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REVIEW ARTICLE

# Analgesia nociception index and high frequency variability index: promising indicators of relative parasympathetic tone

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**Abstract**
At present, there is no objective and absolute measure of nociception, although various monitoring techniques have been developed. One such technique is the Analgesia Nociception Index (ANI), which is calculated from heart rate variability that reflects the relative parasympathetic tone. ANI is expressed on a non-unit scale of 0–100 (100 indicates maximal relative parasympathetic tone). Several studies indicated that ANI-guided anesthesia may help reduce intraoperative opioid use. The usefulness of ANI in the intensive care unit (ICU) and during surgery has also been reported. However, some limitations of ANI have also been reported; for example, ANI is affected by emotions and some drugs. In 2022, a high frequency variability index (HFVI), which was renamed from ANI and uses the same algorithm as ANI, was commercialized; therefore, ANI/HFVI are currently in the spotlight. Unlike ANI, HFVI can be displayed along with other biometric information on the Root® monitor. ANI/HFVI monitoring may affect the prognosis of not only patients in the perioperative period but those in ICU, those who receive home medical care, or outpatients. In this article, we present an updated review on ANI that has been published in the last decade, introduce HFVI, and discuss the outlooks of ANI/HFVI.

**Keywords** Analgesia nociception index (ANI) · High frequency variability index (HFVI) · Heart rate variability · Nociception · Opioid sparing · Root® monitor

## Introduction

Pain is one of the utmost concerns for patients. A person's report of an experience as pain should be respected [1]. However, there to date is no objective and absolute measure of nociception and pain [2], and there is no gold standard to quantify nociception [3]. To evaluate pain intensity, several subjective and numerical indications [e.g., Numerical Rating Scale (NRS), Visual Analogue Scale (VAS)] are commonly used in the clinical setting. In these indications, patients evaluate pain themselves; for example, in NRS, they score their pain from 0 (no pain) to 10 (worst pain imaginable). However, the NRS/VAS cannot be used during general anesthesia or when consciousness is impaired (e.g., during sedation, in severely ill patients, and in pediatric patients). Of course, inability to communicate does not negate the possibility that a human experiences pain [1]. In these patients, fluctuations of blood pressure and heart rate in response to nociceptive stimuli, several scores evaluated by medical staff, such as the Behavioral Pain Scale (BPS) and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale [4], in combination with the staff's own experience and intuition, are used to estimate nociception/pain. However, because these indicators include some subjectivity on the part of the evaluator, they cannot be said to be a complete objective evaluation of nociception/pain.

To address this issue, various nociception monitoring techniques have been developed [2, 5], such as Skin Conductance (MedStorm innovations, AS, Oslo, Norway) [6], Pupillometry (IDMED, Marseille, France) [7], Surgical Pleth Index (SPI, GE Healthcare, Helsinki, Finland) [8], nociception index (NOL, Medasense, Ramat Gan, Israel) [9], and Analgesia Nociception Index (ANI, Mdoloris Medical Systems, Loos, France). These utilize changes in the activation of sympathetic activity or decreases in relative parasympathetic tone that occur as a response to noxious stimuli [2]. Although many studies have been conducted to investigate these nociception monitoring techniques, a

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standard nociception/pain index has not been established to date, and none are widespread in many facilities.

Very recently, the high frequency variability index (HFVI, Mdoloris Medical Systems), which can be used to monitor relative parasympathetic tone, has appeared on the market in Japan. While ANI is exclusively for pain monitoring, the HFVI may be applied to other evaluation targets although they use the same algorithm. Therefore, understanding ANI is essential to achieve mastery of the HFVI. Since many studies on ANI have been conducted in various fields, and there are some previous reviews on ANI, in the present article, we present an updated review on articles on ANI that have been published in the last decade, introduce the HFVI, and discuss the outlooks of both ANI and HFVI.

The studies addressed in this narrative review were searched using a common electronic database (PubMed) about the ANI and HFVI published in 2011–2022. The keywords "analgesia nociception index" and "high frequency variability index" were used to find 226 potential articles from the database. One of the authors (KY) assessed the title, abstract, and full text of the articles. Since it is not possible to review all studies published in the last decade, randomized controlled trials and clinical studies with large numbers of subjects were prioritized and included in this review as key papers. We also included some papers that we judged to have important implications.

Although the two terms 'nociception' and 'pain' are sometimes confused, they have different meanings. The former is a physiological term, which has been used to describe processing noxious stimuli [10], the latter is a subjective feeling. In the present review, nociceptive reaction by noxious stimuli applied from the outside of the body are referred to as 'nociception', whereas 'pain' is the pain that is subjectively expressed by patients.

## What is ANI and HFVI?

To properly interpret the results of monitoring instruments, it is important to understand the underlying technique and confounders. This section outlines the principles of ANI/HFVI.

The interval of R–R waves of the electrocardiogram (ECG) changes periodically due to the influence of the autonomic nervous system. This is called heart rate variability (HRV) and it has been studied for more than 50 years [11]. HRV can be observed by plotting the R–R interval of the ECG on a time series. When spectral analysis is performed on the periodic changes in HRV, HRV can be separated into a high frequency (HF) component that forms a peak in the frequency band of 0.15–0.4 (or 0.5) Hz and a low frequency (LF) component that forms a peak in 0.04–0.15 Hz [12]. The HF component reflects respiratory sinus arrhythmia, and it is known that the efferent vagal activity is a major contributor to the HF component [13].

ANI uses HRV to assess relative parasympathetic tone, and identifies R waves by 250 Hz digitized ECG. The obtained R–R samples are divided into 64 s moving windows and normalized by the following procedure [14].

First calculate the mean:

$$M = \frac{1}{n}\sum_{i=1}^{n}\left(\mathrm{RR}_i\right)$$

($M$: mean value, $n$: the number of samples in the window, $\mathrm{RR}_i$: each R–R sample value).

Then calculate the norm value:

$$N = \sqrt{\sum_{i=1}^{n}(\mathrm{RR}_i - M)^2}$$

($N$: norm value, $n$: the number of samples in window, $\mathrm{RR}_i$: each R–R sample value, $M$: mean value).

Then divide each resulting R–R sample by the norm value (N):

$$\frac{\mathrm{RR}_i - M}{N}$$

($\mathrm{RR}_i$: each R–R sample value, $M$: mean value, $N$: norm value).

The mean-centered and normalized R–R series is automatically filtered by a fast wavelet transform, and as a result of the computation of the R–R series, only the HF component is extracted in real time [14, 15].

With changes in parasympathetic tone, the R–R series changes with breathing. When the parasympathetic tone is decreased, the effect of respiratory changes is reduced. As shown in Fig. 1, ANI divides the 64 s moving window into four 16 s sub-windows, and analyzes each sub-window. To eliminate the influence of changes in respiratory rate, local maxima are connected together as well as local minima, and the areas between the lower and upper envelopes [referred to as the area under the curve (AUC)] are analyzed [16]. The amplitude of the normalized and filtered R–R series ranges from 0 to 0.2 normalized unit [16]. The minimum AUC in each sub-window is defined as $\mathrm{AUC}_{\mathrm{min}}$, and their total is defined as $\mathrm{AUC}_{\mathrm{total}}$; the maximum possible $\mathrm{AUC}_{\mathrm{total}}$ is 0.2 normalized unit × 64 s = 12.8 s. ANI calculates the percentage of the $\mathrm{AUC}_{\mathrm{total}}$ with a value between 0 and 100 using the following formula [14]:

$$\mathrm{ANI} = 100 \times \frac{(\alpha \times \mathrm{AUC}_{\mathrm{min}} + \beta)}{12.8}$$

The constants of $\alpha$ and $\beta$ in the above formula are set to 5.1 and 1.2, respectively, by empirical determination in a general anesthesia dataset [17]. The average ANI for 2 and 4 min are continuously displayed on the monitor.

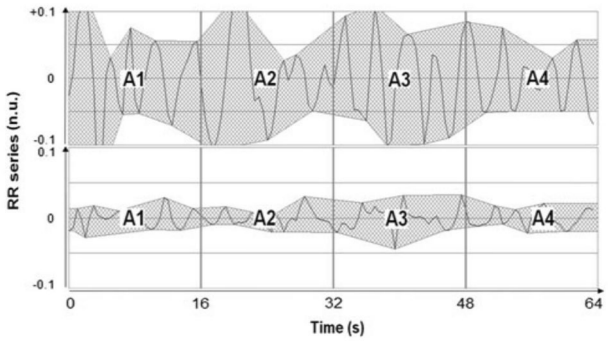


**Fig. 1** The normalized and filtered R–R series are represented by solid lines. Each gray area (A1, A2, A3, and A4) is where the respiratory influence on the R–R series was measured. The upper panel is a high relative parasympathetic state with a sufficient antinociception state, and the lower panel is a low relative parasympathetic state with an insufficient antinociception state, in which the patient's heart rate and blood pressure are increased. The respiratory cycle has a greater effect on the R–R series in the upper panel. (Modified and reproduced with permission) (Springer Nature; *J Clin Monit Comput*) [14]

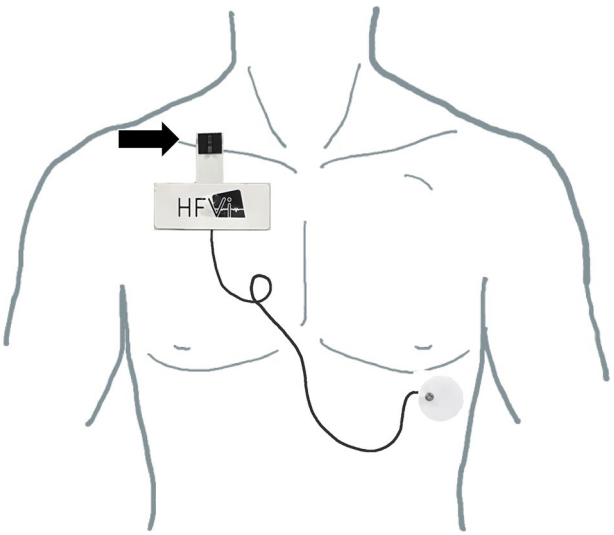


**Fig. 2** The position to attach the HFVI sensor. As shown in the figure, a large convex sensor is attached to just below the right clavicle, a small round sensor is attached to the left hypochondrium, and the part indicated by the arrow is connected to the module

HFVI (Mdoloris Medical Systems) uses the same algorithm as ANI; therefore, ANI and HFVI are the same variables although they have different names. While ANI only is displayed on the ANI monitor initially, HFVI can be displayed along with other biometric information (e.g., electroencephalogram and percutaneous oxygen saturation) on the Root® (Masimo Corp.) monitor, using a dedicated module. Similar to ANI, HFVI also obtains ECG waveforms using two sensors positioned on the anterior chest (Fig. 2). HFVI was just commercialized in July 2022; therefore, no studies investigating HFVI have yet been published at the time of writing.

## ANI for pain/nociception assessment

This section reviews randomized controlled trials and clinical studies with large numbers of subjects, with the aim of examining the usefulness and limitations of ANI in pain/nociception indicators. Due to the absence of absolute standard, clinical studies on nociception and pain are challenging, and each study considered the optimal timing to measure ANI and setting of outcome. When interpreting each study, the timing of ANI recording and the timing of nociception/pain set as the outcome are important.

Regarding the association between postoperative pain and ANI using a non-unit scale between 0 and 100 (100 indicates maximal relative parasympathetic tone), some observational studies have examined the association between ANI and NRS at post-anesthesia care unit (PACU) [18, 19]. A study investigating NRS and ANI in 200 post-surgery patients upon arrival at PACU reported a negative linear relationship between ANI and NRS ($r^2 = 0.41$) and that the ANI thresholds to identify NRS > 3 and > 7 were 57 and 48, respectively [19]. In addition, Bosselli et al. investigated the association between ANI immediately before extubation and NRS immediately after arrival at the PACU in 200 patients who had undergone surgery under general anesthesia with inhalation and remifentanil [20]. They reported that if ANI < 50 before extubation is used as the threshold, pain with NRS > 3 can be predicted with a sensitivity of 86% and a specificity of 86% [area under the receiver-operating characteristic (ROC) curve (AUC): 0.89]. This result suggests that ANI may be able to predict postoperative pain in advance.

Several studies have compared ANI to other nociception monitoring techniques, that is, comparing ANI to SPI [21–24] and comparing ANI to pupillometry [25]. ANI and SPI are altered by nociceptive events under both inhalation [23] and propofol anesthesia [24]. It should be noted that SPI is the opposite of ANI, where 0 indicates complete analgesia and 100 indicates maximum nociception [26]. Charier et al. reported that pupillometry was more closely associated with a postoperative VAS score > 4 than ANI (AUC of 0.92 and 0.39, respectively) [25]; therefore, ANI does not appear to be superior to other nociception monitoring techniques. Further research is needed in this area.

The usefulness of ANI in children has also been investigated. In a study that analyzed ANI and hemodynamics for 5 min before the start of and for 5 min after the start of the surgical procedure under general anesthesia in children aged 2 to 12 years [27], it was reported that hemodynamics did not reflect the surgical stimulus while ANI did. In a study of

children undergoing muscle biopsy under analgesia and light sedation, it was reported that there were negative correlations between the ANI and the FLACC scale [28]. Gall et al. examined ANI and FLACC scale in children younger than 7 years old in the recovery room who had undergone surgery or imaging studies (no surgical invasion) under general anesthesia [29]. They reported that the ANI cutoff value for predicting FLACC ≥ 4 was 56 (AUC, 0.94). The results of these studies suggest the utility of ANI in pediatric patients who may not be able to adequately describe their pain.

There are some interesting studies on the use of ANI in the intensive care unit (ICU). Chanques et al. investigated BPS and ANI during routine care at ICU [30]. As a result, instant-ANI (ANIi, an average calculated over a 64 s period) correlates with BPS ($r = -0.30$), and they revealed that BPS > 5 could be diagnosed with a sensitivity of 61.4%, a specificity of 77.4%, and a negative predictive value of 37.0% when ANIi 42.5 was used as a threshold. Another study was conducted in ICU in 21 patients with traumatic brain injury. It reported that there was a negative linear relationship between BPS and ANI ($r^2 = -0.469$), and that it is possible to detect BPS ≥ 5 with a sensitivity of 73% and a specificity of 62% when the threshold of ANI is set to 50 [31]. Thus, in patients who cannot self-report pain, such as sedated patients, unconscious patients, or children, ANI can be useful in detecting the degree of pain and distress by setting the cutoff value to around 50, which was also suggested by the manufacturer.

## Does ANI contribute to opioid-sparing anesthesia?

In recent years, opioid-sparing anesthesia with a multimodal approach in the perioperative period has been the common perception [32], and the same is true in the ICU [33]. This is because Enhanced Recovery After Surgery, or ERAS, which is aimed at good postoperative patient outcomes and early recovery, has been the focus of much attention [34]. The papers addressed in this section were extracted with the aim of scientifically examining the pros and cons of ANI's contribution to opioid-sparing anesthesia.

Many studies have been conducted on whether using ANI during general anesthesia reduces intraoperative opioid consumption [15, 35]. Several studies have adjusted the dose of remifentanil or fentanyl to maintain the ANI around 50–70 during general anesthesia, and they revealed that ANI-guided management can reduce intraoperative opioid consumption without deteriorating postoperative outcomes [36–40]. Sabourdin et al. investigated ANI-guidance versus standard care in elective gynecologic surgery ($n = 80$) under target-controlled infusion of propofol and remifentanil [37]. They showed that intraoperative remifentanil consumption was lower in the ANI-guided group [4.4 vs 5.8 μg/kg/h, difference of −1.4; 95% confidence interval (95% CI) −2.6 to −0.2, $p = 0.0026$] with no difference in postoperative morphine consumption.

In contrast, Tribuddharat et al. conducted a prospective, randomized controlled study in 60 patients who underwent mastectomy under general inhalation anesthesia, and they reported that there was no difference in intraoperative fentanyl consumption, intraoperative heart rate and blood pressure, or postoperative pain score and morphine consumption between the ANI-guided group (received additional fentanyl when the ANI falls below 50) and the control group (received opioids based on hemodynamics such as tachycardia and increased blood pressure) [41]. In addition, Szental et al. reported that the rate of moderate/severe pain (VAS ≥ 50 mm) within the first postoperative hour was similar between the ANI-guided group (3–5 mg of morphine was added when the intraoperative ANI fell below 30–50) and the control group (anesthesiologist adjusted the drug without looking at the ANI) in 120 patients who had undergone laparoscopic cholecystectomy under general anesthesia (50.8% vs 45.0%, difference of −5.8%; 95% CI −23.7 to 12.1%, $p = 0.58$) [42]. Moreover, a meta-analysis that analyzed 10 studies of intraoperative opioid consumption and nociception monitoring (ANI, SPI, and pupillometry) revealed that nociception measurement-guided management reduces intraoperative opioids, while their subgroup analysis showed that intraoperative opioid consumption did not change between the ANI guidance and normal care groups [43]. Thus, no conclusion has been reached as to whether ANI contributes to opioid-sparing anesthesia. One reason for this is that the anesthetics used to maintain general anesthesia have different effects on HRV, and it has been pointed out that ANI may be more useful with propofol and remifentanil than with sevoflurane and fentanyl [44]. Interpretation of the results of studies on this topic also requires attention to the kinds of anesthetics used. Further studies on ANI with different anesthetics are needed.

## General management with ANI monitoring

Studies on various ideas about how to utilize ANI for intraoperative management are being conducted. Jendoubi et al. investigated ANI in 100 patients who had undergone cesarean section under spinal anesthesia [45]. They reported that ANI at 3 min after spinal anesthesia declined significantly from baseline in the group with hypotension (systolic blood pressure decreased by 20% after spinal anesthesia or below 100 mmHg) compared with the group without hypotension. There may be little significance as ANI and blood pressure start to decline almost at the same time; however, the attempt to investigate the use of ANI as a predictor of hemodynamic

changes is interesting. In addition, there have been several studies investigating changes in hemodynamics and ANI due to noxious stimuli during surgery in adult [14, 46–49] and pediatric patients [50, 51]. Jeanne et al. reported that in 27 patients who underwent total knee replacement under general anesthesia with propofol and sufentanil, the ANI threshold to detect hemodynamic reactivity was 63, with a sensitivity of 80% and a specificity of 88% (AUC: 0.92) [48]. In all of these studies, ANI seems to be more sensitive in assessing nociception than heart rate or blood pressure. Thus, monitoring ANI during general anesthesia may reduce adverse cardiovascular events and improve the safety of anesthesia [52].

In addition to changes in hemodynamics, there have been several studies exploring the potential of ANI. Xie et al. reported that in 98 patients who underwent painless abortion, ANI was significantly lower in the group with intraoperative movement ($n=42$) than in the group without ($n=56$) [53]. Le Guen et al. monitored ANI in 45 parturient women who underwent epidural anesthesia and reported that labor pains significantly reduced ANI. They also showed that the ANI cutoff value for predicting uterine contraction pain of VAS > 30 was 49 [54]. Furthermore, there are studies that have used ANI to determine the effectiveness of regional anesthesia [35, 55]. Migeon et al. analyzed 39 successful and 19 unsuccessful regional anesthesia (defined as 10 bpm increase in heart rate within 2 min from the start of surgery) in children with peripheral nerve block or central neuraxial block. They described that ANI < 51 can identify regional anesthesia failure with a sensitivity of 78% and a specificity of 62% (AUC: 0.747) [55]. Thus, the association between various outcomes and ANI as well as opioid titration and hemodynamic changes detected during general anesthesia has been studied. However, the number of studies is small; therefore, further research in various population groups is needed to make the most of ANI. Compared to ANI, the newly named HFVI may be more easily understood not as a pain index but as values that indicate relative autonomic balance. Studies that apply HFVI to the general management of patients may increase in the future.

## Limitations of ANI

ANI utilizes respiratory fluctuations in the ECG. Therefore, it cannot be used in patients with severe arrhythmias, arterial fibrillation, implanted pacemaker, or cardiopulmonary bypass, or in patients treated with antimuscarinic drugs, etc. [15]. In addition, some studies have reported that ANI values in patients differ when under general anesthesia and when in a conscious state [56]; thus, ANI in an awake state is difficult to interpret [57]. Baroni et al. performed a meta-analysis of nine studies that assessed ANI and self-reported measures in conscious patients [58]. They found a weak negative correlation between ANI and NRS in the post-anesthetic recovery room ($r=-0.0984$; 95% CI −0.397 to 0.220, $I^2=95.82\%$). They described that one possible reason for the variation in ANI in a conscious state is the influence of emotion. Jess et al. investigated ANI in conscious volunteers when receiving four stimuli of expected/unexpected electrical pain and expected nonpainful/sham stimuli, and reported that ANI was changed by stress and emotion [59]. Furthermore, other studies were performed on changes in ANI with emotional changes elicited by music [6] and with negative emotional stimuli through videos [17]. Both studies revealed that ANI was a good indicator of parasympathetic changes related to the emotional state. Although ANI may be an objective indicator of emotional changes, at present, it is not possible to assess postoperative nociception/pain by ANI alone in conscious patients.

In addition, regarding the effects of drugs on ANI, ephedrine has been reported to affect ANI [60]. Meanwhile, it was shown that ANI was less affected by esmolol in septic shock piglet model [61]. Although ANI may be affected by anesthetics such as those mentioned above [44], Bollag et al. reported that intravenous administration of ketamine 0.5 mg/kg had no effect on ANI [62]. However, it should be noted that the effect of higher doses of ketamine on ANI has not been investigated yet. It can be said that when interpreting ANI, it is necessary to refer to the clinical situation and trends of ANI, even during general anesthesia. Despite advances in nociception monitoring technology and availability, limitations of HRV-derived indicators presently override their benefits in routine anesthesia care at this time. Thus, future research is needed to understand the implications of ANI/HFVI changes and their value itself in a situation where the ANI/HFVI assessment of pain is unreliable.

## Outlooks of ANI/HFVI

In this section, we will discuss how ANI/HFVI can be used other than to monitor nociception/pain by reviewing some of the literature. Regarding the potential of ANI, Anderson et al. described that ANI-based analgesia has the potential to be good for individualized titration of anesthesia management [63], and trials of ANI-based goal-directed analgesia are currently underway [64]. If ANI/HFVI studies are accumulated and their validity is confirmed, ANI-based administration may be realized [37]. A machine learning-based method combining ANI and hemodynamic monitoring has already been investigated with continuous administration of remifentanil [65]. These trends indicate the promising development of automated anesthesia/general management system by combining artificial intelligence and ANI/HFVI.

ANI at the end of life has also been studied. Bauschert et al. investigated simultaneous clinical and ANI evaluations in a palliative care setting, and reported that they were concordant in 77.58% of episodes [66]. This result suggests the possible use of ANI in the care that is performed based on staff's experience and intuition such as the end-of-life care for non-communicative patients.

The impact of ANI on prognosis is also an interesting area. A study of 14 patients with severe coronavirus disease 2019 who required mechanical ventilation reported higher ANI and IL-6 in the non-survivor group [67]. They found that parasympathetic dominance due to sympathetic depletion may lead to a poor prognosis. Thus, further studies on the association between prognosis and ANI/HFVI in various population groups in ICU are necessary. In addition, a study monitoring ANI in one-day surgery reported that the group with ANI ≥ 50 for at least 60% of the time they were under anesthesia had a significantly shorter hospital stay than those with ANI < 50 [165 min (118–212) vs 186.5 min (119–254), $p = 0.0425$] [68]. As such, investigation of association between comprehensive outcomes following day surgery/anesthesia and ANI are also interesting. Such studies may be easier to understand by renaming HFVI from ANI.

## Conclusion

In this article, we reviewed key papers on ANI that have been published in the last decade, introduced HFVI, and discussed the outlooks of ANI/HFVI. At present, ANI has a certain usefulness as a nociception/pain monitor during or immediately after general anesthesia in patients undergoing surgery, and in severely ill patients in the ICU. However, it is currently not possible to evaluate nociception/pain using ANI alone, especially in the awake state. With the commercialization of HFVI, it is expected that the attention of ANI/HFVI will increase. ANI/HFVI has the potential to become a mainstream monitoring method in a next era, not just for nociception/pain monitoring, and further study of its use not only in the operative room and ICU, but in other fields is awaited.

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## Declarations

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**Patient consent for publication** Not applicable.

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