Newborn Infant Parasympathetic Evaluation Index for the Assessment of Procedural Pain in Nonanesthetized Infants: A Multicenter Pilot Study

Wojciech Walas, MD, PhD1 Julita Latka-Grot, MD2 Iwona Maroszyńska, MD, PhD3 Ewelina Malinowska, MMid3 Magdalena Rutkowska, MD, PhD4 Andrzej Piotrowski, MD, PhD5 Monika Wrońska, MD5 Tomasz Szczapa, MD, PhD6 Agata Kubiaczyk, MD6 Michał Skrzypek, PhD7 Julien De Jonckheere, PhD8 Zenon P. Halaba, MD, PhD9

1 Paediatric and Neonatal Intensive Care Unit, University Hospital in Opole, Opole, Poland
2 Department of Neonatal, Children’s Memorial Health Institute, Warszawa, Poland
3 Department of Intensive Care and Congenital Malformations of Newborns and Infants, Polish Mother’s Memorial Hospital Research Institute, Łódź, Poland
4 Department of Neonatology, Institute of Mother and Child, Warszawa, Poland
5 Department of Anaesthesiology and Intensive Care, Children’s Memorial Health Institute, Warszawa, Poland
6 Department of Neonatology, Neonatal Biophysical Monitoring and Cardiopulmonary Therapies Research Unit, Poznań University of Medical Sciences, Poznań, Poland
7 Department of Biostatistics, School of Public Health in Bytom, Medical University of Silesia, Bytom, Poland
8 Clinical Investigation Center-Technological Innovation (CICIT) 1403, University Hospital Center (UHC) Lille, Lille, France
9 Department of Pediatrics, Institute of Medical Sciences, University of Opole, Opole, Poland

Address for correspondence Zenon P. Halaba, MD, PhD, Department of Pediatrics, Institute of Medical Sciences, University of Opole, 48 Oleska Street, 45-052 Opole, Poland (e-mail: zhalaba@uni.opole.pl).

Abstract

Objective The aim of this study is to evaluate the ability of the Newborn Infant Parasympathetic Evaluation (NIPE) index to detect the response to nociceptive stimuli in nonanesthetized infants and to compare these results to simultaneous scoring by behavioral scales.

Study Design Thirty-six nonanesthetized infants admitted to neonatal/pediatric intensive care unit (N/PICUs) were enrolled to the study. Due to faulty records of the data, three patients had to be excluded. To detect pain caused by noxious stimuli, the heart-rate-variability-derived NIPE index and behavioral pain scales designed for measuring procedural pain in nonverbal children were used.

Results Forty-one painful events were available for analysis. We observed in the whole group a statistically significant decrease in NIPE values at 1, 2, and 3 minutes after a painful stimulus, in comparison to the NIPE value at rest and the statistically significant differences between the minimum NIPE value within 3 minutes after the stimulus in comparison to NIPE value at rest in the whole group, as well as in the subgroups of moderate and severe pain. Receiver operating characteristic (ROC) analysis has shown the strong sensitivity and specificity of the NIPE in detecting the noxious stimuli (ROC AUC: 0.767). We also found that the stronger the sensation of pain was, the more rapidly NIPE reached its lowest value.
Discussion Our study indicates that the painful procedures are associated with a significant decrease in the NIPE value within 3 minutes after a noxious stimulus. Based on our observation, the minimum value within 3 minutes from the painful procedure seems to be the most distinctive value.

Materials and Methods
Patients
This multicenter prospective observational pilot study was performed at six distinct N/PICUs in Poland between October 1 and December 15, 2018. The study was approved by the medical ethics committee of Regional Medical Chamber in Opole (270: October 11, 2018). For this pilot study, 36 newborns and infants admitted to N/PICUs were enrolled. Due to the faulty data-recording, three patients had to be excluded from data analysis. Inclusion criteria were as follows: gestational age at birth over 26 weeks and chronological age less than 12 months, not being anesthetized. Exclusion criteria were as follows: bradycardia < 80 bpm, tachycardia > 250 bpm, any cardiac rhythm other than sinus rhythm, chronic use of medication interfering with cardiac rhythm, use of any meds that have known effects on sympathetic and parasympathetic activity, intraventricular hemorrhage IV degree, severe HIE treated by therapeutic hypothermia, severe central nervous system congenital malformations, seizures, and neuromuscular diseases. All guardians were given an information form and gave their approval for the study, and written informed consent was obtained from the parents or legal guardians of all participating patients. The characteristic of the studied group is presented in Tables 1 and 2.

Pain Assessment
To detect pain caused by noxious stimuli, the study used the heart-rate-variability-derived NIPE index and behavioral pain scales designed for measuring procedural pain in newborn and infants. The NIPE index is calculated by the NIPE monitor (Mdoloris Medical Systems, Loos, France) using the ECG signal without the need for additional ECG electrodes. A comprehensive description of the NIPE methodology has been published by De Jonckheere et al. The NIPE serves as a surrogate parameter of the sympathetic/parasympathetic balance in newborns and infants up to 2 years of age, enabling pain detection and assessment in conscious patients. The NIPE monitor displays two values: the NIPEmin is the minimum value within 3 minutes after a noxious stimulus, whereas the instantaneous NIPE provides information regarding short-term HRV-analysis, showing the result of a 64 seconds moving window with an update frequency of 1 second. In this study, we only used the NIPEmin, as we intended to examine acute changes after a noxious stimulus. Continuous recording of NIPE values began at least 5 minutes before the painful procedure and continued until

American Journal of Perinatology

Neonates and infants are frequently subjected to painful procedures and the more immature the babies, the more often they receive the highest number of painful events. The prevention and treatment of pain in this group of patients is important, not only because it is ethical but most of all because exposure to repeated painful stimuli early in life is known to have short- and long-term consequences which in some cases may carry over into adulthood. Despite great progress during last years, pain remains untreated or undertreated in newborns and infants. One of the major obstacles is the lack of reliable assessment tools. To treat pain effectively, it must be detected and quantified. The assessment of infants’ pain is mainly based on evaluation scales. However, behavioral scales are not free from bias and have some limitations, and therefore it is difficult to implement them in routine neonatal/pediatric intensive care unit (N/PICU) care. Moreover, their reliability and discriminant validity have been questioned even when performed by well-trained caregivers. In addition, many of them require prolonged clinical observation, and pain scoring is intermittent, which can lead to the overlooking of some painful episodes. Finding solid, real-time, and reliable measures presents a challenge to all those fighting pain and stress in this group of patients. New technologies to measure pain responses, such as heart rate variability (HRV), skin conductance, pupillary reflex dilatation, and near-infrared spectroscopy, hold promise in the development of tools that can be reliable, offer quantification, and be capable of detecting pain even when there is no perceptible response to that pain.

The NIPE index is based on the respiratory fluctuations of heart rate that mainly reflect the parasympathetic tone. The NIPE monitor is noninvasive and allows continuous electrocardiogram (ECG) signal acquisition through a connection to the cardiac monitor. In adults, the usefulness has been proved of HRV analysis based on the Analgesia Nociception Index (ANI) in the assessment of pain during surgery, in the postoperative period and in intensive therapy. There are also some publications which have demonstrated that HRV analysis may be useful in the assessment of procedural pain. While there are several papers on detecting insufficient antinociception and assessing analgesia by using heart-rate-variability-derived NIPE index in anesthetized infants, to date only one study by Cremillieux et al have attempted to probe the utility of NIPE in spotting reactions to painful stimuli in nonanesthetized infants. Hence, there is a necessity to verify more exhaustively the utility and reliability of this new method in assessing procedural pain in nonverbal children.

The primary objective of our study was to evaluate the ability of the NIPE index to detect the response to standardized nociceptive stimuli in nonanesthetized newborns and infants.
scores were evaluated after a painful procedure was performed. Trained observers scoring the sensation of pain did not have the insight into the NIPE index values.

### Statistical Analysis
The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20.0, software (IBM, Armonk, NY). Comparison of NIPE at T0, T1, T2, T3, and T4 were performed using a Friedman’s nonparametric statistical test followed by a Wilcoxon’s test when significant. Tests were performed for the whole population as well as for each pain level group (no/mild pain–moderate pain–severe pain). Considering Bonferroni correction, we considered a p-value <0.0125 as significant. Receiver operating characteristic (ROC) curve was computed to evaluate the NIPE ability to distinguish T4 versus T0. Data are presented as median and first to third quartile.

### Results
A total of 41 painful events in 33 patients were available for analysis. The interval between two events in the same patient was at least 4 hours. In the case of 24 (58.5%) events, we observed severe pain using the behavioral scales assessment; in nine (22.0%) we observed moderate, and in eight (19.5%) no/mild pain. The painful procedures included: 22 (56.1%) capillary blood sampling by heel prick, 14 (34.2%) venipuncture for blood sampling or obtaining intravenous access, 1 (2.4%) lumbar puncture, and 3 (7.3%) subcutaneous injection of vaccine. There were not statistically significant differences between mean values of NIPE in subgroups at the time T0. Taking into account 41 measured painful events, we observed a statistically significant decrease in NIPE values at 1 (T1), 2 (T2), and 3 (T3) minutes after a painful stimulus in comparison to the NIPE value at rest (T0). Analyzing changes separately, on the basis of pain perception in the subgroups, in the subgroup of no/mild and moderate pain the decreases recorded at predefined points of time (T1, T2, and T3) were not statistically significant in comparison to the NIPE value at rest (T0). A statistically significant decline was observed only at 1 minute of noxious stimulus (T1) in the subgroup of severe pain. We could also observe the statistically significant differences between the minimum NIPE value (T4) within 3 minutes after the stimulus in comparison to NIPE value at rest (T0) in the whole group, as well as in the subgroups of moderate and severe pain. The changes in the NIPE values after a noxious stimulus are presented in Table 3 and Fig. 1. The individual courses of the 41 recorded events are presented in Fig. 2. The area under the ROC curve computed between T0 and T4 was 0.767 (95% confidence interval [CI]: 0.666–0.868) for the whole group, and 0.791 (95% CI: 0.665–0.917) for the severe pain subgroup (Fig. 3). For patients in the moderate and no/mild pain subgroups ROC AUCs were not computed due to the small number of patients in these subgroups. The second important observation was that the stronger the sensation of pain, the more rapidly NIPE reached its lowest value: for severe pain 72 (39–150) seconds, for moderate 111 (62.5–188) seconds, for no/mild 157 (13.8–172.8) seconds, and the elapsed time between the painful stimulus and NIPE reaching its minimum

### Table 1 Characteristics of the studied group

<table>
<thead>
<tr>
<th>Overall characteristics (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Spontaneously breathing</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Noninvasive ventilation support</td>
</tr>
</tbody>
</table>

Note: Results are shown as mean ± standard deviation or n (%).

### Table 2 Characteristics of the studied group at the time of the events (n = 41)

<table>
<thead>
<tr>
<th>Days of life (d)</th>
<th>25 ± 26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (0–98)</td>
</tr>
</tbody>
</table>

Postmenstrual age (wk) 38.1 ± 4.5

Weight (g) 2,743 ± 997

Note: Results are shown as mean ± standard deviation and median (minimum–maximum).

For premature infants up to 36 weeks postmenstrual age (PMA), the Premature Infant Pain Profile (PIPP) was used, while for infants over 36 PMA up to 2 months of age the Neonatal Infant Pain scale (NIPS) was employed. For older babies the Face, Legs, Activity, Cry, Consolability scale (FLACC) was used. PIPP is a 7-indicator composite measure. The score ranges from 0 to 21, with the higher score indicating more pain.22 NIPS is a 6-indicator composite measure. Results are obtained by summing up the scores for the six indicators, where 0 indicates no pain and a score greater than 3 indicates pain, with a maximum score of 7.23 FLACC includes five indicators. The scale is scored in a range of 0 to 10, with 0 representing no pain. It is used to evaluate pain in preverbal children from 2 months to 7 years.24 According to pain scale scores, we divided the population studied into three subgroups: no pain/mild pain (PIPP: 0–6, NIPS: 0–3, FLACC: 0–3), moderate pain (PIPP: 7–12, NIPS: 3–4, FLACC: 4–6), and severe pain (PIPP > 12, NIPS > 4, FLACC > 6). Analysis was performed using data related to predefined events. An event was defined as the noxious stimulus. To analyze the response of the NIPE to a painful stimulus, we selected five instantaneous NIPE values: 1 minute before when the baby was at rest (T0), then 1 (T1), 2 (T2), 3 (T3) minutes, and a minimum value (T4) within a period of 3 minutes after a noxious stimulus. The PIPP, NIPS, or FLACC scores were evaluated after a painful procedure was performed.
value was inversely correlated with pain level assessed by behavioral scales ($r = -0.35$, $p = 0.027$). Analyzing the ability of the elapsed time between T0 and T4 to distinguish between no/mild and moderate/severe pain, we found in a ROC analysis ($AUC = 0.727$; 95% CI: 0.568–0.885) a threshold of 120 seconds with a sensitivity of 65%, and a specificity of 87.5%, and positive predictive value of 95.5%, and a negative predictive value of 61% (Fig. 4).

**Discussion**

Reliable pain assessment tools are essential for the detection, rating, and management of pain. Repeated painful exposures in newborns and infants have the potential for deleterious consequences. They include altered brain development, and abnormal neurodevelopment, somatosensory and stress response systems which can persist into childhood.\(^{25-27}\) During the last two decades, a variety of analgesia monitoring systems have become commercially available. One of them is the Newborn Infant Parasympathetic Evaluation monitor (MDoloris Medical Systems, Loos, France), allowing the assessment of the parasympathetic response to a painful stimulus. The index of nociception and analgesia is derived from an algorithm evaluating short-term heart-rate variability in real time. It is reported on a scale of 0 to 100, with 100 being indicative of the patient’s highest comfort level. The main objective of our study was to

---

**Table 3** NIPE instantaneous values 1 minute before, 1, 2, and 3 minutes after a painful stimulus and minimum NIPE instantaneous values within 3 minutes from stimulus for the whole group and subgroups grouped on the basis of the severity of pain sensation.

<table>
<thead>
<tr>
<th>NIPE instantaneous value at</th>
<th>All $(n = 41)$</th>
<th>No/mild pain $(n = 8)$</th>
<th>Moderate pain $(n = 9)$</th>
<th>Severe pain $(n = 24)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>53.0 (44.0–60.0)</td>
<td>49.0 (43.3–58.5)</td>
<td>52.5 (45.3–62.3)</td>
<td>55.5 (45.6–62.0)</td>
</tr>
<tr>
<td>T1</td>
<td>47.0 (42.5–56.0)</td>
<td>46.0 (43.3–52.5)</td>
<td>49.5 (42.3–56.8)</td>
<td>49.0 (45.6–56.0)</td>
</tr>
<tr>
<td>T2</td>
<td>47.0 (42.0–59.0)</td>
<td>45.0 (40.5–59.3)</td>
<td>46.5 (41.8–59.5)</td>
<td>46.5 (41.8–59.5)</td>
</tr>
<tr>
<td>T3</td>
<td>47.0 (39.0–56.0)</td>
<td>47.5 (36.5–60.8)</td>
<td>47.5 (39.8–57.3)</td>
<td>47.5 (39.8–57.3)</td>
</tr>
<tr>
<td>T4</td>
<td>43.0 (36.0–47.5)</td>
<td>43.0 (33.8–48.3)</td>
<td>43.5 (37.5–47.8)</td>
<td>43.5 (37.5–47.8)</td>
</tr>
</tbody>
</table>

Abbreviation: NIPE, Newborn Infant Parasympathetic Evaluation Index.

Note: Results are shown as median (1–3th quartile), $p$-value for Friedman’s test.

*Wilcoxon’s test $p < 0.0125$ versus T0.

T0: instantaneous value 1 min before the stimulus.
T1: instantaneous value 1 min after the onset of the stimulus.
T2: instantaneous value 2 min after the onset of the stimulus.
T3: instantaneous value 3 min after the onset of the stimulus.
T4: minimum instantaneous value within the 3 min after the onset of the stimulus.

---

**Fig. 1** Changes in the NIPE after a painful procedure. NIPE values 1 minute before (T0), 1 (T1), 2 (T2), and 3 (T3) minutes after a noxious stimulus and a minimum value (T4) within a period of 3 minutes after a noxious stimulus. NIPE, Newborn Infant Parasympathetic Evaluation Index.
evaluate the ability of the Newborn Infant Parasympathetic Evaluation monitor to detect procedural pain sensation in infants. Our results have shown that the NIPE index values, recorded at three predetermined points (T1, T2, and T3), decreased significantly over the time interval of 3 minutes after a painful stimulus. Also, ROC analysis has shown the strong sensitivity and specificity of the NIPE in detecting the noxious stimuli (ROC AUC: 0.767). Our study contradicts that of Cremillieux et al., who did not find any significant variations of the NIPE index throughout the three periods: T1, 5 minutes before the painful stimulus, T2, just during the painful procedure, and T3, 3 minutes after the noxious stimulus. A similar response time after a painful stimulus to that observed by ourselves was found in older children by Sabourdin et al. They evaluated the profile of the Analgesia–Nociception Index (ANI), a monitor providing an evaluation of the parasympathetic activity based on HRV, and using the same pain-level evaluation algorithm as the NIPE monitor, in anesthetized children aged 3 to 15 years, after a standardized nociceptive stimulation. They noticed that the decrease in ANI occurred within 2 minutes following the stimulation. Similar results were also obtained by Zhang et al in their pilot study on 55 children aged 1 month to 2 years undergoing elective surgery. They noticed a statistically significant decrease in the NIPE value at 1 minute from endotracheal intubation and skin incision. Other authors also used a longer time interval to detect changes in heart-rate-variability index after painful stimuli. In our
study, the instantaneous minimum value in the subgroup experiencing severe pain occurred between 39 and 150 seconds, median 72 seconds. Using quite a different method for evaluating the response to a painful procedure, based on the direct measurement of the cortical hemodynamic response to the noxious stimulus by near-infrared spectroscopy, Slater et al also found a latency of several seconds in the maximum response from the time of a painful procedure. In our study, despite the statistically significant decrease in the NIPE value observed at 3 minutes in the whole group, after analyzing these changes separately for subgroups based on the degree of pain sensation, the NIPE values at 3 minutes did not differ significantly from those at rest. Thus, Cremillieux et al, measuring the NIPE values just during a painful procedure and at 3 minutes after it, could have observed a time interval when reaction had not yet occurred or had just disappeared. When we divided our study group into three subgroups according to the severity of pain experienced, in the subgroups of moderate and severe pain we could observe statistically significant differences between the NIPE values at rest and the minimum NIPE values occurring after a painful procedure. Quite similar results were obtained by Faye et al. They evaluated pain in 28 neonates over 35 gestational weeks of age after a major surgical procedure and found a significant correlation between the NIPE index and the pain scale (EDIN) assessment. Very interesting observations have been made by Weber et al. In their research performed on infants under sevoflurane anesthesia, they observed that NIPE values less than 50 might be indicative of insufficient antinociception. The other important observation was that the NIPE could be a better measure of the nociception/antinociception balance than heart rate. They did not observe any reaction of NIPE values after surgical incision in patients who had a caudal block. Also, some older papers using a methodology based on heart-rate variability but different from the NIPE algorithm, evaluating both premature and born-at-term babies, had shown the ability of heart-rate-variability methods to monitor pain after painful procedures. Our next observation is that the more pain that was experienced by the patient, that is, the higher their scores were, the faster the minimum NIPE value was observed. This result is hard to explain and will need further and more-detailed studies on pain physiology.

Our study has some limitations. The study group was small and included babies of various degrees of prematurity and chronological age. It is well known that prematurity is associated with different perception of pain in comparison with babies born at term. Furthermore, we measured changes in the NIPE values elicited by different painful procedures, which may also produce different intensities of pain. Also, we did not carry out any regression analysis because in the whole group only four patients had multiple measurements.

In conclusion, the results of this pilot study indicate that the painful procedures are associated with a statistically significant decrease in the NIPE value within 3 minutes after a noxious stimulus. Furthermore, the higher the degree of pain sensation, the faster this statistically significant decrease in the minimum NIPE value is achieved. Based on our observations, the instantaneous minimum value within 3 minutes from the painful procedure seems to be the most distinctive value. We think that the decrease in NIPE value in newborn infants may help to identify infants potentially experiencing pain and could be used as a routine tool for monitoring this fifth vital sign. However, this issue will require further research.

Funding
None.

Conflict of Interest
J.D.L. is a shareholder of and a scientific consultant for MDoloris Medical systems (that commercialized NIPE monitor). The other authors declare no conflict of interests.

References