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Development of a Hemodynamic Model Using Routine Monitoring Parameters for Nociceptive Responses Evaluation During Surgery Under General Anesthesia

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Manuscript Preparation E
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Background: Routine hemodynamic monitoring parameters under general anesthesia, such as heart rate (HR), systolic blood pressure (SBP), and perfusion index (PI), do not solely reflect intraoperative nociceptive levels. We developed a hemodynamic model combining these 3 parameters for nociceptive responses during general anesthesia, and evaluated nociceptive responses to surgical skin incision.

Material/Methods: We first retrospectively performed discriminant analysis using 3 values – HR, SBP, and PI – to assess response to skin incision during tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy to determine if combined use of these parameters differentiates nociceptive levels among these 3 surgeries. Secondly, ordinal logistic regression analysis was applied using the 3 parameters to develop an equation representing nociceptive response during general anesthesia, and then evaluated its utility to discern nociceptive responses to skin incision.

Results: We developed the following hemodynamic model as calculated nociceptive response= −1+2/(1+ exp(−0.01 HR −0.02 SBP +0.17 PI)), and prospectively determined that calculated nociceptive responses to small skin incision for laparoscopic surgery were significantly lower than responses to large skin incision for laparotomy.

Conclusions: Our hemodynamic model using HR, SBP, and PI likely reflects nociceptive levels at skin incision during general anesthesia, and quantitatively discerned the difference in nociceptive responses to skin incision between laparoscopy and laparotomy. This model could be applicable to assess either real-time nociceptive responses or averaged nociceptive responses throughout surgery without using special equipment.

MeSH Keywords: Laparoscopy • Laparotomy • Nociception • Stress, Physiological

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Background

Perioperative surgical stress and nociception cause pathophysiological changes in hemodynamics, metabolism, and the immune system [1], and increase postoperative morbidity [2,3]. The suppression of intraoperative nociceptive stimuli by anesthetic management is an important factor affecting postoperative outcomes [1].

Anesthesiologists have assessed nociceptive levels empirically using changes in heart rate (HR), blood pressure, and peripheral blood flow indices (e.g., plethysmographic pulse wave amplitude, skin temperature, and perfusion index) during surgery. Although these hemodynamic parameters, which are routinely monitored during anesthesia, do not solely reflect intraoperative nociceptive levels [4], our previous study showed that discriminant analysis using these 3 parameters together is of value in assessing the averaged nociceptive levels throughout surgical procedures [5,6].

On the other hand, several investigative modalities, such as pupillometry, skin conductance, surgical pleth index, analgesia nociception index, and the nociception level index, have been developed to assess the balance between nociception and anti-nociception during general anesthesia [7]. Each modality, however, requires specific monitoring equipment. Development of a new modality that is can be used anytime and anywhere without special equipment, is required to assess nociceptive levels during anesthesia.

We developed a novel hemodynamic model representing the nociceptive response at the time of surgical stimuli using an equation composed of the 3 parameters – HR, systolic blood pressure (SBP), and perfusion index (PI) – and then performed a prospective study to assess the validity of this model by evaluating the differences in nociceptive levels at skin incision between laparoscopic and open abdominal surgery under general anesthesia.

Material and Methods

This study was approved by the Ethics Committee of Hyogo College of Medicine. For the retrospective study, written formal consent is not required, but for the prospective study, written formal consent was obtained from each patient. This was registered in the UMIN Clinical Trial Registry (UMIN000027822).

We first conducted a retrospective cohort study to confirm the validity of analysis using these 3 variables (HR, SBP, and PI) to assess and compare intraoperative nociceptive levels among tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy, using discriminant analysis as described previously [5]. The nociceptive levels increased during these surgeries in the order described [8–11]. PI was derived from plethysmographic pulse wave amplitude via pulse oximetry (MASIMO, Irvine, CA, USA). We then performed ordinal logistic regression analysis to develop a hemodynamic model for nociceptive responses comprising 3 variables (HR, SBP, and PI) retrospectively. Finally, we prospectively compared the hemodynamic responses to skin incision, including this model, to investigate differences in nociceptive responses to skin incision between laparoscopy and laparotomy.

The retrospective study to develop hemodynamic model

For tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy, general anesthesia was induced with propofol (1.5 mg/kg), fentanyl (2 μg/kg), and 1–2 MAC of sevoflurane. Rocuronium (0.9 mg/kg) was injected intravenously to facilitate endotracheal intubation for laparoscopic cholecystectomy and open gastrectomy. Supraglottic airways were utilized for tympanoplasty, without the use of a neuromuscular blocking agent. Mechanical ventilation was performed using an oxygen concentration of 40% to obtain normocapnia (end-tidal carbon dioxide range 35–40 mmHg). All surgeries were performed in the supine position. Anesthesia was maintained with 0.6–0.7 MAC of sevoflurane to maintain a bispectral index (BIS) value of 40–60. Intraoperative analgesia comprised continuous infusion of remifentanil (0.04–0.5 μg/kg/min) with additional fentanyl for the management of postoperative pain. Where needed, rocuronium was used for muscle relaxation. Peripheral nerve blocks were not performed in any of the patients, but patients undergoing tympanoplasty received subcutaneous infiltration of 0.5% lidocaine by the surgeon before skin incision. All patients received standard of care treatment.

We identified 1054 patients who received general anesthesia using sevoflurane between 2011 and 2016. Of these, 729 underwent elective tympanoplasty, 195 underwent laparoscopic cholecystectomy, and 130 underwent open gastrectomy. All patients were between 20 and 64 years of age and American Society of Anesthesiologists Physical Status (ASA-PS) I–II. For each patient, the averaged values of HR, SBP, and PI were obtained within 5 to 15 min after skin incision, using our institutional anesthesia database (ORSYS, PHILIPS, Amsterdam, Netherlands) with data-search software (Vi-Pros, DOWELL, Sapporo, Japan). HR, SBP, and PI were recorded every minute. This was entered in our anesthesia database from which we obtained mean values of these variables. Canonical discriminant analysis using these averaged values was performed to confirm if differences of nociceptive levels among these surgeries could be discerned.

To rate stimuli intensities at skin incision for these 3 surgeries, we referenced previous reports which defined relative

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nociceptive levels to skin incision under general anesthesia [4,12]. Rantanen et al. defined stimulus intensity as no noxious stimulus=0, minor noxious stimulus=0.5, moderate noxious stimulus (small skin incision for laparoscopy)=1, large noxious stimulus (large skin incision for breast surgery)=2, severe noxious stimulus (large skin incision for laparotomy)=3, and extreme noxious stimulus=4 [12]. Ben-Israel et al. also defined stimuli intensity as no noxious stimulus=0, minor noxious stimulus=1–2, moderate noxious stimulus (small skin incision)=3–4, severe noxious stimulus (large skin incision)=5–6, and extreme noxious stimulus=7–10 [4]. Then, in the present study, we rated stimuli intensities during skin incision for tympanoplasty (minor noxious stimulus), laparoscopic cholecystectomy (moderate noxious stimulus), and open gastrectomy (severe noxious stimulus) accordingly as 1, 2, and 3, respectively. To develop a hemodynamic model for nociceptive responses, the same data used for discriminant analysis were evaluated to perform ordinal logistic regression analysis, using the mean values of HR, SBP, and PI within 5–15 min after skin incision. This provided us with estimated coefficients (B1, B2, and B3) to calculate probability using the following equation [13]:

$$\text{Probability}=1/(1+\exp(A-B1\times HR-B2\times SBP-B3\times PI)).$$

These estimated coefficients were applied to develop a hemodynamic model for nociceptive responses:

$$=C1+C2/(1+\exp(-B1\times HR-B2\times SBP-B3\times PI)).$$

In patients matched by age and sex in tympanoplasty (n=25), laparoscopic cholecystectomy (n=25), and open gastrectomy (n=25), we obtained the averaged values of HR, SBP, and PI at T0 (1–5 min before skin incision), T1 (1–5 min after skin incision), and T2 (6–10 min after skin incision). We also calculated the averaged values of this hemodynamic model at each time interval, and then evaluated its utility to discern nociceptive responses among the different surgeries.

The prospective study to confirm the validity of hemodynamic model

Using this hemodynamic model for nociceptive responses, we prospectively evaluated the differences in nociceptive responses just after skin incision between laparoscopic surgery (n=10) and open abdominal surgery (n=10). All eligible patients underwent laparoscopic or open gastrectomy (n=5 or 4), otherwise, laparoscopic or open hysterectomy (n=5 or 6) in 2017. General anesthesia was induced with propofol (1.5 mg/kg), fentanyl (2 μg/kg), and 1 MAC_{age} of desflurane. Rocuronium (0.9 mg/kg) was injected intravenously to facilitate endotracheal intubation. Mechanical ventilation was performed using an oxygen concentration of 40% to obtain normocapnia (end-tidal carbon dioxide range 35–40 mmHg). After induction, anesthesia was maintained with 0.7 MAC_{age} of desflurane. Intravenous remifentanil (0.04–0.05 μg/kg/min) was continuously infused to keep the effect site concentration at 1.0 ng/mL before and after the start of skin incision. Peripheral nerve blocks were not performed. Three variables of HR, SBP, and PI were recorded before, 0.5 min, and 1 min after the skin incision. Nociceptive responses were then calculated from the developed hemodynamic model using computer software (Microsoft Excel, Microsoft, Redmond, WA) to determine whether this model discerns between nociceptive levels during small skin incision for laparoscopic surgery *vs.* large skin incision for open abdominal surgery. Vasoactive agents were not administered until 1 min after the skin incision. At 1 min after the skin incision, the continuous dose of remifentanil was increased to 0.1–0.5 μg/kg/min with additional intravenous fentanyl to suppress any further increase in nociceptive responses.

To calculate MAC_{age}, which is the MAC for a given age normalized to MAC_{40} [14], we used MAC_{40} as 2.0 for sevoflurane and 6.0 for desflurane [15] to calculate MAC_{age}.

Statistics

Pearson's chi-square analysis was conducted for categorical variables. Unpaired *t* testing or Mann-Whitney U testing was used for appropriate variables. For multiple comparisons, one-way ANOVA, followed by Bonferroni's post hoc test was used for normally distributed variables. The Kruskal-Wallis test was used, followed by the Mann-Whitney U test with Bonferroni correction for non-normal data. To examine the relationship between stimulus intensities and nociceptive responses, Pearson correlation testing was conducted. The statistically significant level was considered, after a Bonferroni adjustment, as $p<0.016$ and $p<0.003$ when 3 parameters were tested ($0.05/3\approx0.016$ and $0.01/3\approx0.003$), $p<0.0083$ and $P<0.0017$ when 6 parameters were tested ($0.05/6\approx0.0083$ and $0.01/6\approx0.0017$), and $p<0.0056$ and $P<0.0011$ when 9 parameters were tested ($0.05/9\approx0.0056$ and $0.01/9\approx0.0011$). All statistical analyses, including discriminant analysis and ordinal logistic regression analysis, were performed using IBM SPSS Statistics 24 software (Chicago, IL). All values are reported as mean ±SD or median [25^{th}–75^{th} percentiles].

Results

Discriminant analysis

Corrected data from discriminant analysis of our anesthetic database revealed significant differences in age and body mass index (BMI) among the tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy groups (Table 1). MAC_{age} at the time of skin incision during laparoscopic cholecystectomy was

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Table 1. Patient characteristics and hemodynamic data for discriminant analysis.

	Tympanoplasty (n=729)	Laparoscopic cholecystectomy (n=195)	Open gastrectomy (n=130)
ASA-PS (I/II)	313/416	47/148	35/95
Sex (M/F)	333/396	83/112	78/52
Age (years)	44.7±13.8	49.5±10.7**	53.4±9.0**##
BMI (kg/m^2)	22.4±3.1	23.2±3.5*	22.8±3.1
End-expiratory concentration of sevoflurane at the time of skin incision (%)	1.20±0.20	1.25±0.18**	1.17±0.15##
MACage at the time of skin incision	0.61±0.12	0.66±0.12**	0.64±0.09
Continuous dose of remifentanil at the time of skin incision (μg/kg/min)	0.11±0.04	0.15±0.06	0.21±0.07
Mean SBP from 5 to 15 min after skin incision	86.0 [80.7–93.0]	100.0 [91.0–110.8]**	111.8 [102.0–129.8]**##
Mean HR from 5 to 15 min after skin incision	60.4 [54.9–67.1]	63.5 [58.0–70.8]**	70.8 [63.5–81.6]**##
Mean PI from 5 to 15 min after skin incision	3.04 [2.16–4.13]	1.96 [1.24–2.85]**	1.36 [0.84–2.07]**#

ASA-PS – American Society of Anesthesiologists Physical Status; BMI – body mass index; HR – heart rate; MAC_{age} – minimum alveolar concentration (MAC) for a given age as a function of MAC at 40 years of age (MAC_{40}); PI – perfusion index; SBP – systolic blood pressure. * p<0.05, ** p<0.01 *vs.* tympanoplasty, ## p<0.01 *vs.* laparoscopic cholecystectomy, one-way ANOVA followed by Bonferroni test for normal distributed data. ** p<0.003 *vs.* tympanoplasty, # p<0.016, ## p<0.003 *vs.* laparoscopic cholecystectomy, Kruskal Wallis test followed by Mann-Whitney U-test with Bonferroni correction for non-normal distributed data.

significantly higher than that during tympanoplasty. Continuous remifentanil doses at the time of skin incision, however, were the same among the 3 groups. Mean values of SBP and HR from 5 to 15 min after skin incision increased significantly in the following order: tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy. There was a significant decrease in mean PI in the same order (Table 1). Canonical discriminant analysis confirmed that this analysis, using the mean values of HR, SBP, and PI, significantly discerned between nociceptive responses among the 3 surgeries (p<0.001). Figure 1 shows the scatter graph plotted for 2 discriminant scores obtained from this analysis.

Hemodynamic model for nociceptive responses

Ordinal logistic analysis was performed next, analyzing data from the 3 surgical groups, and estimated 3 coefficients for a hemodynamic model. The ratio of each estimated coefficient of HR, SBP, or PI was 0.033: 0.083: –0.583, which is approximately equal to 0.01: 0.02: –0.17 (B1: B2: B3). To increase the calculated values of the hemodynamic model from 0 to 1 in the same order as the nociceptive levels, we selected –1 for C1 and 2 for C2, and developed the following hemodynamic model:

$$\text{Nociceptive response (NR)}=-1+2/(1+\exp(-0.01HR-0.02SBP+0.17PI)).$$

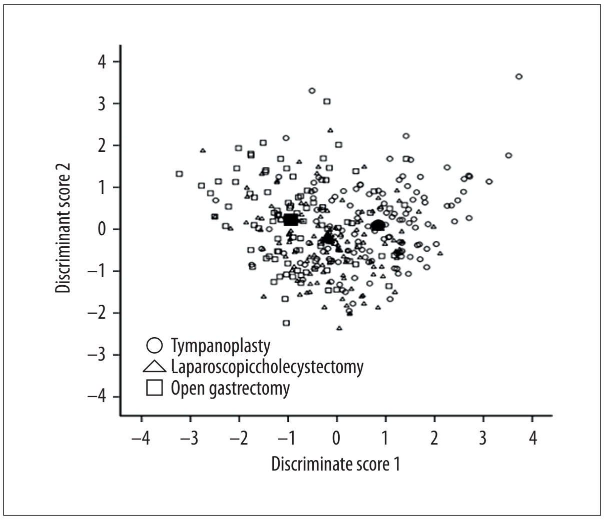

Figure 1. Scatter graph plotted for 2 discriminant scores obtained from discriminant analysis among tympanoplasty (n=729, open circles), laparoscopic cholecystectomy (n=195, open triangles), and open gastrectomy (n=130, open squares). Closed circle, triangle, and square indicate mean discriminant scores in each surgery.

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Table 2. Patient characteristics and anesthetics for the evaluation of utility of the hemodynamic model for nociceptive responses at skin incision during tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy.

	Tympanoplasty (n=25)	Laparoscopic cholecystectomy (n=25)	Open gastrectomy (n=25)
ASA-PS (I/II)	6/19	6/19	6/19
Sex (M/F)	13/12	13/12	13/12
Age (years)	54.9±9.1	54.7±8.6	55.6±9.1
BMI (kg/m^2)	23.1±3.7	26.3±10.0	22.0±3.0
End-expiratory concentration of sevoflurane at the time of skin incision (%)	1.16±0.18	1.22±0.13	1.15±0.22
MACage at the time of skin incision	0.65±0.09	0.67±0.09	0.66±0.08
Continuous dose of remifentanil at the time of skin incision (μg/kg/min)	0.10±0.03	0.14±0.07	0.18±0.07**

ASA-PS – American Society of Anesthesiologists Physical Status; BMI – body mass index; MAC_{age} – minimum alveolar concentration (MAC) for a given age as a function of MAC at 40 years of age (MAC_{40}). ** p<0.01 *vs.* tympanoplasty, # p<0.05, ## p<0.01 *vs.* laparoscopic cholecystectomy, one-way ANOVA followed by Bonferroni test.

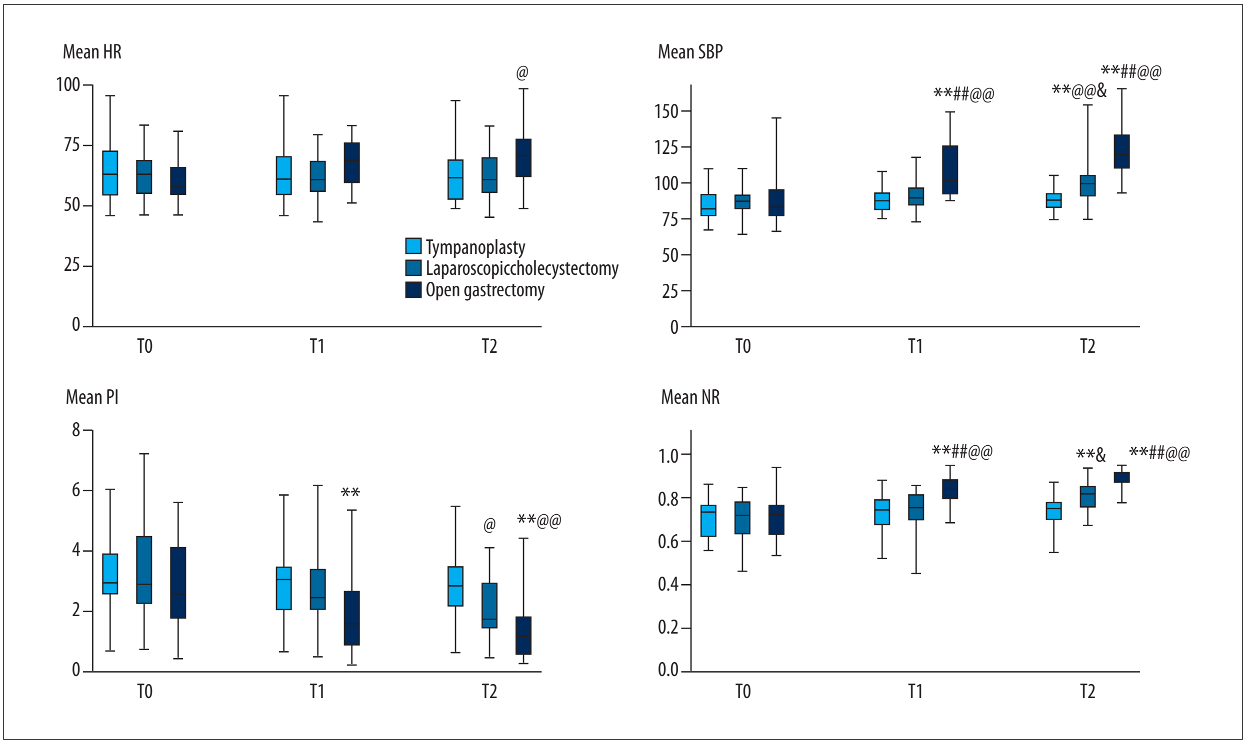

Figure 2. Hemodynamic responses before and after skin incision during tympanoplasty (n=25), laparoscopic cholecystectomy (n=25), and open gastrectomy (n=25). HR – heart rate; NR – nociceptive response; PI – perfusion index; SBP – systolic blood pressure. T0 (from 5 to 1 min before skin incision), T1 (from 1 to 5 min after skin incision), and T2 (from 6 to 10 min after skin incision).** p<0.0011 *vs.* tympanoplasty, ## p<0.0011 *vs.* laparoscopic cholecystectomy, @ p<0.0056, @@ p<0.0011 *vs.* T0, & p<0.0056 *vs.* T1. Kruskal-Wallis test was used to analyze differences in each hemodynamic parameter. Mann-Whitney U test with Bonferroni correction was used to compare between-group and within-group differences.

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Table 3. Patient characteristics for the evaluation of utility of the hemodynamic model for nociceptive responses at skin incision for laparoscopy and laparotomy.

	Laparoscopy (n=10)	Laparotomy (n=10)
ASA-PS (I/II)	2/8	0/10
Sex (M/F)	5/5	5/5
Age (years)	53.6±14.3	57.9±14.5
BMI (kg/m^2)	21.5±2.9	22.6±2.3

ASA-PS – American Society of Anesthesiologists Physical Status; BMI – body mass index.

We applied this equation to compare hemodynamic responses before and after skin incision in age- and sex-matched patients in the 3 surgical groups. There were no significant differences in patient characteristics and anesthetics used at the time of skin incision among the 3 groups, except that the continuous remifentanil dose of the open gastrectomy group was significantly higher than that of the tympanoplasty group (Table 2). Although mean HR showed no significant differences among 3 groups before and after skin incision, both mean SBP and mean NR, calculated from the hemodynamic model during 6 to 10 min after skin incision, were significantly different among the 3 groups respectively (Figure 2). NRs before skin incision for tympanoplasty, laparoscopic cholecystectomy, and open gastrectomy accordingly were 0.73 [0.62–0.76], 0.71 [0.64–0.78], and 0.72 [0.63–0.76], respectively, and there were no significant differences between surgeries. Although NR during 6 to 10 min after skin incision for tympanoplasty was 0.75 [0.70–0.77], which was no significant difference compared to NR before skin incision, it increased significantly to either 0.81 [0.76–0.85] for laparoscopic cholecystectomy or 0.90 [0.87–0.91] for open gastrectomy respectively compared to NR before skin incision (Figure 2).

Nociceptive responses to skin incision

There were no significant differences in patient characteristics in the prospective study, performed under a constant level of desflurane-remifentanil anesthesia (Table 3). HR, SBP, and PI showed no significant differences either 0.5 min or 1 min after skin incision between 2 surgeries. On the other hand, NRs gradually increased at 0.5 min and 1 min after skin incision in

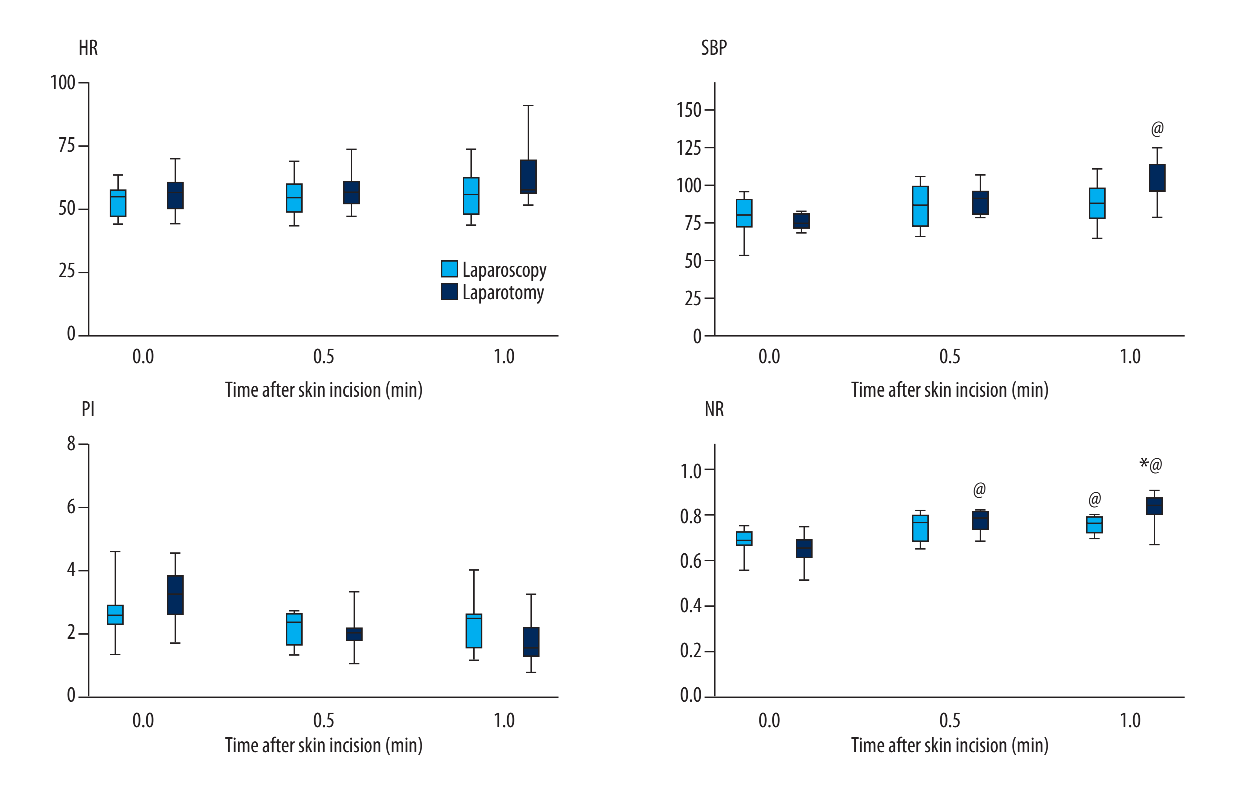

Figure 3. Hemodynamic responses just after skin incision during laparoscopic (n=10) and open abdominal surgeries (n=10). HR – heart rate; NR – nociceptive response; PI – perfusion index; SBP – systolic blood pressure. * $p<0.0083$ *vs.* laparoscopic surgery, @ $p<0.0083$ *vs.* 0 min. Kruskal-Wallis test was used to analyze differences in each hemodynamic parameter. Mann-Whitney U test with Bonferroni correction was used to compare between-group and within-group differences.

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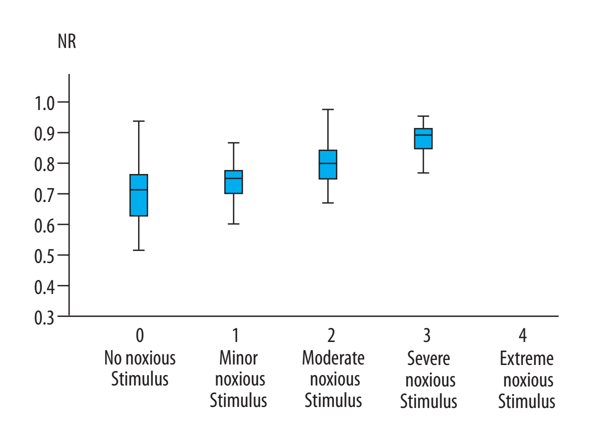

Figure 4. Noxious responses to stimulus intensity of no noxious stimulus (n=95), minor noxious stimulus (n=25), moderate noxious stimulus (n=35), severe noxious stimulus=3 (n=35), and extreme noxious stimulus (no data). NR – nociceptive response.

both surgeries. NRs before skin incision were 0.68 [0.67–0.72] for laparoscopic surgery and 0.65 [0.60–0.69] for laparotomy, and showed no significant difference between the 2 surgeries. NRs at 1 min after skin incision, however, increased to 0.76 [0.72–0.80] for laparoscopic surgery and 0.85 [0.82–0.90] for laparotomy, and showed a significant difference between the 2 surgeries (Figure 3).

Nociceptive response estimation

Figure 4 represents the relationship between stimulus intensity and NR using data obtained from Figures 2 and 3, although data for extreme noxious stimulus were missing. The relationship between stimulus intensities (no noxious stimulus=0, minor noxious stimulus=1, moderate noxious stimulus=2, severe noxious stimulus=3, and extreme noxious stimulus=4) and NRs were the following; NR=0.06 stimulus intensity+0.7 (R^2=0.38, $p<0.001$). By referencing previous reports [4,12] and considering the present results together, we created NR estimation, where no noxious stimulus is estimated as ≤0.70, minor noxious stimulus as >0.70, moderate noxious stimulus as >0.75, severe noxious stimulus as >0.85, and extreme noxious stimulus as >0.90 (Table 4).

Table 4. NR estimation.

Stimulus	Stimulus intensity	NR
No noxious stimulus	0	≤0.70
Minor noxious stimulus (very small incision, stitching)	1	>0.70
Moderate noxious stimulus (small skin incision, laparoscopic surgery)	2	>0.75
Severe noxious stimulus (large skin incision, laparotomy, tracheal intubation)	3	>0.85
Extreme noxious stimulus (multiple trauma, sternotomy)	4	>0.90

This estimation was made in reference to Figure 4.
NR – Nociceptive response.

Discussion

A hemodynamic model using routine anesthetic monitoring for nociceptive response was developed in the present study. NR values, which are calculated from this model, responded well to the level of stimulus intensity, and quantitatively discerned the difference in nociceptive responses between small and large skin incisions.

Previous reports have revealed diverse hemodynamic responses when examining HR, SBP, and PI separately. Under sevoflurane-remifentanil anesthesia, skin incision decreased PI, and increased mean blood pressure without changes in HR during various surgeries [16]. During propofol-remifentanil anesthesia, mean blood pressure increased without alterations in HR in patients undergoing various surgeries [17]. However, another report showed that desflurane-remifentanil anesthesia increased both HR and SBP after skin incision for ear, nose, and throat or lower limb orthopedic surgery [18]. These large diversities of hemodynamic responses to skin incision in the previous studies might have been caused by mixed data obtained from various surgeries.

Although several devices have been developed to assess nociceptive levels during general anesthesia [7], their clinical usefulness has also been estimated with mixed responses to skin incision during various surgeries [4,17–21]. On the other hand, our present study evaluated each hemodynamic data in each type of surgery, and revealed that different responses in NR were observed in proportion to the type of surgery performed. NRs calculated from our hemodynamic model increased along with increased levels of stimulus intensity, and discerned them between small and large skin incisions.

Chronic postsurgical pain is an important clinical problem after surgery, and type of skin incision during surgery is one of the risk factors [22,23]. The incidence of chronic postsurgical pain after large skin incision for laparotomy is reportedly higher than that after small skin incision for laparoscopic surgery [24,25]. NR monitoring provides us either real-time nociceptive levels including at the time of skin incision or averaged nociceptive levels by calculating mean values of NRs throughout surgery. Therefore, monitoring NR might be beneficial for prevention of

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chronic postsurgical pain by suppressing noxious stimuli with appropriate anesthetic management. Moreover, this model is advantageous to other previous modalities in terms of not requiring special equipment.

There are some limitations to the present study. First, our method is based on the concept that noxious stimuli will increase HR and SBP, and decrease PI. Although vasopressors or vasodilators also induce changes in these variables, we supposed that combining these 3 parameters can reduce artifacts produced by the transient effects of vasopressors or vasodilators. This method, however, may not be reliable in critically ill patients, who receive high doses of vasoactive agents under cardiovascular dysfunction. Second, certain tools, such as the surgical pleth index, the analgesia nociception index, and the nociception level index, are not clinically available in Japan. Further investigation is needed to compare the validity of our method to these previous methods.

Conclusions

Our hemodynamic model quantitatively discerned nociceptive differences at skin incision under general anesthesia. The calculated values from this model could serve as an indicator of either real-time intraoperative nociceptive levels or averaged nociceptive responses throughout surgery, which need to be suppressed by anesthetic management for better postoperative outcomes.

Conflict of interest

None.

References:

1. Banz VM, Jakob SM, Inderbitzin D: Review article: Improving outcome after major surgery: Pathophysiological considerations. Anesth Analg, 2011; 112: 1147–55
2. Katz J, Clarke H, Seltzer Z: Review article: Preventive analgesia: Quo vadimus? Anesth Analg, 2011; 113: 1242–53
3. Karanika S, Karantanos T, Theodoropoulos GE: Immune response after laparoscopic colectomy for cancer: A review. Gastroenterol Rep (Oxf), 2013; 1: 85–94
4. Ben-Israel N, Kliger M, Zuckerman G et al: Monitoring the nociception level: A multi-parameter approach. J Clin Monit Comput, 2013; 27: 659–68
5. Hashimoto K, Miyawaki H, Iwayama S et al: Comparison of the level of intraoperative nociception between laparoscopic and open hepatic resection. Hepatogastroenterology, 2015; 62: 358–62
6. Hashimoto K, Iwayama S, Sano Y et al: Preoperative anxiety induces no clinically relevant effect on intraoperative nociceptive levels during breast surgery under general anesthesia. J Anesth, 2015; 29: 967–70
7. De Jonckheere J, Bonhomme V, Jeanne M et al: Physiological signal processing for individualized anti-nociception management during general anesthesia: A review. Yearb Med Inform, 2015; 10: 95–101
8. Madsen SN, Engguist A, Badawi I, Kehlet H: Cyclic AMP, glucose and cortisol in plasma during surgery. Horm Metab Res, 1976; 8: 483–85
9. Engquist A, Fog-Møller F, Christiansen C et al: Influence of epidural analgesia on the cathecholamine and cyclic AMP response to surgery. Acta Anaesth Scand, 1980; 24: 17–21
10. Schietroma M, Carlei F, Franchi L et al: A comparison of serum interleukin-6 concentrations in patients treated by cholecystectomy via laparotomy via laparoscopy. Hepatogastroenterology, 2004; 51: 1595–99
11. Nishioka M, Ishikawa M, Hanaki N et al: Perioperative hemodynamic study of patients undergoing abdominal surgery using pulse dye densitometry. Hepatogastroenterology, 2006; 53: 874–78
12. Rantanen M, Yli-Hankala A, van Gils M et al: Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. Br J Anaesth, 2006; 96: 367–76
13. Wu Y, Jiang X, Wang S et al: Grid multi-category response logistic models. BMC Med Inform Decis Mak, 2015; 15: 10
14. Nickalls RWD, Mapleson WW: Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth, 2003; 91: 170–74
15. Forman SA, Ishizawa Y: Inhaled anesthetic pharmacokinetics: Uptake, distribution, metabolism, and toxicity. Miller's Anesthesia 8th ed. Miller RD, Cohen NH, Eriksson LI et al. (eds.), Philadelphia, PA, U.S.A. 2015; P638–69
16. Takeyama M, Matsunaga A, Kakihana Y et al: Impact of skin incision on the pleth variability index. J Clin Monit Comput, 2011; 25: 215–21
17. Martini C, Boon M, Broens SJ et al: Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia. Anesthesiology, 2015; 123: 524–34
18. Boselli E, Logier R, Bouvet L, Allaouchiche B: Prediction of hemodynamic reactivity using dynamic variations of analgesia/nociception index (ΔANI). J Clin Monit Comput, 2016; 30: 977–84
19. Huiku M, Uutela K, van Gils M et al: Assessment of surgical stress during general anaesthesia. Br J Anaesth, 2007; 98: 447–55
20. Ledowski T, Averhoff L, Tiong WS, Lee C: Analgesia Nociception Index (ANI) to predict intraoperative haemodynamic changes: Results of a pilot investigation. Acta Anaesthesiol Scand, 2014; 58: 74–79
21. Edry R, Recea V, Dikust Y, Sessler DI: Preliminary intraoperative validation of the Nociception Level Index: A noninvasive nociception monitor. Anesthesiology, 2016; 125: 193–203
22. van Rijckevorsel DC, de Vries M, Schreuder LT et al: Risk factors for chronic postsurgical abdominal and pelvic pain. Pain Manag, 2015; 5: 107–16
23. Theunissen M, Peters ML, Schepers J et al: Recovery 3 and 12 months after hysterectomy: Epidemiology and predictors of chronic pain, physical functioning, and global surgical recovery. Medicine (Baltimore), 2016; 95: e3980
24. Li J, Wang X, Feng X et al: Comparison of open and laparoscopic preperitoneal repair of groin hernia. Surg Endosc, 2013; 27: 4702–10
25. Fletcher D, Stamer UM, Pogatzki-Zahn E et al: Chronic postsurgical pain in Europe: An observational study. Eur J Anaesthesiol, 2015; 32: 725–34

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