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Response of Arterial Mechanical Impedance to Different Concentrations of Remifentanil during Abdominal Laparoscopic Colectomy

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ABSTRACT

A specific and reliable method for monitoring analgesia during general anesthesia is urgently required. Previously, we introduced a method that indicates arterial mechanical properties for estimating arterial wall stiffness (K). However, whether the response of K actually indicates changes in remifentanil target concentrations under continuous surgical stress, is unclear. Thus, we aimed to evaluate how K responds to different remifentanil target concentrations.

This prospective study enrolled 30 patients who underwent laparoscopic colectomy. The patients received 3 different effect-site concentrations (2, 4, and 6 ng/ml) of remifentanil 3 times during the study period. The K values at 4-ng/ml administration were used as control values ($K_{control}$). K values at 6-ng/ml administration (K_{6ng}) and those at 2-ng/ml administration (K_{2ng}) were normalized by dividing them by the control values. The results showed that K responded to the changes in remifentanil concentration, significantly decreasing at 6-ng/ml remifentanil effect-site concentration and increasing at 2-ng/ml concentration. The stress response at low analgesia was higher than that at high analgesia, and, as predicted, normalized K_{2ng} was significantly greater than normalized K_{6ng}. In conclusion, we found that K is a sensitive stress response monitor and dynamically responds to changes in remifentanil concentration in invasive stimulation during laparoscopic colectomy.

Key words: *Photoplethysmogram*, *Anesthesia*, *Nociceptive reflex*

INTRODUCTION

Accurate monitoring of stress response during surgical procedures is crucial for adjustment of the optimal dose of analgesic drugs and the prevention of intraoperative morbidity and delayed postoperative recovery. The lack of opioids during surgical procedures may increase sympathetic neural activity and biochemical reactions, increasing blood pressure and heart rate. Conversely, overdose of opioids can produce respiratory depression, bradycardia, and opioid-induced hyperalgesia[2,12]. Clinicians use skin sweating, skin conductance, muscle tension, and hemodynamic parameters such as heart rate and arterial pressure to judge the adequacy of nociceptive reflex suppression by analgesics[5,7,18]. However, hemodynamic parameters are easily affected by administration of cardiovascular agents. Therefore, a specific and reliable method for monitoring analgesia during general anesthesia is urgently required.

A photoplethysmogram (PPG) is well known to be able to sensitively monitor the skin vasomotor response[11]. However, photoplethysmograms provide information about blood flow rather than direct information about the characteristics of the artery that affect skin vasomotor response[7]. Thus, theoretically, photoplethysmograms cannot distinguish whether blood flow change is induced by circulatory changes or by the skin vasomotor response. In 2003, our group introduced a new method that graphically indicates arterial mechanical properties, using the pressure–volume relationship of peripheral arteries[15–17]. This method estimates changes in periph-

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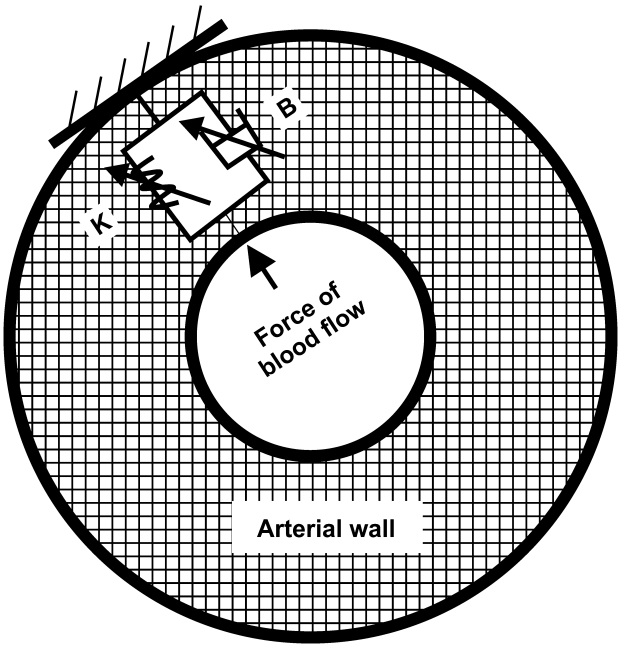

Figure 1 Schema of the arterial wall mechanical impedance model. The characteristics of the arterial wall are considered to be in an arbitrary radial direction. Arterial pressure is assumed to be proportional to the force of blood flow, and the photoplethysmogram results are proportional to the arterial radius. The mechanical components are presented as K and B, which indicate stiffness and viscosity, respectively. This figure is taken from a study by Nakamura et al.[8] with slight modification.

eral arterial wall stiffness (K) and viscosity (B) induced by sympathetic nerve activity. These values are derived from the force of blood flow to the arterial wall and the arterial radius, which are calculated from direct arterial pressure waveform and photoplethysmographic amplitude measurements (Figure 1). The value of K indicates the change in the elastic properties of the arterial wall, and therefore, is theoretically independent of circulatory changes. Recently, we reported that the value of K has a greater response than B and it can be used as a sensitive stress response monitor during general anesthesia[14].

However, it is unclear whether response of K actually indicates changes in remifentanil target concentrations under continuous surgical stress. Therefore, we examined the relationship between remifentanil target concentrations and the value of K during laparoscopic colectomy.

MATERIALS AND METHODS

Patients and preparation for measurements

The present study (unique ID issued by UMIN: UMIN000016130) was approved by the Ethics Review Board of our hospital (Permission ID: Rin-513), and written informed consent was obtained from all patients prior the study. We enrolled 30 patients, who underwent laparoscopic colectomy between January 8 and June 23, 2015. A total of 87 measurements were obtained from the 30 study patients. However, 18 measurements were excluded owing to the inadequate data of K and B obtained using the least square fitting process (low determination coefficients of the data or negative data of K or B), and the remaining 69 measurements were analyzed. The exclusion criteria were as follows: arterial fibrillation, impairment of blood flow in the upper arm, nervous system disorders, inappropriate invasive arterial pressure monitoring at the radial artery, and cerebral vascular diseases.

Anesthesia was induced with propofol, remifentanil, and rocuronium, and was maintained with desflurane, remifentanil, and rocuronium during the surgery. The concentration of desflurane was determined by an anesthesiologist within the range of 3% to 5% and was fixed during the measurement period. Administration of remifentanil also depended on the choice of the anesthesiologist, except during the measurement period, during which remifentanil was administered according to a predefined protocol. Rocuronium was administered if needed.

On the day of the surgery, patients did not receive any pre-medications. Prior to induction of anesthesia, a pulse oximetry probe (TL-271T, Nihon Kohden, Tokyo, Japan) was attached to the thumb of the left hand, an electrocardiography probe was attached to the chest, and an electroencephalography sensor of the Entropy Module® of the CARESCAPE Monitor B850 (GE Healthcare, Little Chalfont, UK) was attached to the forehead. After induction of anesthesia, a 22G catheter was placed in the left radial artery for invasive arterial pressure monitoring. During anesthesia, electrocardiogram waveforms, direct arterial pressure, and photoplethysmogram data were monitored using a bedside monitor (BSS9801, Nihon Kohden) and recorded on a personal computer. The values of K and B were then calculated and displayed using an online personal computer. The state entropy of the Entropy Module® was maintained within 30–60. The environmental temperature was maintained at 23–25°C throughout the study.

Calculation of K and B

The K and B values were calculated according to the arterial mechanical impedance model (Figure 1). The details of the calculation have been explained previously[14]. In brief, the K and B values were calculated by inputting both arterial pressure and photoplethysmogram data at time t into the following formulas:

$$dP_b(t) = K dP_l(t) + B dP_l(t) \quad (1)$$

$$dP_b(t) = P_b(t) - P_b(t_0) \text{ and } dP_l(t) = P_l(t) - P_l(t_0) \quad (2)$$

where t_0 is the start time of displacement, and $P_b(t)$ and $P_l(t)$ are arterial pressure and photoplethysmogram data at time t, respectively. Each K and B were decided from beat to beat by inputting the measured signals of every beat to Formula (1) and by using the least square fitting method. It is considered that K reflects the stiffness of the arterial wall and B reflects the viscosity of the arterial wall[14–17]. When the determination coefficient was less than 0.95, or K and/or B were negative, the heartbeat data were excluded from the analysis.

Measurement

During the surgery, to ensure the highest and most

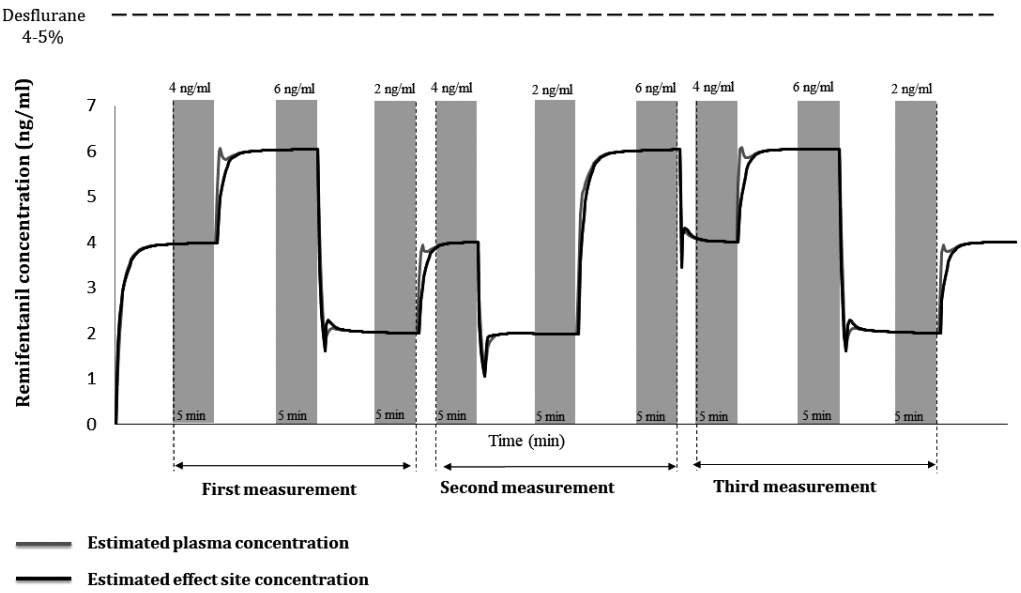

Figure 2 Outline of the study protocol. The grey line represents the estimated plasma concentrations of remifentanil, and the black line represents the estimated effect-site concentrations of remifentanil. The vertical abscissa represents the range of each measurement, and the vertical gray area represents duration of the procedures performed with control values the measured time of control values, values at high remifentanil concentration, and values at low remifentanil concentration.

constant intensity of noxious stimulation possible, we selected cases in which the surgical procedures were expected to last over 15 min and started each measurement. If the surgical procedure was changed (e.g., conversion from endoscopic surgery to laparotomy) or the body position was changed (e.g., from head down to supine) the measurement was halted, and these cases were excluded from the analysis.

As shown in the protocol in Figure 2, 3 measurements were performed during the study. When each measurement was started, remifentanil was administered according to a predefined protocol. The remifentanil administration protocol was determined using the effect-site concentration, with alteration of the dosage based on the body weight to minimize the influence of plasma concentration and patient background (age, sex, and BMI). The effect-site concentrations of remifentanil were calculated by using the Minto model of remifentanil, which is adopted in many clinical situations for minimizing the influence of age, sex, and BMI[13]. According to the study protocol, the patients received 3 different effect-site concentrations (2, 4, and 6 ng/ml) of remifentanil during each measurement. The order for administering the different remifentanil concentrations was randomly selected from either a) 4, 2, and 6 ng/ml; 4, 6, and 2 ng/ml; and 4, 2, and 6 ng/ml (15 patients) or b) 4, 6, and 2 ng/ml; 4, 2, and 6 ng/ml; and 4, 6, and 2 ng/ml (15 patients). Immediately before each measurement, the bolus dose, pause duration of a continuous dose, and continuous speed of a remifentanil dose were calculated to achieve the predefined effect-site concentration. When arterial pressure at a remifentanil concentration of 2 or 6 ng/ml was increased or reduced over ±50% of the pressure at 4-ng/ml remifentanil concentration, the measurements were ceased.

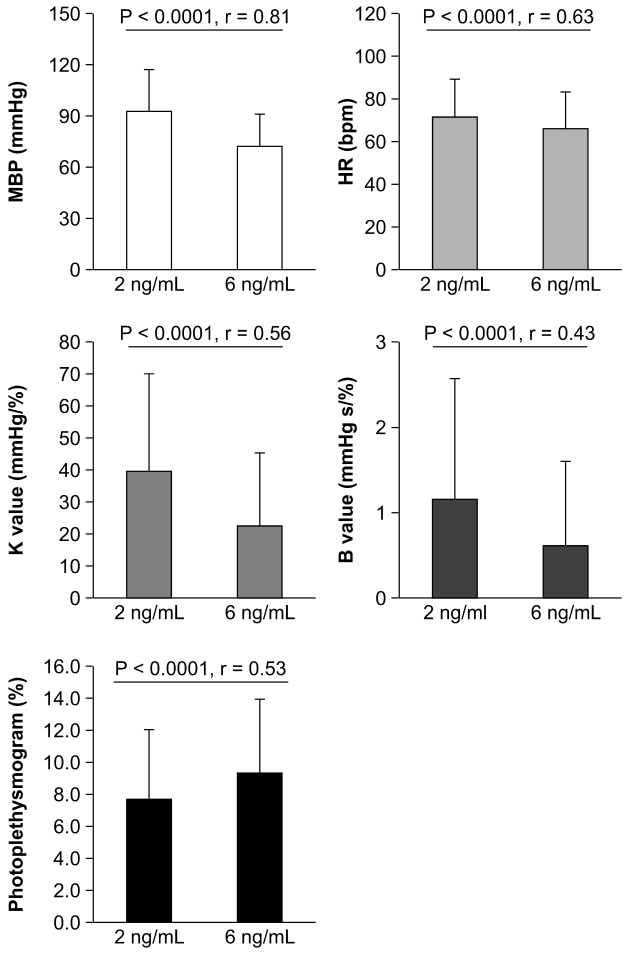

Figure 3 Changes in variables at different remifentanil effect-site concentrations. The measured raw values of heart rate, mean arterial pressure, K, B, and photoplethysmogram data at remifentanil effect-site concentrations of 2 ng/ml and 6 ng/ml are presented.

Data processing and statistics

The measured values of arterial stiffness K at remifentanil effect-site concentrations of 4, 2, and 6 ng/ml were considered as control values ($K_{control}$), values of low remifentanil concentration (K_{2ng}), and values of high remifentanil concentration (K_{6ng}), respectively. When the difference between the estimated effect-site concentration and estimated plasma concentration of remifentanil was less than 0.1 ng/ml, the measurement was commenced. Measurement of $K_{control}$ continued for 5 min, whereas K_{2ng} and K_{6ng} measurements were performed for 5 min when the difference between the estimated effect-site concentration and plasma concentration was within 0.1 ng/ml. To minimize the duration, we did not pause for an additional 5 min before $K_{control}$ measurement; however, we paused before K_{2ng} and K_{6ng} measurements for 5 min to ensure a steady remifentanil concentration. The precision of the measurement of the control was low; however, it was a reference value and a small effect was observed on the comparison between 2-ng/ml and 6-ng/ml concentrations. The measured values of arterial viscosity B at remifentanil effect-site concentrations of 4, 2, and 6 ng/ml were considered as control values ($B_{control}$), values of low remifentanil concertation (B_{2ng}), and values of high remifentanil concentration (B_{6ng}), respectively. The values of photoplethysmogram (PPG) at remifentanil effect-site concentrations of 4, 2, and 6 ng/ml were measured at the same time as K measurements, and these values were considered as $PPG_{control}$, PPG_{2ng}, and PPG_{6ng}, respectively.

The primary analysis involved K_{6ng} and K_{2ng}. The measured K_{6ng} was normalized by dividing K_{6ng} by $K_{control}$, and the measured K_{2ng} was normalized by dividing K_{2ng} by $K_{control}$. To compare the response of K at different remifentanil concentrations, we used normalized K_{2ng} (nK_{2ng}) and normalized K_{6ng} (nK_{6ng}). Similarly, normalized B_{2ng} (nB_{2ng}) and normalized B_{6ng} (nB_{6ng}) were used to compare the response of B at different remifentanil concentrations, and normalized PPG_{2ng} ($nPPG_{2ng}$) and normalized PPG_{6ng} ($nPPG_{6ng}$) were used to compare the response of photoplethysmogram at different remifentanil concentrations. Typically, the responses of K and B and the response of photoplethysmogram are opposite; therefore, normalized PPG_{2ng} was calculated by dividing $PPG_{control}$ by PPG_{2ng} and normalized PPG_{6ng} was calculated by dividing $PPG_{control}$ by PPG_{2ng}.

Data are expressed as mean ± standard deviation. The paired *t*-test and Pearson's correlation analysis were used for statistical analyses, and the level of significance was set at $P < 0.05$. To estimate the performance of normalized K, normalized B, and normalized photoplethysmogram for the classification of remifentanil concentrations, receiver operating characteristic (ROC) curve analysis was performed. In the ROC curve, we defined high remifentanil concentration as true positive and low remifentanil concentration as true negative and plotted the sensitivities and the specificities at various threshold settings. The effect size was presented by *r*, and *r* was calculated as the square root of the following formula, where *t* indicates the *t* value and *df* indicates the degree of freedom: $r^2 = t^2 / (t^2 + df)$. Prior to the study, power analysis was performed using free software (G*power 3.1.0, published at http://www.gpower.hhu.de/). To obtain a power of 0.80 with an estimated difference between 2 different remifentanil concentrations of 25%, a total sample size of 73 measurements was needed. We assumed that the mean number of measurements in each patient would be approximately 2.5. Thus, we determined that 30 patients would be appropriate for the study.

RESULTS

Baseline characteristics

The patients' demographic data are shown in Table 1. There were no patients with severe Class 3 complications according to the physical status classification of the American Society of Anesthesiologists. None of the patients received opioids, major tranquilizers, antidepressants, or anticonvulsants in the preoperative period and none had life-threatening hypertension, hypotension, tachycardia, or bradycardia during the measurements. Additionally, no patients had complications after anesthesia. No measurements were terminated because of excessive hypertension, hypotension, or changes in surgical procedure. Moreover, no patients needed an increase in the remifentanil concentration at endotracheal intubation because of hypertension during laryngoscopy.

Arterial wall stiffness responds to changes in remifentanil concentration

Figure 3 shows the changes in K, mean arterial pressure, heart rate, and photoplethysmogram at remifentanil effect-site concentrations of 2 ng/ml and 6 ng/ml. Hemodynamic properties, such as mean arterial pressure and heart rate, were significantly higher at remifentanil effect-site concentrations of 2 ng/ml than at 6 ng/ml. By contrast, the photoplethysmogram value was significantly higher at a remifentanil effect-site concentration of 6 ng/ml than at 2 ng/ml. Interestingly, the responses of arterial mechanical properties, including arterial wall stiffness and viscosity were also significantly higher at low remifentanil concentrations than at high remifentanil concentrations.

Stress response at low analgesia is higher than at high analgesia

Figure 4 shows a comparison of the responses of normalized K_{2ng} and normalized K_{6ng}. As predicted, normalized K_{2ng} was significantly greater than normalized K_{6ng}.

K is a more sensitive stress response monitor than B and PPG

Figure 5 shows the ROC curves of each normalized value of K, B, mean blood pressure, heart rate, and photoplethysmogram data. The areas under the curve (AUCs) of normalized K, B, mean blood pressure, heart rate, and photoplethysmogram data were 0.80, 0.71, 0.85, 0.58, and 0.75, respectively. The optimal threshold

Table 1 Clinical characteristics and physical status of patients.

Variables	Value (n = 30)
Age (years)	59.7 ± 9.7
Sex (M/F)	15/15
Height (cm)	162.5 ± 9.4
Weight (kg)	60.6 ± 11.4
ASA PS (1/2/3)	9/21/0
Fluid in (mL)	3179.0 ± 841.2
Fluid out (mL)	406.0 ± 272.4
Bleeding (g)	96.5 ± 135.6
Time of operation (minutes)	336.7 ± 121.8
Time of anesthesia (minutes)	442.2 ± 137.6
State Entropy of the Entropy Module®	35.8±8.5
Disorders and other characteristics	Diabetes mellitus-5, Hypertension-7, smoker-4, Hyperlipidemia-1, Obeisity-6, Hypoalbuminemia-1, Glaucoma-2, Anemia-1

Data are presented as mean ± standard deviation or number.
ASAPS, American Society of Anesthesiologists physical status.

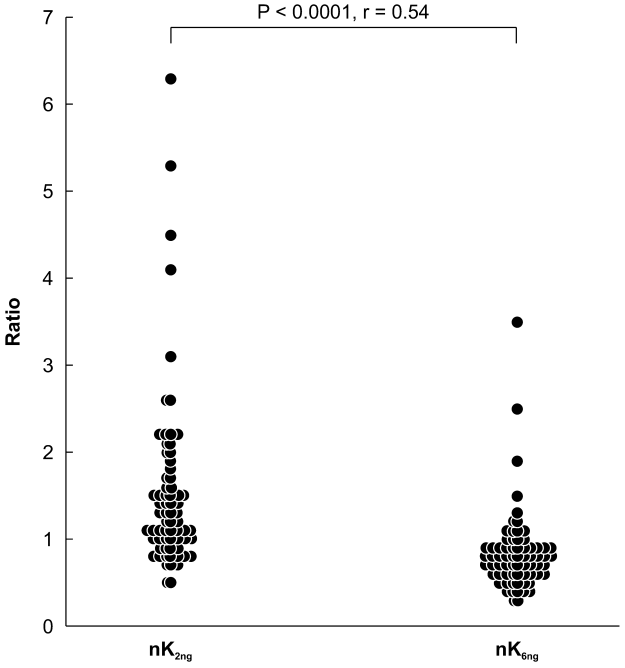

Figure 4 Comparison of the responses of K at high and low remifentanil concentrations. Comparison of the normalized values of K at remifentanil effect-site concentrations of 2 ng/ml and 6 ng/ml. nK_{6ng}: normalized values of K at 6 ng/ml. nK_{2ng}: normalized values of K at 2 ng/ml. Ordinate is expressed using the common log scale.

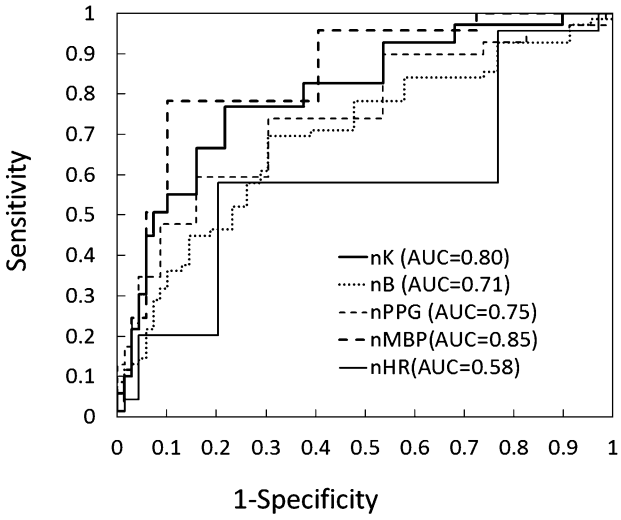

Figure 5 Receiver operating characteristic curves of normalized K, normalized B, normalized mean blood pressure, normalized heart rate, and normalized photoplethysmogram data. The measurements at a remifentanil effect-site concentration of 2 ng/ml were treated as true positive, and the measurements at a remifentanil effect-site concentration of 6 ng/ml were treated as true negative. K, arterial mechanical impedance monitoring value for peripheral arterial stiffness; B, arterial mechanical impedance monitoring value for arterial viscosity; PPG, photoplethysmographic amplitude; MBP, mean blood pressure; HR, heart rate.

of normalized K was 1.0 and the sensitivity and specificity of this threshold were 76.8% and 78.3%, respectively.

DISCUSSION

In this prospective study, arterial mechanical impedance changed in response to changes in the remifentanil concentration to 2 ng/ml and 6 ng/ml from the baseline of 4 ng/ml, under continuous surgical stress with desflurane anesthesia. The response of K differed significantly between the high and low analgesic conditions; as predicted, normalized K_{2ng} was significantly greater than normalized K_{6ng}. These findings indicate that K is a sensitive stress response monitor and responds to changes in remifentanil concentration during invasive stimulation.

We previously reported that arterial stiffness can reflect changes of sympathetic nerve activation[14]. However, it is unclear whether K can reflect different levels of sympathetic nerve activity. Two possible approaches are available to change the activity of the sympathetic nervous system during continuous surgery, including a change in the level of surgical stress or a change in the analgesic drug concentration. Based on our clinical practice we chose laparoscopic colectomy, because once the operation is started, the intensity of the stress, induced by a painful procedure, is relatively constant during lapa-

roscopic colectomy. In addition, achieving precisely constant stress stimulation for patients during a surgical procedure is highly difficult. Remifentanil is used as an analgesic agent, which suppresses the nociceptive reflex induced by sympathetic activation[3]. Because none of the patients received opioids in the preoperative period, the possibility of opioid hypersensitivity was low in our study. Therefore, we hypothesized that a change in remifentanil concentration may reflect a change in the nociceptive reflex and aimed to examine whether K can detect and dynamically respond to changes in the concentration of remifentanil during an operation. The lower arterial pressure and heart rate at 6-ng/ml remifentanil concentration in contrast to that at 2 ng/ml in our results indicated that the autonomic nervous system was more suppressed under high analgesic conditions. This may indicate that different remifentanil concentrations induce different levels of nociceptive stimulation.

Indicators of the nociceptive reflex other than photoplethysmogram also exist, such as skin sweating, skin conductance, muscle tension, and the surgical pleth index, during general anesthesia[1,4–7,11,18–20]. Among these other indicators, the surgical pleth index is particularly appropriate for clinical use because of its readily available signal source. The surgical pleth index is calculated as a simple addition of the change in photoplethysmogram data and the change in heart rate. The heart rate is easily altered by the administration of beta-adrenergic receptor blockers or calcium channel blockers, and therefore, both the surgical pleth index and heart rate itself are unreliable nociceptive reflex monitors during the administration of such drugs. Even in Figure 5, the AUC of mean blood pressure is greater than K. Nevertheless, arterial pressure is easily altered by the administration of alpha- and beta-adrenergic receptor agonists; therefore, mean blood pressure is not a reliable nociceptive reflex monitor during the administration of such drugs. The indicators of nociceptive stimuli, which use photoplethysmogram data, monitor the α_1 adrenergic receptor-induced skin vasomotor response; therefore, α_1 adrenergic receptor agonists might influence the measurement of such indicators, including K[7]. Arterial pressure is also altered by changes in cardiac output resulting from the administration of a beta-adrenergic agent. Photoplethysmogram data are considered to not be influenced by the administration of a beta-adrenergic agent[7]. However, photoplethysmogram data reflect fingertip blood flow; therefore, photoplethysmogram data are theoretically influenced by an alteration in cardiac output resulting from the administration of a beta-adrenergic agent even when noxious stimulation is unchanged. By contrast, K, which indicates the peripheral vascular resistance but not the blood flow, theoretically remains stable even when cardiac output changes. In our study, the AUC of normalized K was greater than that of normalized PPG. K depends mainly on PPG; however, our results indicated that the responses of K were more precise because the effects of cardiac output change were eliminated.

Kutluk et al. monitored autonomic nervous activity using arterial mechanical impedance during endoscopic transthoracic sympathectomy[8–10]. Nakamura et al. compared the response of arterial mechanical impedance assessed with a photoplethysmogram for noxious stimuli and fentanyl administration under propofol anesthesia[14]. They suggested that K is a sensitive stress response monitor during general anesthesia. These previous studies reported that K responds to the addition and termination of noxious stimulation. However, it was previously unclear whether K can detect and dynamically respond to changes in remifentanil concentration, which was clarified in the present study as a novel finding.

In conclusion, we found that K significantly decreases at remifentanil effect-site concentrations of 6 ng/ml and increases at remifentanil effect-site concentrations of 2 ng/ml. The stress response at low analgesia was higher than at high analgesia, and, as predicted, normalized K_{2ng} was significantly greater than normalized K_{6ng}. This indicates that K is a sensitive stress response monitor and dynamically responds to changes in remifentanil concentration in invasive stimulation during laparoscopic colectomy.

Limitations

Although K reflects the change of stress intensity, it is unclear whether it is useful for the titration of analgesic infusion during general anesthesia in clinical settings. We are planning a new study to evaluate whether K-monitored management of analgesic administration could suppress hemodynamic changes. In the present study, we could not determine the usefulness of B. The changes in B values were not consistent for all patients, indicating that other factors might influence B. Therefore, B cannot be used as a reliable indicator of the nociceptive reflex. Although we speculated that the reason for the higher precision of K than PPG was the elimination of the effect of cardiac output, we did not measure changes in cardiac output quantitatively during the alteration of remifentanil concentrations.

Changes in K are generally expected to depend on remifentanil concentration. This study was conducted using general anesthesia with desflurane, which may have an influence on the value of K by affecting the analgesia. In addition, no previous study has evaluated the response of K to different remifentanil concentrations with other anesthetic agents. Therefore, additional studies are needed to clarify the effects of anesthetic agents on the ability of K.

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Disclosures

The authors have no conflicts of interest to declare.

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