based on our average annual number of anesthetics performed in children younger than 2 years, should be sufficient to include ≥50 participants.

Data analysis was performed using Prism 7 for Mac OS X (Version 7.0e, GraphPad Software Inc, La Jolla, CA). Continuous data were presented as mean (SD). *P* values <0.05 were considered significant.

3 | RESULTS

3.1 | Participant demographics and general patient information

A total of 74 patients (female/male: 20/54) was recruited for participation, of which 7 patients had to be excluded from data analysis due to the permanent data logging failure. Age and weight of the remaining 67 patients were 36.7 ± 21.5 weeks (postnatal age) and 8.03 ± 2.34 kg, respectively. Information regarding the surgical procedures and anesthesia techniques are given in Table 1.

TABLE 1 Distribution of surgical procedures performed, together with anesthesia technique

	Anesthesia technique	
Type of surgery	General anesthesia	Anesthesia with caudal block
Ear nose & throat surgery	3	
Ophthalmological surgery	5	
General pediatric surgery	8	10
Neurosurgery	15	
Oral & maxillofacial surgery	9	
Orthopedic surgery	1	1
Plastic surgery	1	1
Urological surgery		13

Data are presented as total numbers.

A total of 54 events (intraoperative opioid drug administration) was recorded, of which 14 had to be excluded from analysis due to incidental data logging errors. Another 25 datasets describing the course of the NIPE in patients receiving caudal analgesia were recorded, of which 4 had to be excluded from analysis due to incidental data logging errors. Incidental data logging errors were mainly due to missing data when surgical diathermy was applied. Complete datasets of the course of the NIPE and HR around the time of surgical incision, recorded in patients who had not received regional anesthesia were available for analysis in 35 patients.

3.2 | Course of NIPE and HR values around opioid administration due to perceived insufficient antinociception

Data from 10 events recorded in patients with NIPE values <50 at the time of decision ($Decision_{NIPE\ <50}$), were available for analysis. RM-ANOVA revealed no evidence of a difference between NIPE-values at the time of decision to give opioid drugs due to a perceived need for additional opioid drug analgesia and NIPE-values 30, 60, 90, and 120 seconds before. The reasons to give additional opioid drugs were either a perceived rise in heart rate, patient movement or the subjective impression of the anesthetist. Due to the relatively low number of total events we were unable to perform a meaningful subgroup analysis as to the reason to give additional opioid drugs. We found evidence of an increase in NIPE values 90 and 120 seconds after drug administration (fentanyl 1.6 ± 0.6 µg/kg [n = 25], sufentanil 0.2 µg/kg [n = 5], or increasing remifentanil infusion at the discretion of the anesthetist [n = 10]) compared to the moment of the intervention and a weak evidence of such a difference 60 seconds after drug administration. There was no evidence of a change in heart rate during the entire period (before decision: $P = 0.165$; after opioid administration: $P = 0.063$). Data from 30 events recorded in patients with NIPE values ≥50 at the time of decision ($Decision_{NIPE\ ≥50}$), showed stable NIPE- and HR values during the entire period before and after opioid drug administration. For details see Figure 1 and Table 2.

A Wilcoxon matched-pairs signed rank test comparing the lowest NIPE/HR values during a 120 seconds. period prior to opiod drug administration to NIPE/HR 120 seconds after opiod administration showed higher NIPE values after opioid administration in cases with predecision values <50 (n = 16), but not with predecision values ≥50 (n = 26). We found no evidence of a difference in heart rate before and after opioid drug administration. For details see Table 3.

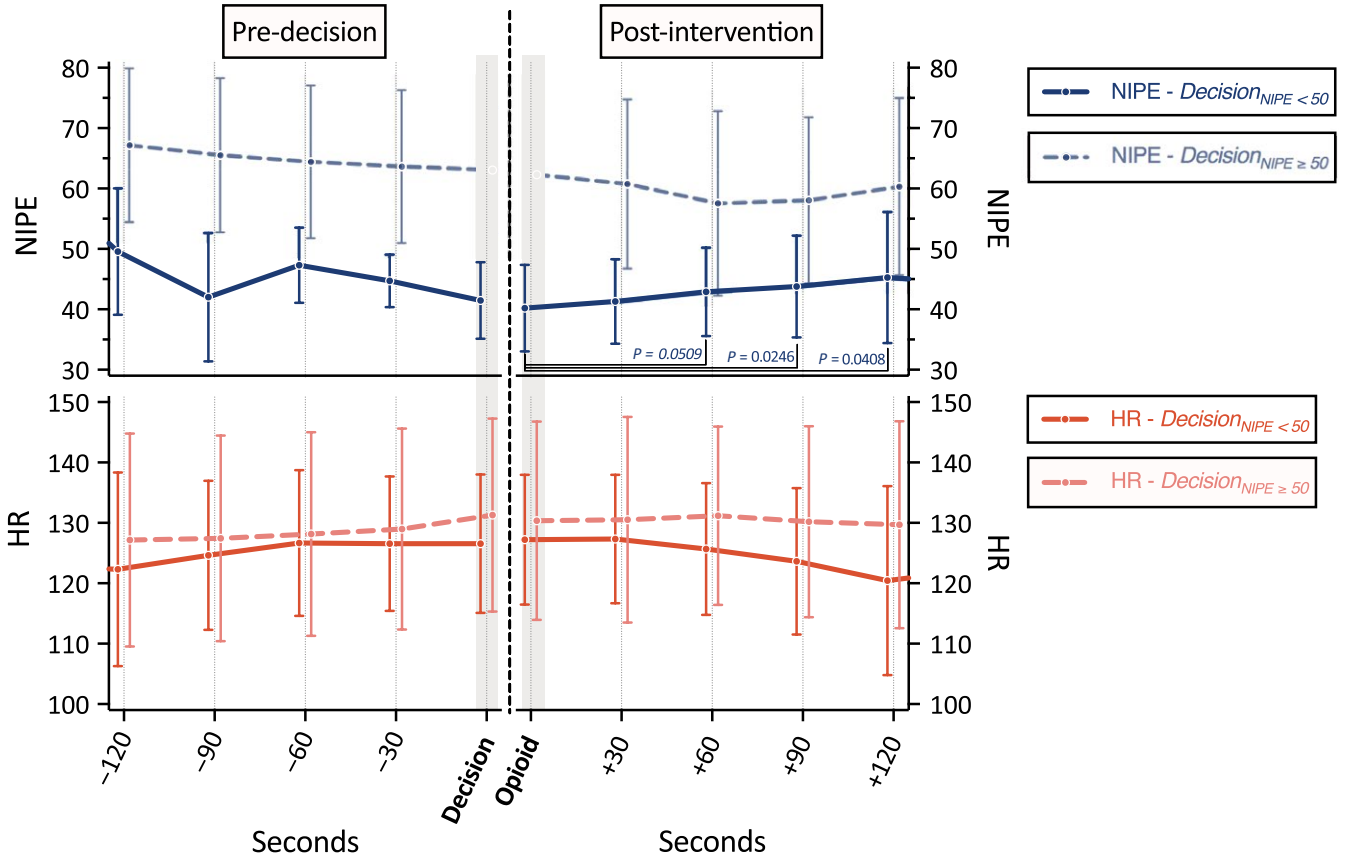

FIGURE 1 Course of the Newborn Infant Parasympathetic Evaluation Index (NIPE) and heart rate (HR) before and after iv opioid drug administration associated with NIPE-values <50 (n = 10) and ≥ 50 (n = 30) at the moment of decision to administer opioids. Data are presented as mean ± SD [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Repeated measures one-way ANOVA with Dunnett's multiple comparisons test comparing NIPE values over time

	Mean Diff.	95% CI of diff.	Adjusted *P* value
NIPE <50 at time of decision (n = 10) [see Figure 1]			
Decision vs −120 s	−8.1	−18.88 to 2.68	0.154
Decision vs −90 s	−0.5	−13.02 to 12.02	0.999
Decision vs −60 s	−5.8	−13.91 to 2.31	0.181
Decision vs −30 s	−3.2	−7.23 to 0.82	0.127
Intervention vs + 30 s	−1.1	−2.94 to 0.74	0.295
Intervention vs + 60 s	−2.7	−2.94 to 0.75	0.051
Intervention vs + 90 s	−3.6	−6.71 to −0.49	0.025
Intervention vs + 120 s	−5.1	−9.99 to −0.22	0.041
NIPE ≥50 at time of decision (n = 30) [see Figure 1]			
Decision vs −120 s	−4.1	−9.01 to 0.81	0.123
Decision vs −90 s	−2.4	−6.86 to 2.06	0.451
Decision vs −60 s	−1.3	−4.69 to 2.09	0.719
Decision vs −30 s	−0.6	−3.85 to 2.72	0.976
Intervention vs + 30 s	1.6	−0.78 to 3.92	0.271
Intervention vs + 60 s	4.7	−1.09 to 10.56	0.137
Intervention vs + 90 s	4.2	−0.75 to 9.22	0.114
Intervention vs + 120 s	2.0	−3.44 to 7.37	0.753
NIPE around per protocol administration of morphine (n = 9) [see Figure 2]			
Intervention vs + 60 s	5.0	−8.1 to 18.1	0.656
Intervention vs + 120 s	3.8	−7.27 to 14.82	0.733
Intervention vs + 180 s	11.4	−1.78 to 24.67	0.092
Intervention vs + 240 s	3.9	−8.19 to 15.97	0.770
Intervention vs + 300 s	0.8	−11.57 to 13.13	0.10
NIPE around caudal block (n = 21) [see Figure 3]			
−30 sec vs block	−0.3	−3.1 to 2.44	0.980
−30 sec vs block + 30 s	3.6	−2.45 to 9.59	0.327
−30 sec vs block + 60 s	3.8	−2.04 to 9.66	0.260
−30 sec vs Incision	−1.5	−4.47 to 1.52	0.541
−30 sec vs Inc +30 s	2.2	−3.12 to 7.56	0.681
−30 sec vs Inc +60 s	4.1	−1.5 to 9.73	0.208
−30 sec vs Inc +90 s	4.2	−2.23 to 10.61	0.291
−30 sec vs Inc +120 s	4.67	−3.12 to 12.51	0.371
NIPE around surgical incision (n = 35)			
−10 sec vs Incision	0.3	−0.93 to 1.61	0.895
−10 sec vs Inc +10 s	0.8	−1.21 to 2.86	0.684
−10 sec vs Inc +20 s	0.8	−1.28 to 2.82	0.738
−10 sec vs Inc +30 s	1.49	−1.21 to 4.18	0.431

3.3 | Course of NIPE and HR values around per protocol application of morphine

Data from nine events were available for analysis. RM-ANOVA revealed no evidence of a difference in NIPE and HR values within both 120 seconds windows prior to decision to give morphine (NIPE: $P = 0.573$; HR: $P = 0.709$) and 300 seconds after administration of 0.1 µg/kg morphine (NIPE: $P = 0.170$; HR: $P = 0.183$). The lowest and highest NIPE values after morphine application were 55 ± 12.4 and 65 ± 12.3, respectively. For details see Figure 2 and Table 2.

3.4 | Course of NIPE and HR values in patients with supplemental caudal block

Data from 21 patients were available for analysis. RM-ANOVA revealed no evidence of a difference in NIPE and HR values in

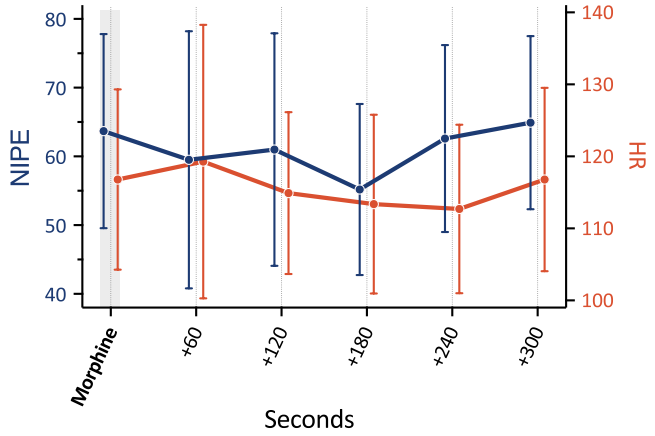

FIGURE 2 Course of the Newborn Infant Parasympathetic Evaluation Index (NIPE) and heart rate (HR) after per-protocol administration of iv morphine for postoperative analgesia; (n = 9). Data are presented as mean ± SD [Colour figure can be viewed at wileyonlinelibrary.com]

response to the application of the caudal block (NIPE: $P = 0.11$; HR: $P = 0.665$) and surgical incision, which was allowed after a minimum of 10 min after caudal block (NIPE: $P = 0.05$; HR: $P = 0.941$); the lowest and highest NIPE values within this dataset were 65.4 ± 17.4 and 71.1 ± 13.7, respectively. For details see Figure 3 and Table 2.

3.5 | Course of NIPE and HR values around surgical incision

Data from 35 patients (no supplemental regional anesthesia) were available for analysis. RM-ANOVA revealed no evidence of a difference in NIPE and HR values in response to surgical incision (NIPE: $P = 0.30$; HR: $P = 0.821$); the lowest and highest NIPE values within this dataset were 62.8 ± 14.6 and 64.3 ± 15.8, respectively. For details see Table 2.

4 | DISCUSSION

The results of this observational pilot study in infants younger than 2 years, anesthetized with sevoflurane, allow us to provisionally suggest the ability of the NIPE to detect insufficient antinociception. This provisional conclusion is derived from the course of 10 events, where NIPE values <50 at the time of opioid drug administration developed positively within 120 seconds (see Table 2 and Figure 1) and of another 30 events, where NIPE values ≥50 remained unchanged after opioid drug administration. Heart rate showed a trend toward higher values prior to opioid drug administration and lower values thereafter, without reaching statistical significance (P preopioid = 0.165; P postopioid = 0.063).

TABLE 3 Wilcoxon matched–pairs signed rank test comparing NIPE/Heart rate values before and after opioid drug application

	Median Diff.	95% CI of diff.	*P* value
NIPE <50 before decision (n = 16)			
NIPE	11	6 to 22	< 0.001
Heart rate	0	−3 to 2	0.692
NIPE ≥50 before decision (n = 26)			
NIPE	−2.5	−17 to 6	0.167
Heart rate	−1.5	−4 to 0	0.094

In our study surgical incision in patients who had a caudal block did not result in a rise of HR, any visible reaction or subsequent lower NIPE values. From a clinical perspective we were able to conclude that our patients had sufficient epidural analgesia. NIPE values confirmed this clinical impression.

Though these are promising findings, any conclusions regarding the performance of the NIPE as a monitor of the nociception/antinociception balance in anesthetized infants are subject to restrictions, for the following reasons: The threshold of an index value of 50 indicating either sufficient or insufficient antinociception has been suggested by the manufacturer of the device; its plausibility has not yet been investigated in the clinical setting of pediatric anesthesia. The NIPE-50-threshold is an extrapolation of the 50 units threshold recommended when using the "adult version" of the device, the Analgesia Nociception Index (ANI), with a growing body of evidence suggesting sufficient antinociception associated with ANI values ≥50, while values <50 are indicative of insufficient antinociception.[1]

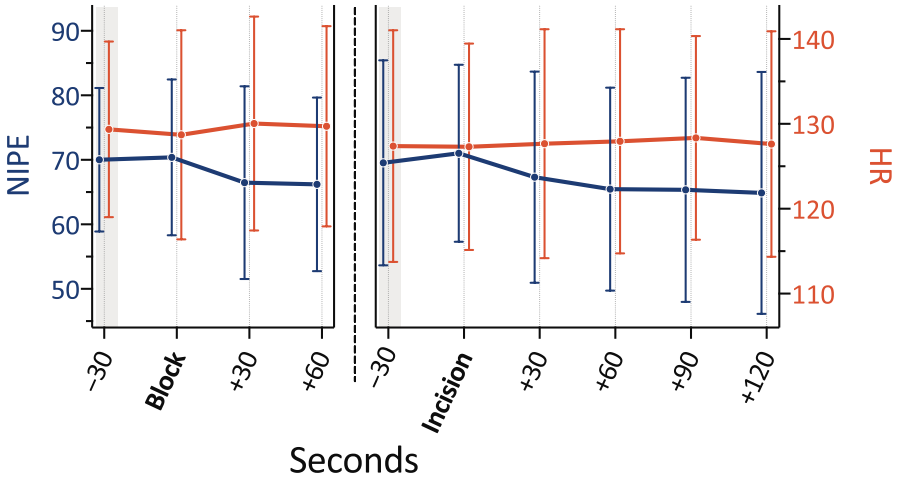

FIGURE 3 Course of the Newborn Infant Parasympathetic Evaluation Index (NIPE) and heart rate (HR) before and after caudal block (left) and surgical incision (right); (n = 21). Data are presented as mean ± SD [Colour figure can be viewed at wileyonlinelibrary.com]

Though NIPE values increased statistically significantly after opioid drug administration in our study, the magnitude of this increase was only 5 units on average, reaching a mean NIPE of no more than 45 after 120 seconds. It remains subject to speculation whether or not this is a clinically relevant difference.

This and other findings can easily be compared to the results of our recent pediatric study with the ANI monitor, using exactly the same study design in patients aged between 2 and 12 years. ANI values <50 before opioid drug administration showed a significantly higher increase in approximately 10 units within 120 seconds, travelling across the 50 units border.[5]

In the current study, as in our aforementioned study with the ANI, NIPE values higher than ±60 at the moment of opioid drug administration, either due to a perceived need for additional analgesia or per protocol administration of morphine for postoperative analgesia, remained stable. The same accounts for heart rate. However, we are still lacking independent research data supporting the intraoperative target range of 50-70 suggested by the device manufacturer. Nevertheless, these data could be a first indication that NIPE values higher than 60 might be indicative of sufficient antinociception. This tentative conclusion by no means suggests a NIPE value of 60 as a threshold value to make a distinction between sufficient and insufficient antinociception.

The NIPE was originally developed as an adaption of the ANI technology for the clinical contexts of pain monitoring in neonates on the neonatal intensive care unit and the maternity unit,[9] with a special focus on prolonged pain assessment.[12] Faye et al[13] applied the NIPE algorithm to investigate high frequency heart rate variability (HRV) as an indicator of prolonged postoperative pain in full-term neonates and found an association between pain decreased HRV, suggesting HRV as a measure of prolonged pain in this particular patient group. Cremillieux et al[14] investigated the performance of the NIPE as an objective tool for acute pain assessment in 29 preterm neonates (mean gestational age 29.9 ± 4.2 weeks) and found no correlation between the NIPE and two validated clinical pain scales. In the present study, no premature infants were included.

In conscious subjects, HRV is a well-established measure of cardiac autonomic control, primarily mediated by the floating balance between sympathetic and parasympathetic tone. From a clinical point of view, HRV can be regarded as a surrogate for (dis-) comfort and/or psychological well-being or stress. Under general anesthesia conditions, with patients being unconscious, we are faced with a completely different scenario. Comfort and pain, both expressions of conscious perception, can by definition not be applied in anesthetized patients. This is not just a semantical question, it describes a significant issue regarding the applicability of HRV-derived devices as monitors of the nociception/antinociception balance in anesthetized patients. In accordance with the current scientific literature we assume that in patients anesthetized with sufficient hypnotic drug concentrations to assure unconsciousness, intraoperative HRV fluctuations are primarily a reflection of the nociception/antinociception balance.[1] This assumption is the all-important prerequisite for any meaningful study on the NIPE in surgical neonates and infants. Unfortunately, the aforementioned assumption has never been proven and we have no idea how this goal could ever formally be reached.

Sevoflurane effect on baroreceptor reflex might be an issue when using HRV derived technology under anesthesia conditions. A clinical study performed in adult patients showed that sevoflurane attenuates the baroreceptor reflex, which is known to contribute to heart rate variability.[15] Kanaya et al[16] found little to no effect of sevoflurane on the high frequency component of heart rate variability, which is used for analysis with the NIPE.

Heart rate variability (HRV) analysis has recently gained a great deal of attention, especially in neonatology research. HRV is significantly positively correlated with gestational age, like blood pressure, while heart rate shows a negative correlation[17]; these findings are very likely related to the degree of maturation of the autonomic nervous system.[18]

4.1 | Shortcomings

We did not use blood pressure (BP) values as surrogate parameters of the nociception/antinociception balance in our study, which could be regarded as a shortcoming. In our hospital, noninvasive BP measurements, performed at 5 minutes intervals are the standard of care. It would make no sense to compare a single BP value recorded every 5 minutes to a NIPE- or HR-value with update frequencies of 1 per second. Invasive BP registrations with a continuous recording would be an interesting parameter to investigate in relation to both NIPE and HR, but we only use them in selected high-risk patients undergoing major surgery.

There may be some criticism regarding the 120 seconds observation window after opioid drug administration, because it could be that 120 seconds is too short a period of time for the opioid drugs delivered to have reached their peak effect. On the other hand, extending that period to 180 or 240 seconds comes with an increased risk of significant variation in surgical noxious stimulation. However, the possibility remains that we missed some opioid drug effect.

It might as well be that, at least in some patients, the amounts of fentanyl/sufentanil/remifentanil applied were insufficient to re-establish sufficient antinociception. Furthermore, we cannot entirely rule out occasional misjudgments in the decision-making regarding the need for additional opioid drugs; in other words: there was no real "proof" of insufficient antinociception.

Due to the design of this strictly observational pilot study, there was a multitude of different noxious stimuli influencing the nociception/antinociception balance. A standardized noxious stimulus and a standardized anesthetic protocol would be desirable, but requires an intervention study design, which would have been inappropriate to perform at that stage.

4.2 | Future directions

The results of this study can help to design sufficiently powered future studies investigating the performance of the NIPE in anesthetized infants. A reliable NIPE cut-off value to distinguish between sufficient

and insufficient antinociception is desirable, though we are aware that this will be a major methodological challenge. Furthermore, future NIPE studies should focus on dose-response relationships of intraoperative opioid-drug administration in neonates and infants.

5 | CONCLUSION

The results of this observational study allow the following careful first conclusions regarding the performance of the NIPE in term-neonates and infants anesthetized with sevoflurane: NIPE values <50 might be indicative of insufficient antinociception. Whether or not an average rise of 5 NIPE units within 120 seconds after opioid drug administration reflects re-establishment of sufficient antinociception remains unclear. A rise in NIPE values after opioid drug administration is not necessarily associated with changes in heart rate. Whether or not the finding that a rise in NIPE values after opioid drug administration is not necessarily associated with changes in heart rate is due to a superiority of the NIPE over heart rate as a measure of the nociception/antinociception balance needs to be addressed in future clinical studies.

ETHICAL APPROVAL

Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam, The Netherlands, MEC-2016-501; date of approval: August 9, 2016.

CONFLICT OF INTEREST

No conflict of interest declared.

ORCID

Frank Weber https://orcid.org/0000-0001-6644-3435

Thomas G. de Leeuw https://orcid.org/0000-0001-9516-3088

REFERENCES

1. Daccache G, Jeanne M, Fletcher D. The analgesia nociception index: tailoring opioid administration. *Anesth Analg*. 2017;125:15-17.
2. Gruenewald M, Ilies C. Monitoring the nociception-anti-nociception balance. *Best Pract Res Clin Anaesthesiol*. 2013;27:235-247.
3. Migeon A, Desgranges F-P, Chassard D, et al. Pupillary reflex dilatation and analgesia nociception index monitoring to assess the effectiveness of regional anesthesia in children anesthetised with sevoflurane. *Pediatr Anesth*. 2013;23:1160-1165.
4. 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 remifentanil. *Pediatr Anesth*. 2013;23:149-155.
5. Weber F, Geerts N, Roeleveld Hg, Warmenhoven At, Liebrand Ca. The predictive value of the heart rate variability-derived analgesia nociception index in children anaesthetized with sevoflurane: an observational pilot study. *Eur J Pain*. 2018;22:1597-1605.
6. Boselli E, Bouvet L, Begou G, et al. Prediction of hemodynamic reactivity during total intravenous anesthesia for suspension laryngoscopy using analgesia/nociception index (ANI): a prospective observational study. *Minerva Anestesiol*. 2015;81:288-297.
7. Gruenewald M, Herz J, Schoenherr T, et al. Measurement of the nociceptive balance by analgesia nociception index and surgical pleth index during sevoflurane-remifentanil anesthesia. *Minerva Anestesiol*. 2015;81:480-489.
8. Gruenewald M, Ilies C, Herz J, et al. Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol-remifentanil anaesthesia. *Br J Anaesth*. 2013;110:1024-1030.
9. Butruille L, De jonckheere J, Marcilly R, et al. Development of a pain monitoring device focused on newborn infant applications: The NeoDoloris project. *IRBM*. 2015;36:80-85.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
11. Mdoloris Medical Systems. Newborn Infant Parasymathetic Evaluation (NIPE) Product Brochure (Website). August 07, 2018. https://www.mdoloris.com/en/technologies/nipe-newborn-infant-parasympathetic-evaluation/. Accessed August 7, 2018.
12. De Jonckheere J, Rakza T, Logier R, et al. Heart rate variability analysis for newborn infants prolonged pain assessment. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:7747-7750.
13. Faye PM, De Jonckheere J, Logier R, et al. Newborn infant pain assessment using heart rate variability analysis. *Clin J Pain*. 2010;26:777-782.
14. Cremillieux C, Makhlouf A, Pichot V, Trombert B, Patural H. Objective assessment of induced acute pain in neonatology with the newborn infant parasympathetic evaluation index. *Eur J Pain*. 2018;22:1071-1079.
15. Tanaka M, Nishikawa T. Arterial baroreflex function in humans anaesthetized with sevoflurane. *Br J Anaesth*. 1999;82:350-354.
16. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A. Differential effects of propofol and sevoflurane on heart rate variability. *Anesthesiology*. 2003;98:34-40.
17. Cardoso S, Silva MJ, Guimaraes H. Autonomic nervous system in newborns: a review based on heart rate variability. *Childs Nerv Syst*. 2017;33:1053-1063.
18. Javorka K, Lehotska Z, Kozar M, et al. Heart rate variability in newborns. *Physiol Res*. 2017;66:S203-S214.

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