

## RESEARCH REPORT

# The performance of the heart rate variability-derived Newborn Infant Parasympathetic Evaluation Index as a measure of early postoperative pain and discomfort in infants—A prospective observational study

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**Abstract**

**Background:** The heart rate variability-derived Newborn Infant Parasympathetic Evaluation (NIPE™) Index is a continuous noninvasive tool for the assessment of pain and discomfort in infants. Little is known about its performance in the early postoperative setting, where assessment of pain/discomfort is usually based on discontinuous observational scoring systems or personal experience of medical staff.

**Aims:** To investigate the performance of the NIPE as a measure of early postoperative pain and/or discomfort in infants.

**Methods:** The potential of the NIPE to detect pain/discomfort, as assessed by two clinical scoring systems (FLACC and COMFORT-B scale), was investigated in postoperative infants (0–2 years).

**Results:** Receiver operating curve (ROC) analyses investigating the power of the NIPE to distinguish between comfort and pain/discomfort, revealed areas under the curve (AUC) of 0.77 for the FLACC, 0.81 for the COMFORT-B score, and 0.77 for a combination of FLACC & COMFORT-B. Logistic regression analysis provided initial evidence that the NIPE is an independent predictor of a FLACC score  $\geq 4$  and/or a COMFORT-B score  $\geq 17$ , though  $R^2$  values were below .2. NIPE values associated with a FLACC  $\geq 4$  (48 [45–56]), a COMFORT-B score  $\geq 17$  (47 [42–53]), and a FLACC  $\geq 4$  & COMFORT-B  $\geq 17$  (47 [42–57]) were lower than NIPE values associated with a FLACC  $< 4$  (60 [53–68], 95% CI of difference  $-14$  to  $-8$ ,  $p < .0001$ ), a COMFORT-B score  $< 17$  (61 [54–68], 95% CI of difference  $-16$  to  $-10$ ,  $p < .0001$ ), and a FLACC  $< 4$  & COMFORT-B score  $< 17$  (60 [53–68], 95% CI of difference  $-15$  to  $-8$ ,  $p < .0001$ ). We found no evidence of a predictive value of the NIPE regarding the occurrence of pain.

**Conclusions:** The NIPE detected pain and discomfort in infants after general anesthesia with reasonable areas under the ROC curve ( $\pm 0.8$ ), whereas it was not predictive of clinically detectable pain or discomfort.

Verweij and Weber contributed equally to this manuscript

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**KEYWORDS**

infant, monitors, neonate, pain

**Clinical Implications**

What is already known about the topic

- Heart rate variability analysis is a reliable noninvasive objective assessment method for stress.
- The heart rate variability-derived Newborn Infant Parasympathetic Evaluation Index (NIPE) has been shown to be able to distinguish between sufficient and insufficient antinociception in anesthetized infants.

What new information this study adds

- The validity of NIPE monitoring as an assessment tool for pain and/or discomfort in postoperative infants appears to be comparable to established clinical scoring systems.
- The NIPE does not seem to be predictive of clinically detectable pain and/or discomfort.

**1 | INTRODUCTION**

Reliable assessment of early postoperative pain in infants and preverbal children is both relevant and methodologically challenging. Contrary to adults, self-reporting pain scales, even when specifically designed for children, are not applicable before the age of 4 years.

The FLACC scale<sup>1</sup> and the COMFORT-B score<sup>2</sup> are two clinical scoring systems aiming to detect pain and/or discomfort; both have been specifically validated for use in infants. However, at least in our institution, early postoperative pain in infants is most often judged by recovery room staff almost intuitively and/or based on personal experience. Many other hospitals do it just the same.

The heart rate variability (HRV)-derived Newborn Infant Parasympathetic Evaluation Index (NIPE™; Metrodoloris, France), designed to assess the parasympathetic/sympathetic tone balance in neonates and infants up to 2 years of age, may help assess early postoperative pain and or discomfort. The NIPE provides continuous information regarding the parasympathetic/sympathetic tone balance, while clinical scoring systems deliver discontinuous information on pain and/or discomfort.

Initial publications describing the use of the NIPE in anesthetized infants were promising.<sup>3,4</sup> A recent study performed in awake premature neonates showed the NIPE not to be a reliable tool for assessment of procedural pain in this particular setting,<sup>5</sup> whereas another study in a comparable setting found initial evidence of the applicability of the NIPE.<sup>6</sup> A third study found no correlation between the NIPE and the COMFORT-B scale during a painful procedure in awake infants admitted to a pediatric intensive care unit.<sup>7</sup> Data describing the performance of the NIPE during the initial postoperative period in infants have not yet been published.

We evaluated the NIPE as a measure of infant pain and/or discomfort during the initial period of recovery from general anesthesia. The primary endpoint of this study was the potential of the NIPE to detect pain and/or discomfort. A major secondary outcome was the predictive value of the NIPE regarding the development of pain and/or discomfort.

**2 | MATERIALS AND METHODS**

This single-center prospective observational pilot study was approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam, The Netherlands (MEC-2013-1131; November 23, 2017), and was conducted in accordance with the Declaration of the World Medical Association. 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<sup>8</sup> between January and April 2018.

**2.1 | Patients and data-collection**

Pediatric patients aged 0–2 years, admitted to the pediatric postanesthesia care unit (PACU) at Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands, after a surgical procedure under general anesthesia (with or without additional locoregional analgesia) were eligible for inclusion, provided they were breathing spontaneously at the time of PACU admission. Patients with a heart rhythm other than a sinus rhythm or an implanted pacemaker or receiving drugs known to interfere with the autonomic nervous system pre- or intraoperatively were not considered eligible for inclusion.

Besides constant clinical patient observation by our dedicated PACU nurses, monitoring consisted of pulse-oximetry and ECG. We allowed children to have their ECG stickers removed should they become upset from being attached to them.

**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 our standard anesthesia patient monitoring system, without the need for additional ECG electrodes.

The NIPE is the result of a 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.<sup>9</sup> 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.<sup>10</sup>

An in-depth description of the NIPE methodology and the development of the algorithm has been published by Butruille et al.<sup>9</sup> In anesthetized surgical infants, the NIPE serves as a surrogate parameter of the nociception/anti-nociception balance, showing a decline in values (indicating a shift toward less parasympathetic activity) in case of insufficient antinociception and a rise in values (indicating an opposite shift toward more parasympathetic activity) after re-establishment of adequate antinociception by opioid drug administration.<sup>3</sup> In conscious patients, comfort and psychological well-being or discomfort and psychological stressors have profound effects on heart rate variability.<sup>11</sup> Therefore, in awake infants, the NIPE may be a stress monitor in the first place, independent of the precipitating factors of stress. Pain is, of course, one of the factors that trigger stress.

The NIPE monitor calculates two types of NIPE indices: The NIPE<sub>m</sub> is computed as a mean value over 20 min, whereas the instantaneous NIPE<sub>i</sub> provides information regarding short-term HRV analysis. The NIPE<sub>i</sub> is a moving average value representing the previous 64 s with an update frequency of 1/sec.<sup>12</sup> In this study, we only used the NIPE<sub>i</sub>; for simplicity's sake, we shall refer to it as the NIPE.

### 2.3 | FLACC and COMFORT-B monitoring

FLACC is an acronym representing the five categories Face, Legs, Activity Cry, and Consolability. The FLACC scale is a behavioral tool that has been validated for postoperative pain assessment in young children (2 months–4 years).<sup>1</sup> Observations in each of the five categories can be scored between 0 and 2; a total score of 4–6 represents moderate pain, scores  $\geq 7$  indicate severe pain and/or discomfort.

The COMFORT-B scale is an observational tool designed to assess comfort in young children. Six categories with five levels each result in a maximum score of 30. A COMFORT-B score of  $\geq 17$  has been suggested as a threshold for discomfort,<sup>2</sup> while the additional execution of a visual analog scale is required for pain assessment. The two researchers who took the COMFORT-B scores in our study (L.M.V. and J.K.) had followed an online training in advance. The researcher who took the clinical scores was blinded to the screen of the NIPE monitor.

We defined pain and discomfort based on the previously described clinical scores in the first place. A FLACC score  $\geq 4$  was defined as pain, and a COMFORT-B score of  $\geq 17$  was defined as discomfort. We also applied a composite value of FLACC  $\geq 4$  plus COMFORT-B  $\geq 17$  as an alternative indicator of pain.

FLACC and COMFORT-B scores were assessed at 5 min intervals and in case of observations indicating a change in patient comfort (ie, crying).

### 2.4 | Statistics

Receiver operating curve (ROC) analyses were performed to investigate the performance of the NIPE in detecting discomfort and pain, simultaneously clinically assessed by means of the FLACC and the COMFORT-B score. Besides sensitivity and specificity, Likelihood Ratios [LR = sensitivity/(1-specificity)] were calculated. Furthermore, logistic regression analysis was performed to examine the association of the NIPE index and FLACC and/or COMFORT-B above and below threshold values (FLACC  $\geq 4$ , COMFORT-B  $\geq 17$ ).

Newborn Infant Parasympathetic Evaluation values associated with FLACC and or COMFORT-B scores both above and below the predefined threshold values were compared by means of a Mann-Whitney test.

To investigate the ability of the NIPE to predict pain or discomfort, NIPE values corresponding to either a FLACC score  $\geq 4$  and/or a COMFORT-B score  $\geq 17$  were compared to NIPE values recorded 5–4–3–2–1 min before that event. A significant downward trend in NIPE values before clinical signs of pain and/or distress is observed by means of FLACC and COMFORT-B assessment would be regarded as predictive value of the NIPE to detect pain or discomfort. These data were analyzed by fitting a repeated measures mixed model, capable of handling missing values.

Statistical analyses were performed using Prism 9 for macOS, version 9.1 (GraphPad Software, San Diego, CA, U.S.A.) and MedCalc Statistical Software, version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium).

Due to a lack of published data, we were not able to perform a meaningful sample size calculation.

We assumed that data from at least 100 patients should provide us with sufficient information to draw sound conclusions regarding the applicability of the NIPE in the early postoperative setting in 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  $\geq 100$  patients.

Continuous data are presented as mean (sd) or median[IQR] as appropriate, and *p*-values  $<.05$  are considered significant.

## 3 | RESULTS

A total of 1222 observations/datasets (FLACC & COMFORT-B score) were recorded in 121 patients. In 60 datasets (4.9%), no NIPE values were available due to insufficient ECG signal quality caused by patient motion artifacts. 1162 complete datasets (NIPE/FLACC/COMFORT-B score) were available for analysis. For details regarding patient characteristics and surgical procedures, see Table 1. 69% of our patients were unresponsive to their environment at the time

TABLE 1 Patient characteristics

Age (months)	8.3 (5.3)
Female/Male	37/84
Weight (kg)	7.9 (2.4)
Height (cm)	69 (11)
Duration ECG registration (min)	41 (25)
Type of procedure	
General surgery	37
Cardiac catheterization	2
Plastic surgery	23
Neurosurgery	1
Urologic surgery	43
Ophthalmologic surgery	6
Orthopedic surgery	6
Oncology treatment	3
Endoscopy (airway)	4
MRI scan	1

Note: Patient data (except Female/Male) are given as mean (sd).

Five patients had two procedures during one anesthetic, resulting in 126 procedures performed in 121 patients.

of arrival at the PACU (as assessed by the COMFORT scale) and no more than 16% were fully awake. After 30 min, 33% of the patients were still unresponsive and 35% fully awake infants. Thereafter, the percentage of fully awake patients decreased to zero, as there was no longer any reason to keep them (awake and comfortable) at the PACU.

Receiver operating curve (ROC) analyses investigating the power of the NIPE to distinguish between comfort and pain/discomfort revealed areas under the curve (AUC) of 0.77 for a FLACC  $\geq 4$ , 0.81 for a COMFORT-B score  $\geq 17$  and 0.77 for a combination of both FLACC  $\geq 4$  & COMFORT-B score  $\geq 17$  (see Figure 1). More detailed information regarding ROC analysis is given in Table 2. Logistic regression analysis provided initial evidence that the NIPE is an independent predictor of a FLACC score  $\geq 4$  and/or a COMFORT-B score  $\geq 17$ , for details see Figure 2.

Median [IQR] NIPE values associated with a FLACC  $\geq 4$  [48 [45–56], a COMFORT-B score  $\geq 17$  [47 [42–53], and a FLACC  $\geq 4$  & COMFORT-B  $\geq 17$  [47 [42–57] were significantly lower than median NIPE values associated with a FLACC  $< 4$  [60 [53–68], 95% CI of difference  $-14$  to  $-8$ ,  $p < .0001$ ), a COMFORT-B score  $< 17$  [61 [54–68], 95% CI of difference  $-16$  to  $-10$ ,  $p < .0001$ ), and a FLACC  $< 4$  & COMFORT-B score  $< 17$  [60 [53–68], 95% CI of difference  $-15$  to  $-8$ ,  $p < .0001$ ).

The results of a mixed-effects analysis, resembling a one-way repeated measures analysis of variance capable of handling missing values, revealed no evidence of a predictive value of the NIPE regarding the occurrence of pain [FLACC  $\geq 4$ : 54 events, 78/324 (24%) missing values] and combined pain & discomfort [FLACC  $\geq 4$  & COMFORT-B score  $\geq 17$ : 44 events, 62/264 (23%) missing values]. For the occurrence of discomfort [COMFORT-B score  $\geq 17$ : 77 events, 96/462 (20%) missing values], Dunnett's multiple comparison test revealed weak evidence of a difference between NIPE values at the time of the event and 4 min before ( $p = .049$ ); for details, see Table 3 and Figure 3.

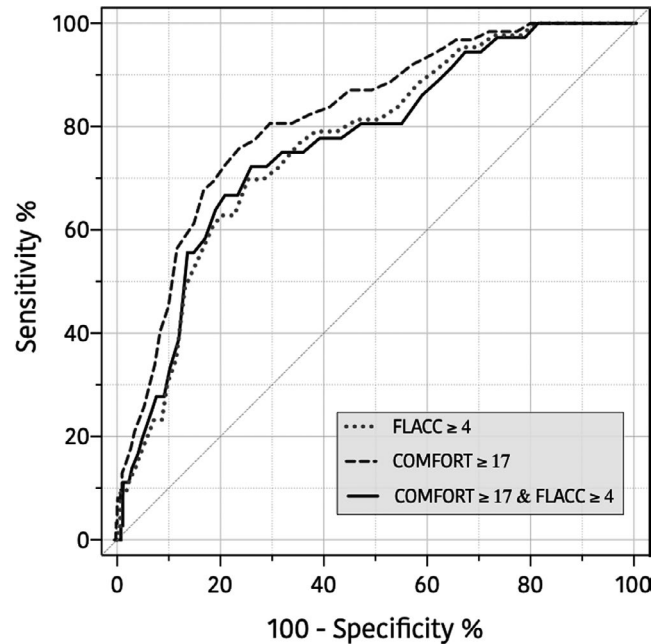


FIGURE 1 Receiver operating curve analyses. Receiver operating curve (ROC) analyses of NIPE values associated with the clinical scores FLACC  $\geq 4$  (pain), COMFORT  $\geq 17$  (discomfort), and FLACC  $\geq 4$  & COMFORT  $\geq 17$  (pain)

TABLE 2 Receiver operating curve (ROC) analysis

Scale	NIPE cutoff	Sensitivity (95% CI)	Specificity (95% CI)	LR
FLACC $\geq 4$	AUC 0.77 (SE 0.03), 95% CI 0.70–0.83; $p < .0001$			
	$< 67$	95 (85–99) %	33 (31–36) %	1.4
	$< 55$	70 (55–81) %	72 (69–74) %	2.5
	$< 42$	16 (8–30) %	96 (94–97) %	3.7
COMFORT $\geq 17$	AUC 0.81 (SE 0.03), 95% CI 0.76–0.86; $p < .0001$			
	$< 65$	95 (87–99) %	36 (34–39) %	1.5
	$< 54$	76 (64–85) %	76 (73–78) %	3.1
	$< 42$	21 (13–33) %	96 (95–97) %	5.4
FLACC $\geq 4$ & COMFORT $\geq 17$	AUC 0.77 (SE 0.04), 95% CI 0.69–0.85; $p < .0001$			
	$< 67$	94 (82–99) %	30 (28–33) %	1.4
	$< 55$	72 (56–84) %	72 (69–74) %	2.5
	$< 42$	19 (10–35) %	96 (94–97) %	4.5

Note: Receiver operating curve (ROC) analyses for NIPE values corresponding to clinical scores above predefined intervention targets. For each clinical scenario, NIPE cutoff values (with 95% confidence intervals) corresponding with either 95% sensitivity, 95% specificity, or the optimal combination of sensitivity and specificity are presented. Abbreviation: LR, positive likelihood ratio.

## 4 | DISCUSSION

In this study, investigating the performance of the Newborn Infant Parasympathetic Evaluation Index (NIPE™) as a measure of pain and discomfort in infants after general anesthesia, we found reasonable areas under the ROC curve ( $\pm 0.8$ ) and Likelihood Ratios ranging from 1.4 to 5.4, depending on the applied clinical scoring scales and the

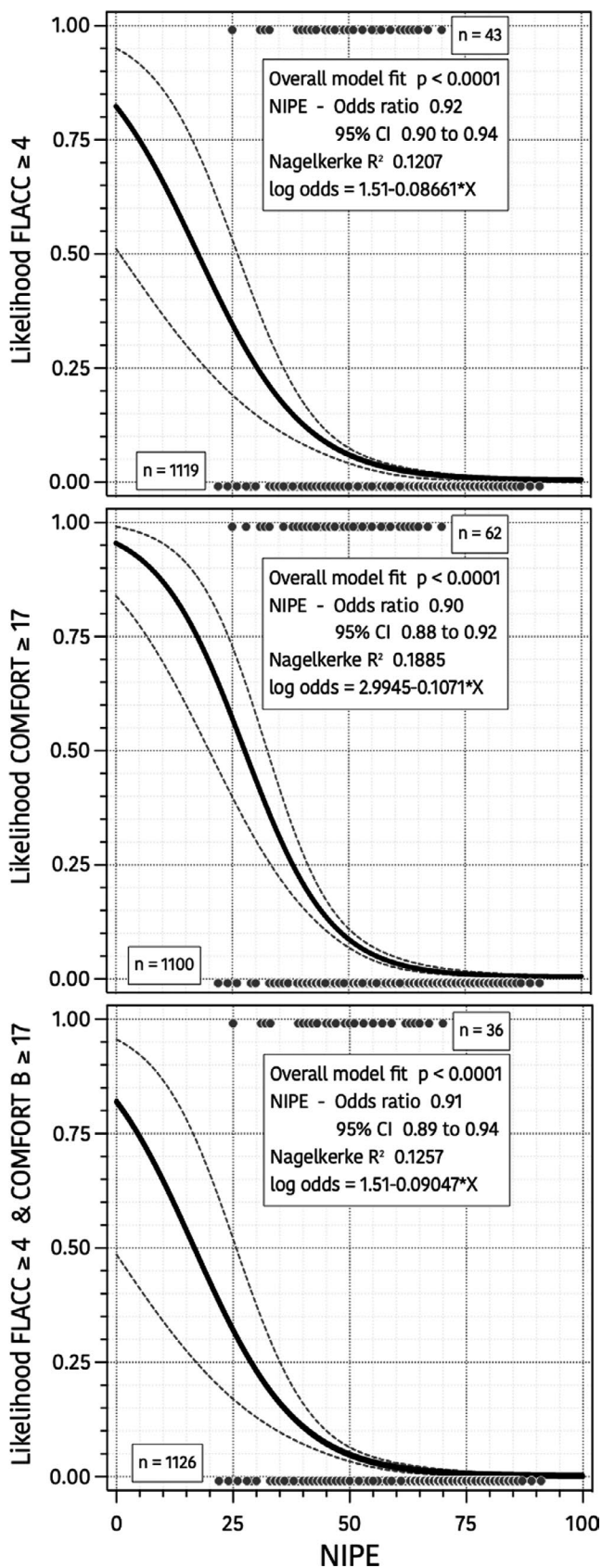


FIGURE 2 Logistic regression analysis. Logistic regression analysis (with 95% confidence intervals) modeling the probability of the clinical scores FLACC ≥ 4 (pain), COMFORT ≥ 17 (discomfort), and FLACC ≥ 4 & COMFORT ≥ 17 (pain) depending on NIPE values

applied thresholds (see Table 2). However, there was no clear evidence of a predictive value of the NIPE regarding the occurrence of clinically detectable pain and/or discomfort.

Heart rate variability (HRV) is a function of the autonomous nervous system; it reflects both parasympathetic and sympathetic activity. A high HRV is indicative of a comfortable state (predominance of parasympathetic activity), whereas a low HRV is indicative of stress (predominance of sympathetic activity), for whatever reason that stress has developed. It can be assumed that in an anesthetized unconscious patient, psychological factors are very unlikely to contribute to the development of a stress reaction. However, insufficient antinociception can trigger a stress reaction, resulting in a lower HRV. In a previous study investigating the NIPE as a measure of the nociception/antinociception balance in anesthetized infants, we found evidence that the NIPE might distinguish sufficient from insufficient antinociception.<sup>3</sup> During emergence and the initial period of recovery from general anesthesia, multiple factors other than insufficient analgesia can contribute to stress (and a low HRV): In our recovery room, we regularly see young children becoming upset when the appearance of their mother is delayed, which is quite an understandable reaction. It can be even more simple: "The child lying in the bed next to me was offered an ice-cream by the nurse, while I was not!" We could effortlessly continue this list of good reasons for a postoperative child to become stressed/upset, not attributed to postsurgical pain or nausea/vomiting could for several pages. In awake patients, from a methodological point of view, HRV might rather be a measure of comfort in a wider sense than specifically a measure of pain or the absence of pain.

The validation of the NIPE, or any other objective pain monitor, involves the following methodological dilemma: The new method (NIPE) must be compared to an established clinical scoring system. If an established method is considered fully valid, it is called a golden standard. In pain monitoring and assessment, no such golden standard exists. Nevertheless, investigating the validity of the NIPE or other pain monitors requires an assessment of the degree of accordance with established, though suboptimal, clinical scoring systems which themselves are due to being replaced by a reliable, objective, and noninvasive tool providing continuous information in real time, or at least with minimal delay.

Both the FLACC and the COMFORT-B score are discontinuous measures, dependent of the ability of a trained observer to correctly assess the various domains of these scoring systems. It is generally accepted that a FLACC score ≥ 4 is indicative of a level of pain that requires a therapeutic intervention. With the COMFORT-B score, it is much more difficult: A COMFORT-B score of ≥ 17 is regarded as indicative of discomfort, for whatever reason,<sup>13</sup> that means it is not necessarily associated with pain. To detect pain, the COMFORT-B score needs to be executed together with a subjective clinical judgment tool designed to assess the need for analgesia. According to van Dijk et al., the combination of a COMFORT-B score ≥ 17 and a Pain-Score ≥ 4 is indicative of pain.<sup>2</sup> In our study, we defined a COMFORT-B score ≥ 17 as a threshold to define discomfort and the combination of a COMFORT-B ≥ 17 and FLACC ≥ 4 as indicative of pain. We also used the FLACC

TABLE 3 Mixed-effects analysis

Event	NIPE—event mean (sd)	Comparison	NIPE Mean diff [95% CI]	Adjusted p-value
FLACC $\geq 4$	50.0 (9.79)	Event vs. -5 min	-3.9 [-9.71 to 2.01]	.313
		Event vs. -4 min	-3.1 [-8.62 to 2.48]	.471
		Event vs. -3 min	-3.1 [-8.44 to 2.15]	.405
		Event vs. -2 min	-2.5 [-7.32 to 2.42]	.563
		Event vs. -1 min	-3.0 [-7.10 to 1.17]	.236
COMFORT $\geq 17$	48.4 (9.32)	Event vs. -5 min	-3.7 [-8.03 to 0.55]	.108
		Event vs. -4 min	-4.1 [-8.20 to -0.01]	.049
		Event vs. -3 min	-3.7 [-7.71 to 0.40]	.092
		Event vs. -2 min	-2.9 [-6.38 to 0.69]	.155
		Event vs. -1 min	-1.2 [-4.31 to 1.89]	.776
FLACC $\geq 4$ & COMFORT $\geq 17$	49.6 (10.43)	Event vs. -5 min	-3.9 [-10.54 to 2.67]	.399
		Event vs. -4 min	-2.9 [-9.26 to 3.45]	.636
		Event vs. -3 min	-2.9 [-8.95 to 3.17]	.605
		Event vs. -2 min	-3.0 [-8.07 to 1.97]	.380
		Event vs. -1 min	-2.8 [-7.51 to 2.0]	.426

Note: Dunnett's multiple comparisons of NIPE values at the time of an event (clinical score above intervention threshold) and 5-4-3-2-1 min before.

as a single measure of pain, using a score of  $\geq 4$  as a threshold. We were able to show that NIPE values corresponding with COMFORT-B—and/or FLACC—scores above the predefined thresholds were significantly lower than those corresponding with COMFORT-B—and/or FLACC—scores below these thresholds. Mean NIPE values associated with clinically detected discomfort or pain were slightly below 50 (see Table 3), which is the cutoff NIPE value suggested by the device manufacturer. Using a NIPE value of 50 as a cutoff would result in a sensitivity of 58%, a specificity of 83%, and a Likelihood Ratio of 3.5. The results of our ROC curve analyses (see Table 2) further show that a sensitivity of  $\approx 95\%$  is associated with a specificity of 30–35%, whereas a specificity of  $\approx 95\%$  is associated with a sensitivity of no more than 16–21%, depending on the clinical scoring system applied.

In our study, Likelihood Ratios increased with lower NIPE threshold values, regardless of the applied clinical scoring system (see Table 2). This implies an association between the NIPE and both the FLACC and the COMFORT-B scale.

Though the results of logistic regression analyses revealed a significant association between the NIPE as an independent predictor of FLACC scores  $\geq 4$  and/or COMFORT-B scores  $\geq 17$ , the steepness of the regression curves (see Figure 2) shows this association is of rather limited clinical relevance in the particular setting of our study, performed in infants during emergence from general anesthesia. A NIPE value of 50, recommended by the device manufacturer as a threshold to distinguish comfort from discomfort, was associated with predicted probabilities as low as 0.056 for a FLACC score  $\geq 4$ , 0.082 for a COMFORT-B score  $\geq 17$  and 0.047 for the combination of FLACC  $\geq 4$  and COMFORT-B  $\geq 17$ . The low Nagelkerke pseudo- $R^2$  values indicated that  $<20\%$  of the variance in classified FLACC and COMFORT-B scores were accounted for by the NIPE.

#### 4.1 | Limitations

The FLACC scale has not yet been validated in infants younger than 3 months of age. In our study, 17 out of 121 patients were younger than 3 months. When we planned our study, we anticipated a relatively low number of neonates. To keep it practical, we decided to use the FLACC scale in all participants rather than using another scale in neonates.

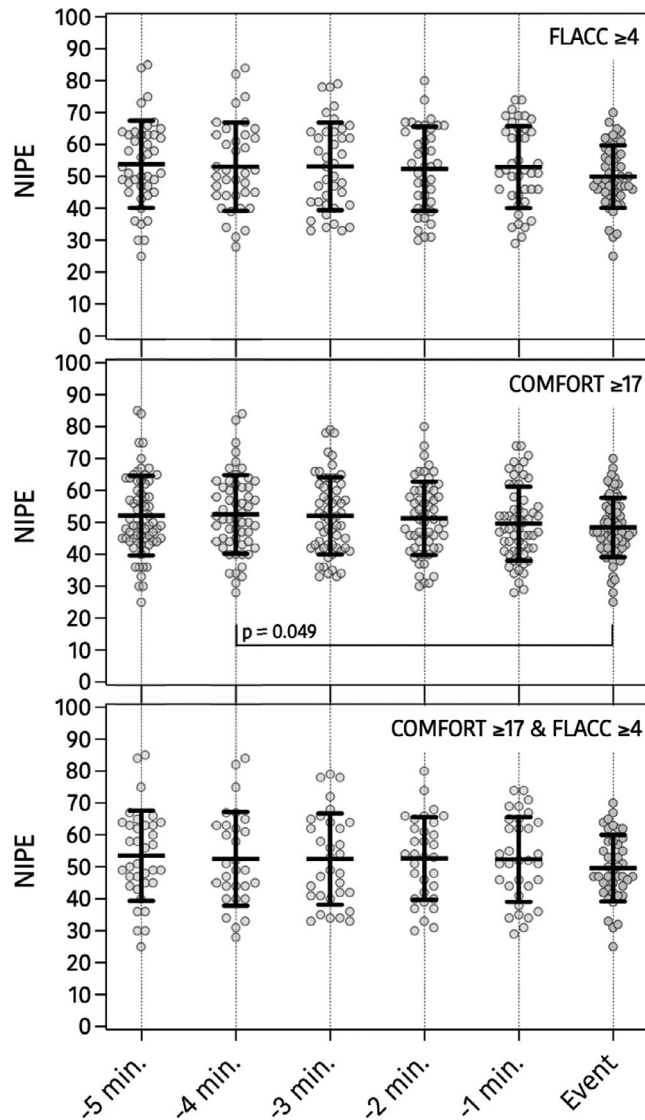
Patient motion causes ECG artifacts, which render HRV analysis useless. Originally, we also wanted to describe the percentage of missing NIPE values due to movement artifacts. However, this proved to be methodologically impracticable. About 5% of our patients were inconsolable until they were disconnected from ECG monitoring.

#### 4.2 | Future directions

Having investigated the NIPE both in anesthetized<sup>3</sup> and postoperative infants, we tentatively conclude that it performs better as a measure of the nociception/antinociception balance in anesthetized infants,<sup>3</sup> than as a pain assessment tool in the early postoperative setting. We recommend that future studies should focus on the potential benefits of NIPE-directed intraoperative antinociceptive drug application.

### 5 | CONCLUSIONS

In this study, investigating the performance of the NIPE as a measure of early pain and discomfort in infants after surgery under general anesthesia, we found reasonable areas under the ROC curve ( $\pm 0.8$ ).



**FIGURE 3** Mixed-effects analysis investigating the predictive value of the NIPE regarding the occurrence of pain & discomfort. Individual datapoints and mean (sd) values

Likelihood Ratios for positive FLACC and COMFORT-B scores increased with lower NIPE thresholds, suggesting an association between the NIPE and the clinical scoring systems. Logistic regression analysis revealed a rather limited value of the NIPE as a predictor of FLACC and COMFORT-B-scores indicating pain and/or discomfort. We also found no evidence of a predictive value of the NIPE regarding the occurrence of clinically detectable pain or discomfort.

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#### CONFLICT OF INTEREST

Laura M. Verweij, Jaap T.S. Kivits, and Frank Weber have no conflicts of interest to declare.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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#### REFERENCES

- Merkel S, Voepel-Lewis T, Malviya S. Pain assessment in infants and young children: the FLACC scale. *Am J Nurs*. 2002;102:55-58.
- van Dijk M, Peters JW, van Deventer P, Tibboel D. The COMFORT behavior scale: a tool for assessing pain and sedation in infants. *Am J Nurs*. 2005;105:33-36.
- Weber F, Roeleveld HG, Geerts NJE, Warmenhoven AT, Schroder R, de Leeuw TG. 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. *Paediatr Anaesth*. 2019;29:377-384.
- Zhang K, Wang S, Wu L, et al. Newborn infant parasympathetic evaluation (NIPE) as a predictor of hemodynamic response in children younger than 2 years under general anesthesia: an observational pilot study. *BMC Anesthesiol*. 2019;19:98.
- Cremillieux C, Makhoulouf 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.
- Walas W, Latka-Grot J, Maroszynska I, et al. Newborn infant parasympathetic evaluation index for the assessment of procedural pain in nonanesthetized infants: a multicenter pilot study. *Am J Perinatol*. 2020. <https://doi.org/10.1055/s-0040-1709458>. Online ahead of print.
- Valencia-Ramos J, Arnaez J, Calvo S, Gomez F, Del Blanco I. Observational study of newborn infant parasympathetic evaluation as a comfort system in awake patients admitted to a pediatric intensive care unit. *J Clin Monit Comput*. 2019;33:749-755.
- von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495-1499.
- 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.
- Systems MM. Newborn Infant Parasympathetic Evaluation (NIPE) Product Brochure. <https://mdoloris.com/technologies/neonates/>. Accessed August 17, 2020.
- Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. *Psychiatry Investig*. 2018;15:235-245.
- De Jonckheere J, Rakza T, Logier R, Jeanne M, Jounwaz R, Storme L. Heart rate variability analysis for newborn infants prolonged pain assessment. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:7747-7750.
- Valkenburg AJ, Boerlage AA, Ista E, Duivenvoorden HJ, Tibboel D, van Dijk M. The COMFORT-behavior scale is useful to assess pain and distress in 0- to 3-year-old children with Down syndrome. *Pain*. 2011;152:2059-2064.

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