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# Surgical pleth index monitoring in perioperative pain management: usefulness and limitations

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Surgical pleth index (SPI) monitoring is a representative, objective nociception-monitoring device that measures nociception using photoplethysmographic signals. It is easy to apply to patients and the numerical calculation formula is intuitively easy to understand; therefore, its clinical interpretation is simple. Several studies have demonstrated its efficacy and utility. Compared with hemodynamic parameters, the SPI can detect the degree of nociception during surgery under general anesthesia with greater accuracy, and therefore can provide better guidance for the administration of various opioids, including remifentanil, fentanyl, and sufentanil. Indeed, SPI-guided analgesia is associated with lower intraoperative opioid consumption, faster patient recovery, and comparable or lower levels of postoperative pain and rates of adverse events compared with conventional analgesia. In addition, SPI monitoring allows for the degree of postoperative pain and analgesic requirements to be predicted through the SPI values immediately before patient arousal. However, because patient age, effective circulating volume, position, concomitant medication and anesthetic regimen and level of consciousness may be confounding factors in SPI monitoring, clinicians must be careful when interpreting SPI values. In addition, as SPI values can differ depending on anesthetic and analgesic regimens and the underlying disease, an awareness of the effects of these variables with an understanding of the advantages and disadvantages of SPI monitoring compared to other nociception monitoring devices is essential. Therefore, this review aimed to help clinicians perform optimal SPI-guided analgesia and to assist with the establishment of future research designs through clarifying current usefulness and limitations of SPI monitoring in perioperative pain management.

**Keywords:** Analgesia; Autonomic nervous system; General anesthesia; Intraoperative monitoring; Nociception test; Pain measurement; Photoplethysmography.

## Introduction

As surgical procedures lead to actual or potential tissue damage, 20%–80% of patients complain of moderate to severe acute postoperative pain [1]. Therefore, it is important to accurately evaluate intraoperative nociception in patients undergoing surgery under general anesthesia and provide appropriate analgesia to reduce postoperative pain.

Various methods and modalities have been developed for quantitative and objective monitoring of nociception during surgery under general anesthesia [2], among which the most widely used and studied device is the surgical pleth index (SPI; GE Healthcare).

The SPI is a monitoring tool that uses the photoplethysmographic signals of finger arterioles to detect the balance between nociceptor activation and analgesia during general anesthesia [3]. The SPI values are calculated using the following equation: SPI = 100 – (0.33 × HBI + 0.67 × PPGA), where HBI is the heartbeat interval and PPGA is the pho-

toplethysmographic waveform amplitude [4]. Using this tool only requires that a pulse oximeter be attached to the finger; no additional consumable medical devices are required for continuous, noninvasive monitoring [5,6].

SPI values range from 0 to 100, with higher values indicating a greater nociceptive (stress) response. The target range for adequate intraoperative analgesia during general anesthesia is usually 20–50 [4]; thus, SPI values should be maintained < 50, and a rapid increase in SPI > 10 should be avoided [7]. Fig. 1 shows the determinants of the SPI value and the mechanism underlying the increase in SPI values due to surgical stimuli.

The first SPI-associated studies published were designed to investigate the correlation between the SPI and the nociception-antinociception balance and changes in stress hormones during the perioperative period [3,8]. Following these studies, randomized controlled trials (RCTs) comparing SPI-guided and conventional analgesia (hemodynamic parameter-guided analgesia) have mainly been conducted [9–12]. Various opioids (e.g., remifentanil, fentanyl, sufentanil, and oxycodone) were used in these studies, and several reported lower intraoperative opioid consumption, faster recovery, and similar postoperative pain scores with SPI-guided analgesia. Subsequently, the results were verified by meta-analyses [6,13]. However, some conflicting results have been reported, as one study found that SPI-guided analgesia alone was not associated with a reduction in intraoperative opioid consumption [14] and another reported that SPI-guided analgesia provides appropriate analgesia with more sufficient intraoperative remifentanil consumption compared to the controls [15]. Moreover, several studies have discussed the various limitations of the two parameters that are used to calculate the SPI (the HBI and PPGA), as they can be influenced not only by surgical stress but also by other confounding factors such as vasoactive drugs, population age, and cardiac arrhythmia [16–20].

Based on the findings of the SPI-related literature to date, this review aimed to provide a summary of the usefulness and limitations of SPI monitoring in perioperative pain management to help clinicians perform more appropriate perioperative analgesia in clinical practice and to assist with the establishment of future research to compare SPI monitoring with other objective tools for measuring nociception.

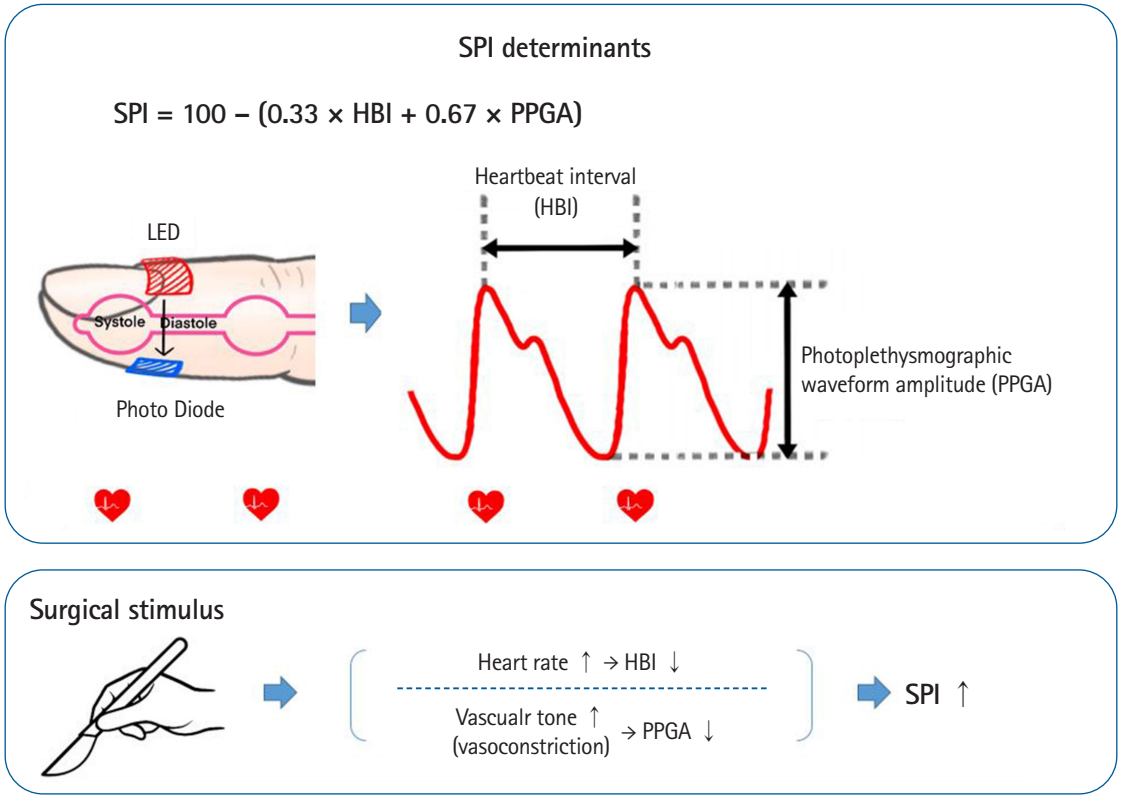


**Fig. 1.** Determinants of the SPI and mechanism of increased SPI values by surgical stimulus. A surgical stimulus increases the heart rate and vascular tone by increasing sympathetic tone; consequently, both the HBI and PPGA decrease, which inversely increases the SPI value. SPI: surgical pleth index, HBI: heartbeat interval, PPGA: photoplethysmographic waveform amplitude, LED: light-emitting diode.


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## Usefulness of intraoperative SPI-guided analgesia during general anesthesia

The effectiveness of SPI monitoring at quantifying nociception has been demonstrated in several clinical settings (Table 1) [5,9–12,21,22]. Although different types of surgery and opioids were assessed in these studies, most compared a group receiving opioids based on conventional hemodynamic parameters (e.g., heart rate and blood pressure) with a group receiving opioids based on SPI-quantified nociception. Most studies reported a significant reduction in intraoperative opioid consumption with SPI-guided analgesia. Accordingly, extubation time was shorter and postoperative pain and adverse events, including postoperative nausea or vomiting, were comparable or lower in the SPI group than in the conventional analgesia group.

During general anesthesia, the SPI can provide reliable quantitative information reflecting nociceptive stimulation and autonomic nervous system activation and can thus be used to guide analgesic administration [22–25]. Several RCTs have suggested that SPI-guided analgesia results in better detection of nociceptive stimuli and more timely administration of analgesics than conventional analgesia during general anesthesia [9,10,12,21]. Hence, SPI-guided analgesia is associated with fewer hemodynamic changes secondary to noxious stimulus [26] and less opioid consumption. Chen et al. [8] reported that the SPI was moderately correlated with stress hormone levels (ACTH, cortisol, epinephrine, and norepinephrine). Funcke et al. [27] also found that, compared to controls, SPI-guided analgesia was associated with lower cortisol and ACTH levels.

In several studies performed in adult patients without severe underlying diseases, including cardiovascular and neurological diseases, opioid titration based on the nociception-antinociception balance using the SPI with a cutoff value of 50 (target range of 20–50 and avoidance of rapid increases > 10 for noxious stimuli) showed a significant reduction in opioid consumption during surgery and a shorter extubation time. Moreover, SPI-guided analgesia using these criteria can help reduce the incidence of intraoperative adverse events such as hypertension, hypotension, tachycardia, and unwanted somatic movement compared to controls using hemodynamic parameter-guided analgesia [5,12,13] and can lead to better or comparable outcomes with regard to postoperative pain and complications as well as intraoperative outcomes in adult patients [12,13,15,28,29]. SPI monitoring has also been found to reduce the dose of anesthetics required during surgery and shorten the length of stay in the recovery room [9,30].

In elderly patients, SPI-guided analgesia is associated with a lower incidence of delirium in the post-anesthesia care unit (PACU) than conventional analgesia [15]. SPI monitoring can also be effective at detecting nociceptor stimulation that is masked by hypotension in the elderly due to decreased myocardial contractility, vascular elasticity, and β-adrenergic response, providing appropriate analgesia with sufficient intraoperative analgesic consumption [15].

However, several studies evaluating SPI-guided intraoperative analgesic administration in children have yielded conflicting results, suggesting that the SPI cannot be used to provide adequate analgesia within the target SPI value range of 20–50 in this population [10,18,31]. As children usually have higher blood vessel distensibility and baseline heart rates than adults [10], and as autonomic control of cardiac chronotropic function is strongly influenced by age [32,33], SPI values may be less valid in children than in adults [18]. This finding suggests that clinicians should be cautious when considering the use of the SPI in pediatric practice. A detailed explanation of the considerations for SPI monitoring according to different age groups is provided below (see *Age*).

## SPI monitoring for the prediction of postoperative pain and analgesic requirements

Another advantage of intraoperative SPI monitoring is that it can be used to predict postoperative pain severity. The SPI values measured before arousal or in response to nociceptive stimuli during surgery are closely related to the degree of postoperative pain and opioid requirements.

Higher SPI values before arousal at the end of surgery were closely associated with moderate-to-severe pain in the PACU [29,34–37]. However, some differences in the results of these studies must be mentioned. Park et al. [36] reported that higher SPI values before arousal from anesthesia were significantly associated with higher pain scores in the PACU, and an SPI value of 60 was defined as the cut-off for moderate-to-severe pain with a numerical rating scale (NRS) ≥ 5. These authors also reported that patients with an SPI value > 60 before arousal from anesthesia required a higher amount of fentanyl during the postoperative 48 h than patients with an SPI < 60. Meanwhile, Ledowski et al. [37] validated that a cut-off point of approximately 30 showed the best sensitivity/specificity to predict moderate-to-severe pain in the PACU; however, these authors suggested that the overall predictive accuracy was poor. These differences appear to be due to variations in the level of consciousness at the end of surgery. Generally, the SPI can be significantly affected by the patient's arousal status [35,37,38] such that the SPI values obtained during the pre-awareness period (anesthesia status) are reliable for predicting postoperative pain and analgesic requirements in the acute post-

**Table 1.** Evidence Summary of the Clinical Effect of Surgical Pleth Index (SPI)-guided Analgesia in Various Clinical Settings

| Author, Year | Study design | Experimental group (n) | Comparator group (n) | Age range at inclusion (mean or median)* | Type of surgery | Anesthetic/ intraoperative opioid | Processed EEG (target) | Primary outcome/main secondary outcomes | Main results and conclusion |
|---|---|---|---|---|---|---|---|---|---|
| Ahonen et al. 2007 [51] | RCT | Esmolol (15) | Remifentanil (15) | 20-65 (32/34) | Gynecological laparoscopic day-care surgery | Desflurane and nitrous oxide/ fentanyl | SE (50) | SPI value | While keeping SE at a predetermined level, SPI was higher in patients receiving esmolol than in those receiving remifentanil during laparoscopy. |
| Chen et al. 2010 [5] | Pilot study, RCT | SPI (40) | Conv. (40) | 18-70 (47/46) | ENT surgery expected to last 1 h | Propofol/ remifentanil | BIS (40-60) | Opioid consumption/ unwanted events, recovery times | SPI resulted in lower remifentanil consumption, more stable hemodynamics, and a lower incidence of unwanted events. |
| Bergmann et al. 2013 [9] | RCT | SPI (76) | Conv. (75) | 18-75 (48/44) | Outpatient orthopedic surgery | Propofol/ remifentanil | SE (40-60) | Recovery time, consumption of anesthetics/complications | SPI reduced the consumption of both remifentanil and propofol and resulted in faster recovery. |
| Gruenewald et al. 2014 [21] | RCT | SPI (42) | Conv. (40) | 18-65 (37/41) | Gynecological and orthopedic procedures | Sevoflurane / sufentanil | BIS (40-60) | Unwanted somatic events/hemodynamics, opioid consumption, recovery times | SPI showed no significant differences from standard care in terms of unwanted somatic events, sufentanil consumption, and recovery times. |
| Gruenewald et al. 2015 [58] | Comparative study | SPI (24) | ANI (24: same patients) | 18-65 (40) | Elective surgery | Sevoflurane/ remifentanil | BIS (30-60) | Prediction probabilities using receiver operating characteristic for change (Δ) in ANI and SPI values | ΔANI and ΔSPI significantly indicated the patient's movement after tetanic stimulation with a prediction probability of 0.74 and 0.84. Both reflected nociceptive stimulation. |
| Colombo et al. 2015 [22] | RCT | SPI (30) | Conv. (30) | 18-50 (46.6/49.9) | Laparoscopic cholecystectomy | Propofol/ remifentanil | SE (40-60) | Sympathetic modulation/hemodynamic variables, opioid consumption, recovery time | SPI led to a more stable sympathetic modulation but did not offer clinically relevant advantages in terms of remifentanil consumption and recovery time. |
| Park et al. 2015 [10] | RCT | SPI (21) | Conv. (24) | 3-10 (7/7) | Adenotonsillectomy | Sevoflurane and nitrous oxide/ fentanyl | SE (40-60) | Opioid consumption/ sevoflurane consumption, postoperative emergence agitation | SPI does not appear to be valid in children due to differences in blood vessel distensibility and increased baseline heart rates. |
| Won et al. 2016 [12] | RCT | SPI (23) | Conv. (22) | 20-65 (54/42) | Thyroidectomy | Sevoflurane/ oxycodone | BIS (40-60) | Opioid consumption/ extubation time, NRS | SPI reduced intravenous oxycodone consumption and extubation time compared with conventional analgesia. |
| Won et al. 2017 [19] | RCT | Nicardipine (15) | Remifentanil (15) | 20-65 (46/46) | Thyroidectomy | Desflurane and nitrous oxide | BIS (50) | SPI value | No difference in SPI values between nicardipine and remifentanil. Calcium channel-blocking vasodilators may confound interpretation of the SPI. |

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**Table 1.** Continued

| Author, Year | Study design | Experimental group (n) | Comparator group (n) | Age range at inclusion (mean or median)* | Type of surgery | Anesthetic/ intraoperative opioid | Processed EEG (target) | Primary outcome/main secondary outcomes | Main results and conclusion |
|---|---|---|---|---|---|---|---|---|---|
| Jain et al. 2019 [29] | RCT | SPI (68) | Conv. (65) | 18-65 (38.4/40.3) | Laparoscopic cholecystectomy | Sevoflurane/ fentanyl | BIS (40-60) | Opioid consumption/ hemodynamic changes, recovery time, VAS, PACU analgesia | Intraoperative fentanyl consumption was higher in the SPI group than in controls. Recovery time and hemodynamic changes were comparable. Postoperative VAS and adjuvant fentanyl were higher in controls. |
| Choi et al. 2019 [68] | RCT | Pectoral nerve block type II (20) | Control (19) | 20-65 (52.7/51.4) | Breast surgery | Propofol/ remifentanil | BIS (40-60) | Opioid consumption/ VAS, PACU analgesia | Pectoral nerve block reduced intraoperative remifentanil consumption by approximately 30% and improved postoperative pain in PACU. |
| Wang et al. 2020 [66] | RCT | Dexmedetomidine (46) | Normal saline (44) | 18-75 (56.8/60.5) | Video-assisted thoracoscopic lung lobectomy | Isoflurane | N/A | SPI and hemodynamic changes/NRS | Dexmedetomidine decreased the intraoperative SPI and NRS scores. Dexmedetomidine attenuated noxious stimuli. |
| Sriganesh et al. 2020 [67] | RCT | Dexmedetomidine (12) | Fentanyl (12) | 18-60 (42.9/42.3) | Craniotomy | Isoflurane | SE (40-60) | SPI changes/biomarkers of surgical stress | No differences were shown in the SPI values or biomarkers, such as cortisol, glucose, and pH, between dexmedetomidine and fentanyl. |
| Kim et al. 2020 [61] | RCT | SPI (43) | Pupillometry (43) | 20-65 (49.4/49.1) | Laparoscopic cholecystectomy | Propofol/ remifentanil | SE (40-60) | Peak NRS/opioid consumption | Pupillometry may reduce intraoperative opioid analgesics, recovery room opioid requirements, and pain scores. |
| Funcke et al. 2020 [27] | Pilot study, RCT | SPI (12) | Conv. (12), PPI (12), NOL (12) | ≥ 18 (64/61/64/62) | Radical retropubic prostatectomy | Sevoflurane/ sufentanil | N/A | Opioid consumption/ adrenocorticotropic hormone and cortisol | Lower sufentanil in the PPI was associated with an increased endocrine stress response. Titration using the SPI resulted in no reduction in opioid consumption compared to the control but was associated with a reduced endocrine stress response. |
| Funcke et al. 2021 [62] | RCT | SPI (23) | Conv. (24), PPI (24), NOL (24) | ≥ 18 (62/61/64/62) | Radical retropubic prostatectomy | Propofol/ remifentanil | BIS (40-50) | Opioid consumption/ adrenocorticotropic hormone and cortisol | Opioid consumption was different for each device (SPI > NOL > PPI). The devices do not seem to be sufficiently validated yet. |
| Gruenewald et al. 2021 [30] | Multicenter, RCT | SPI (246) | Conv. (248) | ≥ 18 (48/48) | Gynecological, ENT and maxillofacial, orthopedic, trauma | Propofol/ remifentanil | SE (40-60) | Unwanted event/eye-open time, PONV, VAS | Entropy and SPI did not reduce adverse events compared with standard monitoring alone. However, there was a reduction in propofol use and shorter emergence time and PACU stay. |
| Guo et al. 2021 [11] | RCT | SPI (31) | Conv. (31) | 18-65 (47.1/48.8) | Laparoscopic cholecystectomy | Propofol/ fentanyl | BIS (40-60) | Opioid consumption/ extubation time, VAS | SPI lowered intraoperative fentanyl consumption with a shorter extubation time. |

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**Table 1.** Continued

| Author, Year | Study design | Experimental group (n) | Comparator group (n) | Age range at inclusion (mean or median)* | Type of surgery | Anesthetic/ intraoperative opioid | Processed EEG (target) | Primary outcome/main secondary outcomes | Main results and conclusion |
|---|---|---|---|---|---|---|---|---|---|
| Stasiowski et al. 2021 [63] | RCT | SPI (31) | Conv. (30), PDR (28) | 18-65 (47.7/49/50.2) | Endoscopic sinus surgery | Propofol/ Remifentanil | SE (40-60) | Boezaart bleeding scale | SPI can optimize the condition of the surgical field and reduce blood loss, whereas monitoring based on PDR reduced the use of anesthetic drugs. |
| Muthukalai et al. 2022 [59] | Observational study, plot study | SPI (50) | ANI (50); same patients | 18-60 (40) | Craniotomy | Sevoflurane/fentanyl | SE (40-50) | Bleeding and noradrenaline infusion – correlation with the SPI and ANI | The SPI was not affected by bleeding or noradrenaline infusion, contrary to the ANI. |
| Yi et al. 2022 [70] | RCT | Deep NMB (64) | Moderate NMB (64) | 19-85 (63/65) | Laparoscopic herniorrhaphy | Sevoflurane/ remifentanil | PSi (25-50) | Opioid consumption/ PACU stay | Deep NMB reduced the remifentanil requirement compared with moderate NMB in SPI-guided remifentanil administration for laparoscopic herniorrhaphy. |
| Park et al. 2022 [73] | Observational study | High MELD (≥ 16) (20) | Low MELD (< 16) (20) | 20-70 (58.6/52.1) | Liver transplantation | Isoflurane/ remifentanil | BIS (40-60) | Opioid consumption/ rescue analgesia | Patients with a higher MELD showed lower remifentanil requirement during surgery but no significant difference during the neo-hepatic phase. |
| Kim et al. 2022 [69] | RCT | Abdominal wall nerve block (24) | Control (28) | 18-70 (57/51) | Inguinal hernia repair | Propofol/ remifentanil | SE (40-60) | Opioid consumption/ VAS and rescue analgesia | Remifentanil dose during surgery was lower in the nerve block group than the control group when using SPI. |
| Koschmieder et al. 2023 [65] | Observational study | SPI (60) | Conv., PPI, NOL (60; same patents) | ≥ 18 (42) | Lower extremities surgery | Sevoflurane/ sufentanil | BIS (< 60) | AUC analyses to predict immediate moderate-to-severe postoperative pain | None of these monitors alone had sufficient diagnostic accuracy to predict early postoperative pain. |

EEG: electroencephalography, RCT: randomized controlled trial, SE: state entropy, ENT: ear nose throat, Conv.: conventional analgesia or standard practice, BIS: bispectral index, ANI: analgesia nociception index, NRS: numerical rating scale for pain, VAS: visual analog scale for pain, PONV: postoperative nausea and vomiting, PACU: post-anesthesia care unit, N/A: data not available, NOL: nociception level, PPI: pupillary pain index, PDR: pupillary dilatation reflex, NMB: neuromuscular blockade, MELD: model for end-stage liver disease, AUC: area under the receiver operating characteristic curve, PSi: patient state index. *Age: age range at inclusion indicates the range indicated in the inclusion criteria, and the values in parentheses are the ages of the included participants.

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operative period. From this point of view, variations in the patients' level of consciousness before arousal may be linked to differences in the results of these studies.

A recent meta-analysis [39] identified studies investigating the association between the SPI at the end of surgery and immediate moderate-to-severe pain in the PACU and revealed that SPI values were higher in patients with moderate-to-severe pain and a higher SPI at the end of surgery could predict moderate-to-severe pain with a sensitivity of 0.71 and a specificity of 0.58. Additionally, according to the summary receiver operating characteristic curve, the overall accuracy was 0.72, suggesting that the SPI may be a useful predictor of postoperative pain in adult patients undergoing general anesthesia. However, given the limited number of studies included in this meta-analysis and high heterogeneity of some of the results, further studies are required to verify these findings.

Jung et al. [40] evaluated whether the highest SPI value during surgical incision was associated with postoperative pain and opioid consumption. These authors recorded the highest SPI value during surgical incision and compared the postoperative NRS scores for pain and opioid consumption during the first 24 h postoperatively between patients with an SPI > 50 or 20–50. Patients with an SPI > 50 showed higher NRS scores for pain in the PACU and 24 h postoperatively and higher fentanyl consumption during the 24 h postoperatively, suggesting that changes in the SPI in response to nociceptive stimuli during the initial surgical incision is closely related to the degree of postoperative pain and opioid consumption.

## Limitations: factors that can affect the reliability of the SPI in various clinical settings

### Age

The SPI is determined by two factors (HBI and PPGA) that are inseparably related age [41]. The reference value for heart rate variability differs for individuals aged < 20 and > 60 years [42]. Vascular properties such as arterial stiffness and elasticity are associated with age [43], and the PPGA depends on vascular wall distensibility and intravascular pulse pressure [44]. Therefore, age is a major confounder of SPI monitoring. Additionally, as pediatric patients exhibit lower vascular wall stress and higher distensibility, they are less likely to show prominent decreases in the PPGA from sympathetic stimulation and have increased baseline heart rates compared with adults, resulting in an underestimation of the SPI value [10,45]. For these reasons, an SPI < 40 is the target range for adequate intraoperative analgesia in pediatric patients rather than an SPI < 50, which is the reference range for adults (Fig. 2B) [10,18,32]. In contrast, in older adults, the delivery of pressure waves is accelerated and the intensity is increased owing to increased stiffness in the small and large arteries. Therefore, changes in the PPGA due to sympathetic stimulation increase with age, whereas changes in the heart rate due to sympathetic stimulation decreases with age because of autonomic functional degeneration [46]. These two factors are offset each other; thus, the SPI is maintained at a range of 20–50, which is similar to that of normal healthy adults (Fig. 2C) [15]. However, as the study assessing the effectiveness and characteristics of SPI monitoring in the elderly had a small sample size, it is difficult to generalize the results; thus, further validation is required.

### Anesthetics

Most previous RCTs assessing SPI monitoring have included patients receiving total intravenous anesthesia (TIVA) for general anesthesia and found that SPI-guided analgesia reduces opioid consumption [47]. In contrast, in the first study conducted by Gruenewald et al. [21] using an inhalation agent (sevoflurane), SPI-guided analgesia did not reduce intraoperative opioid (sufentanil) consumption. The authors thus concluded that the anesthesia regimen may affect the efficacy of SPI guidance. In another study conducted by Jain et al. [29] using sevoflurane, intraoperative fentanyl consumption was higher in the SPI-guided analgesia group than in the control group. However, another study using sevoflurane showed significantly lower intraoperative oxycodone consumption in the SPI guidance group than in the conventional analgesia group [12]. Therefore, the efficacy and feasibility of inhalational anesthesia rather than TIVA for SPI-guided analgesia requires further exploration.

The concentration of propofol in TIVA has also been found to affect the SPI. Hans et al. [48] reported that high propofol effect-site concentrations tended to increase the SPI due to a decrease in pulse wave amplitude; however, the authors did not provide a clear explanation for this finding. Propofol-induced vasoplegia can occur because high propofol concentrations decrease the peripheral vascular resistance [49,50], which may reduce vascular wall distensibility. Consequently, the magnitude of the change in the PPGA in response to sympathetic stimulation could increase, which has similarly been found in the elderly [15].

### Cardiovascular drugs and diseases

The concomitant use of cardiovascular drugs may affect SPI monitoring. Vasoactive agents (ephedrine, phenylephrine, and nicardipine) in particular may affect SPI values by altering the PPGA and HBI, which may interfere with accurate interpretation

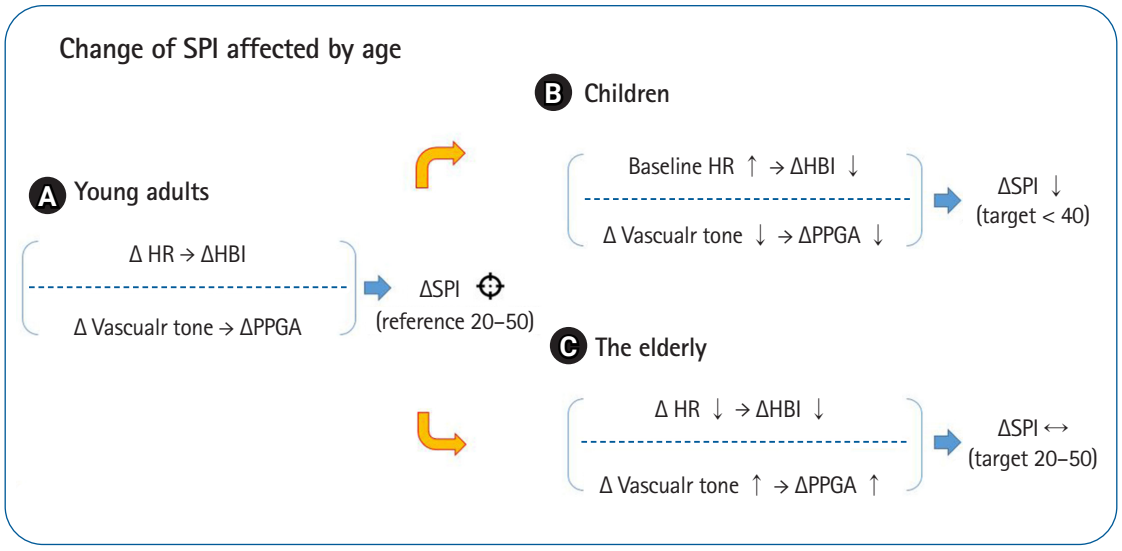


**Fig. 2.** Schematic diagram of the change in the SPI in response to nociceptive stimuli according to population age groups. In adults without severe underlying diseases, the target range of the SPI for adequate intraoperative analgesia during general anesthesia is usually 20–50, based on evidence from numerous studies (A). In children, the increased baseline heart rate results in less of a change in the HBI, and children are less likely to show a prominent reduction in the PPGA from sympathetic stimulation owing to lower vascular wall stress with higher distensibility. These conditions result in an underestimation of the SPI value; thus, an SPI < 40 is the target range for adequate intraoperative analgesia (B). In the elderly, the magnitude of change in the PPGA resulting from sympathetic stimulation is higher due to increased stiffness in the small and large arteries . In contrast, the change in the heart rate in response to stimuli decreases with age because of autonomic functional degeneration. These two factors have the effect of offsetting each other; thus, the SPI is maintained at a reference range of 20–50, similar to that in normal healthy adults (C). Δ: change, SPI: surgical pleth index, HR: heart rate, HBI: heartbeat interval, PPGA: photoplethysmographic waveform amplitude.

of SPI monitoring [19]. Additionally, chronic treatment (regardless of drug type) for hypertension lowers the SPI response [3]. Nicardipine, a calcium channel-blocking vasodilator, increases PPGA levels, thereby lowering the SPI. Therefore, the SPI does not appropriately reflect the level of nociception and may be ineffective as a guide for opioid administration when nicardipine is administered during general anesthesia [19]. In contrast, SPI values have been found to be higher in patients receiving esmolol than in patients receiving remifentanil in gynecological laparoscopic day-care surgery, suggesting that esmolol (a β-adrenergic antagonist) only stabilizes the hemodynamic response during surgical procedures and has no anti-nociceptive action unlike opioids [51]. In this case, the SPI appears to accurately reflect the level of nociception and may be used to guide the administration of opioids during general anesthesia. Finally, atropine, pacemakers, and arrhythmias are confounding factors [52].

## Fluid status

The SPI can be affected by fluid status during steady-state conditions with propofol-remifentanil anesthesia. The SPI is more likely to decrease with worsening hypovolemia [3,48]. However, SPI values are not affected by fluid challenges in normovolemic patients.

## Position

In urological surgery, the SPI was found to increase after a 30° head-up tilt and decrease after a head-down tilt, lasting for at least 45 min [53]. The effect of prone positioning on the SPI during spinal surgery under general anesthesia was also investigated in a previous study [54]. Prone positioning induced a significant increase in the SPI, probably owing to increased sympathetic tone, followed by a gradual reduction over the subsequent 20 min. After moving the patient from supine to prone positioning, the SPI values tended to increase in the absence of noxious stimulation. Therefore, the interpretation of the SPI can be confounded by positioning.

## Consciousness

The sympathovagal balance is influenced by arousal and emotions. Therefore, during consciousness, the SPI shows no correlation with endocrine stress hormones, including ACTH, cortisol, epinephrine, and norepinephrine, but shows a moderate correlation in anesthetized patients [5].


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However, a correlation between the SPI and opioid consumption has been reported in patients with reduced awareness who were conscious but not fully awake in the PACU [34,55,56]. Moreover, in a study performed in healthy volunteers and parturients by Choi et al. [57], an algometer was used to induce bone pain in volunteers until they rated their pain as an NRS score of 5. This procedure was repeated during the administration of remifentanil or normal saline. The parturients' SPI data were collected for 2 min when they rated their pain levels at the NRS score of 0, 5, or 7. The SPI was effective at distinguishing pain intensity, irrespective of remifentanil administration. Therefore, further research on the relationship between the SPI and consciousness is needed.

## Comparison of SPI monitoring with other nociception monitoring devices on perioperative opioid consumption and quantification of nociception during general anesthesia

### Analgesia nociception index

The analgesia nociception index (ANI; MetroDoloris Medical Systems) measures cardiac parasympathetic tone through heart rate variability and shows parasympathetic activity on a scale, ranging from 0 (minimum parasympathetic tone and a high nociceptive level) to 100 (maximum parasympathetic tone and a low nociceptive level). Gruenewald et al. [58] assessed nociceptive balance in terms of the ANI and SPI and the prediction probabilities using the receiver operating characteristic for change in the ANI and SPI values during sevoflurane-remifentanil anesthesia. The ANI and SPI were both significant for indicating patient movement after tetanic stimulation, with a prediction probability of 0.74 and 0.84, respectively. Both the ANI and SPI reflected nociceptive stimulation, although a higher probability was observed for the SPI.

Acute episodes of blood loss are confounding factors in nociception monitoring. The ANI significantly increases during acute intraoperative blood loss and with coadministration of noradrenaline; however, the SPI is not affected [59]. Therefore, the SPI appears to be more reliable during intraoperative bleeding than the ANI.

In addition, the SPI and ANI were compared in a study of conscious patients conducted by Choi et al. [57]. An algometer was used to induce bone pain in the volunteers until they rated their pain as an NRS score of 5 during the administration of remifentanil or normal saline. At an NRS score of 5, the SPI showed similar values irrespective of the solution administered (remifentanil or normal saline), whereas the ANI showed significantly lower values with remifentanil administration. Thus, although both the SPI and ANI were effective indices for detecting pain in healthy volunteers, the SPI showed better performance in terms of the perception of pain intensity, suggesting that the SPI may be useful for pain evaluation even in conscious patients.

### Pupillometry

For pupillometry and its variants, such as the pupillary pain index (PPI) and pupillary dilatation reflex (PDR), an infrared camera is used to measure the dynamic pupillary diameter as the width increases in response to nociceptive stimulation. Several studies have shown that pupillometry can be used to accurately measure nociception during anesthesia [60]. SPI monitoring and pupillometry were compared for perioperative opioid consumption during propofol-remifentanil anesthesia [61], and the pupillometry group was associated with better responsiveness to fentanyl and lower analgesic consumption than the SPI group.

Funcke et al. [27] compared the SPI with the PPI and nociception level (NOL) in a pilot study of patients undergoing radical retropubic prostatectomy. Although PPI monitoring reduced sufentanil consumption compared with SPI monitoring and other methods, it consequently increased the endocrine stress response. Additionally, although analgesic titration with the SPI did not result in a reduction in opioid consumption compared with conventional analgesia, it was associated with a reduction in the endocrine stress response. Another full study with a similar design but a larger number of patients was conducted by Funcke et al. [62]. As in previous studies, the opioid consumption was lower with PPI-guided analgesia but the cortisol levels were higher than with SPI-guided analgesia. In this context, although PPI-guided analgesia has been associated with lower opioid consumption, SPI-guided analgesia may reduce the endocrine stress response.

Stasiowski et al. [63] investigated the volume of intraoperative blood loss and a condition (visibility) of the surgical field using the Boezaart bleeding scale in the SPI, PDR, and control groups. By providing better analgesic guidance, the SPI was found to optimize the condition (visibility) of the surgical field, thereby reducing the amount of bleeding compared with other methods. Similar to the results of previous studies [27,62], PDR monitoring was associated with a reduction in the use of opioids and anesthetics.

### Nociception level

The NOL (Medasense, Ramat Gan) is a multiparameter index for which photoplethysmography, galvanic skin response, temperature, and accelerometry for finger motion are measured using

a finger probe. Similar to the SPI, the NOL values range from 0 (no nociception) to 100 (maximum nociception); however, an NOL range of 10–25 is considered appropriate under general anesthesia [64]. According to the studies conducted by Funcke et al. [27,62], although SPI monitoring resulted in higher opioid consumption than NOL monitoring, the endocrine stress response was lower. PPI monitoring resulted in the lowest opioid consumption but the highest endocrine stress response among the three devices. Therefore, further studies comparing these nociception monitoring devices in terms of intraoperative opioid dosing are needed.

In addition, the predictive capacity of these three devices (SPI, PPI, and NOL) for immediate postoperative pain after arousal from general anesthesia was investigated. The study concluded that none of these monitors alone had sufficient diagnostic accuracy for predicting postoperative pain [65], suggesting that a combination of these nociceptive indices and clinical factors may increase the accuracy of postoperative pain prediction.

## Effect of the anesthetic and analgesic regimen or the underlying disease on the intraoperative SPI or perioperative opioid consumption under SPI-guided analgesia

### Dexmedetomidine

Although opioids are the mainstay analgesics for moderate-to-severe perioperative pain, greater efforts toward opioid-sparing or opioid-free anesthesia have been made to minimize opioid abuse and its related side effects. In this regard, dexmedetomidine is one of the most commonly investigated non-opioid analgesics. In lung lobectomy with isoflurane anesthesia, dexmedetomidine decreased the intraoperative SPI and NRS scores compared to normal saline as a control [66]. In a preliminary study, adult patients undergoing elective craniotomy for brain tumor resection randomly received an infusion of either fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/kg/h. The SPI was similar for both groups during the study period and no differences in biomarkers such as serum cortisol, glucose, or pH were seen between the groups [67].

### Peripheral nerve block

The type II pectoral nerve block reduced remifentanil consumption during breast surgery with TIVA under SPI-guided analgesia [68]. Abdominal wall blocks, including the rectus sheath and quadratus lumborum blocks, were compared with controls in terms of remifentanil consumption under SPI-guided analgesia, and the abdominal wall blocks significantly reduced both the remifentanil dose during surgery and pain scores [69]. Therefore, during general anesthesia, the regional analgesic effect may be confirmed using the SPI.

### Depth of neuromuscular blockade

Yi et al. [70] explored the effects of the depth of neuromuscular blockade (NMB), a triad of anesthesia which consists of narcosis, analgesia and muscle relaxation, on nociception. Deep NMB reduced the remifentanil requirement and length of PACU stay compared to moderate NMB during SPI-guided analgesia. This study is consistent with several other studies that found that deep NMB can reduce postoperative pain [71,72].

### Severe liver dysfunction

The severity of liver dysfunction may affect the intraoperative nociceptive response. In a study by Park et al. [73], liver transplantation patients were assigned according to their median model for end-stage liver disease (MELD) score and divided into low ($< 16$) and high ($\geq 16$) MELD groups. When anesthetic depth was maintained within the bispectral index of 40 to 60 and SPI of 20 to 60, the remifentanil requirement was lower in patients with high MELD scores than in those with low MELD scores during the dissection and anhepatic phases; however, no significant differences were observed during the neohepatic phase. The effect of SPI-guided analgesia on patients with liver dysfunction is not clear; thus, further research is needed to clarify this effect.

## Discussion and directions for future research

Numerous studies of SPI-guided analgesia have been conducted over the past decade, most of which compare SPI-guided analgesia to conventional analgesia. Previous studies have focused on perioperative opioid consumption and postoperative recovery, pain, and adverse events. Although conflicting results have been reported, SPI monitoring has repeatedly been associated with a reduction in intraoperative opioid consumption and the endocrine stress response, faster recovery, and comparable or reduced levels of postoperative pain and rates of adverse events in many studies, including meta-analyses. However, most of these studies were performed in healthy adult populations without underlying diseases. Therefore, further studies involving patients with specific diseases or conditions and of different age groups are warranted. Although some studies have been conducted on children,


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the evidence is insufficient, and SPI studies of elderly patients are limited. Considering the growing elderly population worldwide, further research on SPI-guided analgesia in this population is urgently needed. In addition, studies on concomitant medications (e.g., various anesthetics, including remimazolam or other vasoactive agents) and pain assessment (e.g., postoperative pain in the PACU) in conscious patients would improve our understanding of the proper application of SPI-guided analgesia.

Objective measures of nociception during surgery are important in the management of acute perioperative pain. SPI monitoring has been shown to be useful as a surrogate index for predicting the degree of postoperative pain and for intraoperative analgesia guidance. Although SPI values before patient arousal may be useful for predicting the degree of postoperative pain (though diagnostic accuracy is not sufficient), the range for predicting moderate-to-severe postoperative pain, estimated between approximately 30 and 60, has not yet been fully clarified. Further studies are thus needed to clarify this characteristic.

Other nociception monitoring devices such as the ANI, PPI, and NOL have been developed and are currently available. Although these devices are all based on sympathetic-vagal balance, they operate using different underlying mechanisms and autonomic nervous system marker parameters. Each device may thus evaluate nociception differently according to changes in the patient's physiological condition. Therefore, future studies comparing the strengths and weaknesses of all three devices for more detailed purposes, populations, and clinical situations should be conducted. Considering that none of these monitors alone have sufficient diagnostic accuracy for measuring intraoperative nociception or predicting postoperative pain, future studies investigating the accuracy and efficacy of various combinations of nociception-monitoring devices to measure intraoperative nociception or predict postoperative pain should be conducted.

## Conclusions

This review summarizes the usefulness and limitations of SPI monitoring for perioperative pain management. SPI-guided analgesia generally allows for the administration of appropriate doses of intraoperative analgesia with fewer adverse hemodynamic events, thereby improving patient recovery and resulting in comparable or reduced levels of postoperative pain and rates of adverse events in patients undergoing surgery under general anesthesia. In addition, the SPI values recorded before patient arousal can help clinicians predict the degree of postoperative pain and analgesic requirements. However, the efficacy of SPI monitoring may be limited by various confounding factors, and various anesthetic and analgesic management strategies or underlying conditions may affect SPI values. As reported thus far, SPI-guided analgesia may allow for adequate analgesia through a reduction in the endocrine stress response and optimization of the surgical conditions by providing superior analgesic guidance and reducing bleeding compared with other nociception monitoring devices.

Through an understanding of the characteristics of SPI monitoring provided by this review, anesthesiologists can provide more appropriate perioperative analgesia in clinical practice, and through recognizing the limitations of our current knowledge on SPI monitoring, future research can be designed comparing SPI and other nociception monitoring devices.

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## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

## Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

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