

## Effect of landiolol on bispectral index and spectral entropy responses to tracheal intubation during propofol anaesthesia

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**Background.**  $\beta$ 1-Adrenoceptor antagonists suppress the haemodynamic and arousal responses to tracheal intubation. The Entropy™ Module shows two spectral entropy-based indices, response entropy (RE) and state entropy (SE). The difference between RE and SE (RE–SE) may reflect nociception during general anaesthesia. In the present study, we investigated the effect of landiolol on entropy indices in response to tracheal intubation.

**Methods.** A total of 60 patients were randomly assigned to receive saline (Group S), remifentanyl (Group R), or landiolol (Group L). Anaesthesia was induced by propofol target-controlled infusion. Two minutes after the induction of anaesthesia, infusion with vecuronium bromide and remifentanyl, landiolol, or saline was initiated. Tracheal intubation was performed 7 min after anaesthesia induction. Arterial pressure, heart rate (HR), bispectral index (BIS), and entropy indices were recorded.

**Results.** In Group S, RE increased significantly after tracheal intubation, but there was no significant increase in BIS or SE. These increases in RE were abolished in Groups R and L. RE–SE increased significantly after tracheal intubation in Group S, whereas no increase in RE–SE was observed in Groups R and L. Increases in mean arterial pressure and HR after tracheal intubation were suppressed in Groups R and L compared with Group S.

**Conclusions.** RE increased in response to tracheal intubation, whereas BIS and SE did not. Landiolol and remifentanyl suppressed the increase in RE after tracheal intubation with significant inhibition of RE–SE difference.

*Br J Anaesth* 2008; **101**: 273–8

**Keywords:** anaesthetics i.v., propofol; analgesics opioid, remifentanyl; monitoring, bispectral index; monitoring, electroencephalography; sympathetic nervous system, adrenergic block

Accepted for publication: May 8, 2008

Tracheal intubation during anaesthesia induction is one of the most intensive noxious stimuli and can induce haemodynamic responses and increase the bispectral index (BIS).<sup>1–3</sup> Opioids or  $\beta$ 1-adrenoceptor antagonists<sup>4 5</sup> are widely used to blunt the haemodynamic and processed electroencephalographic (EEG) responses to tracheal intubation.

EEG signals are analysed during anaesthesia to evaluate anaesthetic depth. Among the EEG-derived indices, BIS is most widely used to evaluate hypnotic level during general anaesthesia. Spectral entropy is another EEG-derived index that is used to estimate anaesthesia depth.<sup>6 7</sup> Spectral entropy is determined using raw EEG and frontal electromyography (fEMG) data, resulting in two indices, response entropy (RE) and state entropy (SE).

These indices reflect nociceptive and hypnotic levels during general anaesthesia.<sup>8</sup> Under deep anaesthesia, the EEG signals change from fast-wave activity to slow-wave activity. Spectral entropy is a measure of EEG irregularity and used to evaluate the depth of anaesthesia based on an entropy algorithm. SE, which is calculated over frequencies ranging from 0.8 to 37 Hz, is the entropy of the EEG signal reflecting the patient's cortical activity. RE includes additional higher frequencies up to 47 Hz, reflecting both EEG and fEMG activity. When the EMG power is equal to zero, SE and RE are equal. The difference between RE and SE (RE–SE) reflects EMG activation.<sup>8</sup> Noxious stimulation increases RE, and RE–SE increases after noxious stimulation.<sup>9 10</sup> Furthermore, RE–SE is suggested to be a potential surrogate marker of the adequacy of

antinociception.<sup>11</sup> Tracheal intubation also increases entropy indices during propofol anaesthesia.<sup>12</sup>

Although the mechanism is unknown,  $\beta$ 1-adrenoceptor antagonists, such as esmolol and landiolol, blunt the haemodynamic responses to tracheal intubation and suppress the increase in BIS after tracheal intubation during sevoflurane<sup>5</sup> or propofol<sup>2</sup> anaesthesia. Little is known, however, about the effect of  $\beta$ 1-adrenoceptor antagonists on the entropy index responses to tracheal intubation.<sup>13</sup> In the present study, we investigated the effect of landiolol on BIS and entropy index responses to tracheal intubation in a double-blind manner. We hypothesized that entropy indices, and BIS, increase in response to tracheal intubation and that the antinociceptive effect of landiolol, observed as a reduction in the RE–SE response, suppresses the arousal response to tracheal intubation.

## Methods

Approval for this study was obtained from the Ethics Committee of the National Defense Medical College (Saitama, Japan), and informed consent was obtained from 60 patients, ASA class I–II, 20–69 yr of age, undergoing elective surgery. Exclusion criteria included disease or injury affecting the central nervous system, recent use of psychoactive or analgesic medication, neurological disorders, use of  $\beta$ -adrenergic blocking agents, alcohol, or drug abuse, and body weight <70% or >130% of the patient's ideal body weight.

No premedication was administered before anaesthesia induction. Patients were randomly assigned to one of the three groups: saline (Group S;  $n=20$ ), remifentanyl (Group R;  $n=20$ ), or landiolol (Group L;  $n=20$ ). After the patients entered the operation theatre, non-invasive arterial pressure monitoring, electrocardiography, and pulse oximetry were performed. Anaesthesia was induced by propofol plasma-target-controlled infusion (TCI; a target plasma concentration of  $6 \mu\text{g ml}^{-1}$ ) using a Diprifusor TCI pump (Terumo Corporation, Tokyo, Japan) based on the kinetic set of Marsh and colleagues.<sup>14</sup> Ventilation was controlled to maintain end-tidal  $\text{CO}_2$  at 35–40 mm Hg with a fresh gas flow of  $6 \text{ litre min}^{-1}$  (100% oxygen) via a facemask. Target concentration of propofol was reduced to  $3 \mu\text{g ml}^{-1}$  90 s after anaesthesia induction. Two minutes after anaesthesia induction, vecuronium bromide ( $0.1 \text{ mg kg}^{-1}$ ) was administered and an infusion of remifentanyl, landiolol, or saline was initiated. In Group R, remifentanyl was infused at a rate of  $0.8 \mu\text{g kg}^{-1} \text{ min}^{-1}$  for 1 min and then decreased to  $0.2 \mu\text{g kg}^{-1} \text{ min}^{-1}$ . According to the pharmacokinetic sets published by Minto and colleagues,<sup>15</sup> the infusion rate of remifentanyl produced an effect-site concentration of approximately  $5 \text{ ng ml}^{-1}$  at tracheal intubation, which can suppress the BIS response to tracheal intubation.<sup>16</sup> In Group L, landiolol was infused at a rate of  $0.125 \text{ mg kg}^{-1} \text{ min}^{-1}$  for 1 min and then decreased to

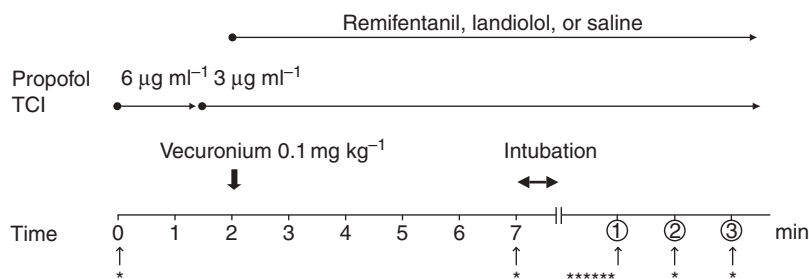
$0.04 \text{ mg kg}^{-1} \text{ min}^{-1}$ , which can suppress the BIS response to tracheal intubation.<sup>5</sup> In Group S, patients were given saline. All drugs were diluted to a comparable volume with saline, and drug concentrations were adjusted to give a similar infusion rate. The investigators were blinded to the drug preparations. Seven minutes after anaesthesia induction, tracheal intubation was initiated. Tracheal intubation was defined as the time at which the cuff was inflated. Non-invasive arterial pressure and heart rate (HR) were recorded every minute from the beginning of propofol infusion. BIS, RE, and SE were recorded before anaesthesia induction, just before tracheal intubation, and after tracheal intubation (10, 20, 30, 40, 50, 60, 120, and 180 s after tracheal intubation). The study protocol is summarized in Figure 1. Possible patient movement (movement of arms, legs, or head) was recorded after tracheal intubation. To avoid awareness during the study period, patients were excluded when the BIS was >65 before tracheal intubation. Patients in whom tracheal intubation could not be performed within 1 min were also excluded.

Non-invasive arterial pressure monitoring, electrocardiography, pulse oximetry, and end-tidal  $\text{CO}_2$  monitoring were performed with an S/5<sup>TM</sup> anaesthesia monitor (GE Healthcare, Helsinki, Finland). BIS was monitored with a BIS XP Monitor (ver. 3.4) with a quarto sensor (Aspect Medical Systems, Norwood, MA, USA). The smoothing time was set at 15 s. RE and SE were monitored with a Datex-Ohmeda S/5 Entropy Module (M-Entropy<sup>TM</sup>) and an Entropy Sensor<sup>TM</sup> (GE Healthcare). Both sensors were applied side-by-side to the forehead. All data were captured offline with a digital video camera (Matsushita Electrical Industrial, Osaka, Japan) and recorded by an investigator blinded to the study protocol.

The number of patients included was based on the means and standard deviation of the BIS response to intubation described by Oda and colleagues.<sup>5</sup> Changes in EEG-derived indices (BIS, RE, SE, and RE–SE), mean arterial pressure (MAP), and HR within groups were analysed with one-way analysis of variance for repeated measures followed by Bonferroni's correction for multiple comparisons test. Differences in EEG-derived indices (BIS, RE, SE, and RE–SE), MAP, and HR between groups were analysed with two-way analysis of variance followed by Bonferroni's correction for multiple comparisons test. The number of patients is indicated by  $n$ . Probability values ( $P$ ) <0.05 were considered statistically significant.

## Results

Patient characteristics are summarized in Table 1. There were no differences in the patient characteristics between groups. Three, four, and three patients in Groups S, R, and L, respectively, were excluded because the BIS was >65 just before tracheal intubation. Two patients in Group R



**Fig 1** Schematic of experimental procedures. Non-circled numbers indicate time after anaesthesia induction (min). Circled numbers indicate time after tracheal intubation. Arrows indicate measurement of arterial pressure and HR. \*Measurement of BIS, RE, and SE. TCI, target-controlled infusion.

and one patient in Group L were excluded because tracheal intubation could not be performed within 1 min. In the postoperative recovery room and the next day, patients were questioned with respect to perioperative memory, but no intraoperative awareness or recall was reported.

One patient in Group S moved after tracheal intubation. BIS and SE did not significantly increase in any of the groups after tracheal intubation (Figs 2 and 3). In Group S, RE significantly increased at 10, 20, and 30 s after tracheal intubation compared with before intubation ( $P < 0.01$ , 0.05, and 0.05, Fig. 4). There was a significant difference in RE at 10, 20, and 30 s after tracheal intubation between Group S and Group R ( $P < 0.01$ , 0.05, and 0.05) and at 10 s after tracheal intubation between Group S and Group L ( $P < 0.05$ ). Changes in RE–SE in response to tracheal intubation are shown in Figure 5. In Group S, RE–SE increased significantly after tracheal intubation at 10 and 30 s ( $P < 0.05$  and 0.05); no increase was observed in Group R or L. RE–SE at 10 and 30 s after tracheal intubation in Groups R ( $P < 0.05$  and 0.05) and L ( $P < 0.01$  and 0.05) was significantly lower than that in Group S. Burst suppression (increase in suppression ratio in BIS monitor and burst suppression pattern in raw EEG wave) was not observed during the study period.

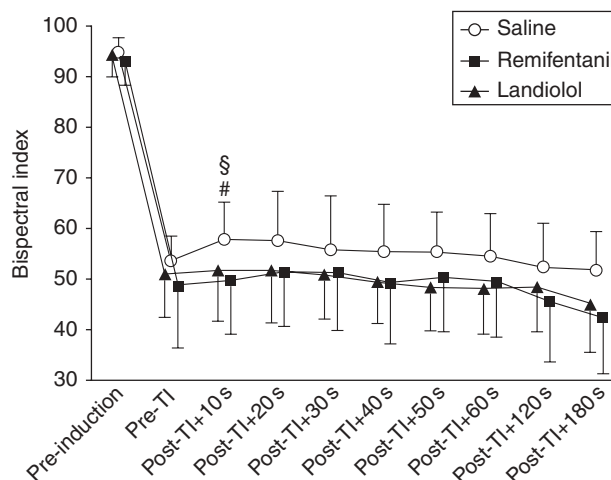
Haemodynamic data are summarized in Table 2. MAP increased significantly at 60, 120, and 180 s after tracheal intubation in all three groups ( $P < 0.01$  for all) compared with before intubation. MAP was significantly lower at 60, 120, and 180 s after tracheal intubation in Group R ( $P < 0.01$  for all) and at 60 s after tracheal intubation ( $P < 0.01$ ) in Group L compared with Group S. After tracheal intubation, HR increased significantly at 60, 120, and 180 s in Group S ( $P < 0.01$ , 0.01, and 0.05), at 60 and 120 s in Group R ( $P < 0.01$  and 0.05), and at 60 s in Group

L ( $P < 0.05$ ), compared with before intubation. After tracheal intubation, HR was significantly lower at 60, 120, and 180 s in Group R ( $P < 0.01$ , for all) and at 60 and 120 s in Group L ( $P < 0.01$  and 0.05) compared with Group S.

## Discussion

We investigated the effects of remifentanyl and landiolol on BIS and entropy indices in response to tracheal intubation. In the present study, RE increased after tracheal intubation, whereas BIS and SE did not. In addition, remifentanyl and landiolol abolished the increases in RE after tracheal intubation. RE–SE increased after tracheal intubation, and this increase was suppressed by the administration of landiolol or remifentanyl. Therefore, landiolol and remifentanyl suppress the RE and RE–SE responses to tracheal intubation.

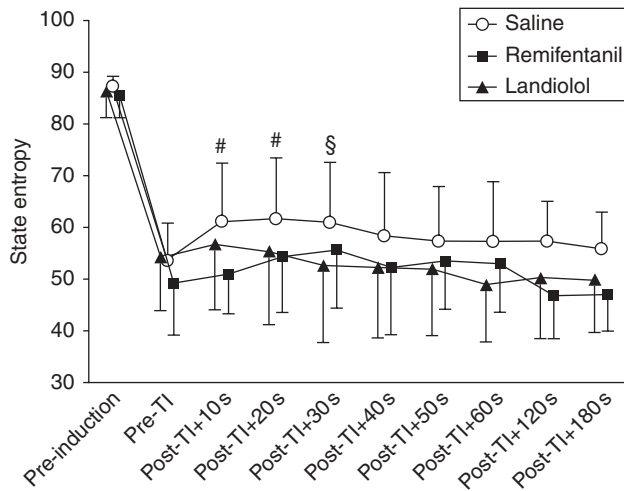
In the present study, tracheal intubation did not induce a significant increase in SE. SE, which is calculated over frequencies ranging from 0.8 to 37 Hz, is the entropy of the EEG signal. In this frequency range, most EMG activity is eliminated and SE did not increase significantly



**Fig 2** BIS before anaesthesia induction (Pre-induction), before tracheal intubation (Pre-TI), and after tracheal intubation (Post-TI+10, 20, 30, 40, 50, 60, 120, and 180 s). # $P < 0.05$  vs remifentanyl group. \$ $P < 0.05$  vs landiolol group.

**Table 1** Patient characteristics. Values are mean (range) or mean (SD). There were no significant differences among the three groups

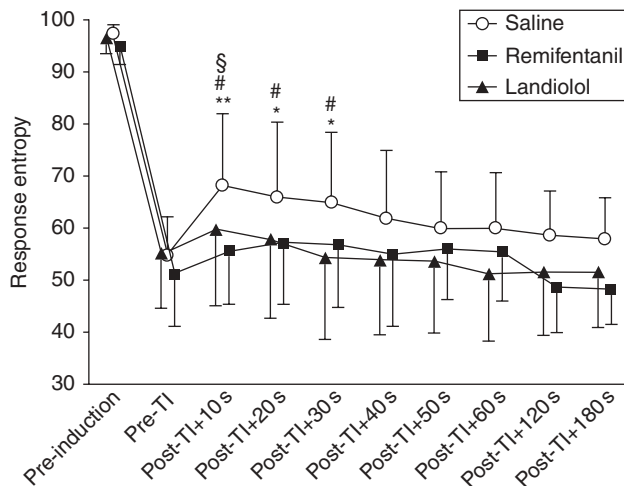
	Saline	Remifentanyl	Landiolol
Sex (male/female)	8/9	4/10	10/6
Age (yr)	55 (21–69)	54 (30–68)	51 (20–69)
Weight (kg)	57 (9)	55 (12)	63 (13)
Height (cm)	160 (10)	160 (10)	165 (11)



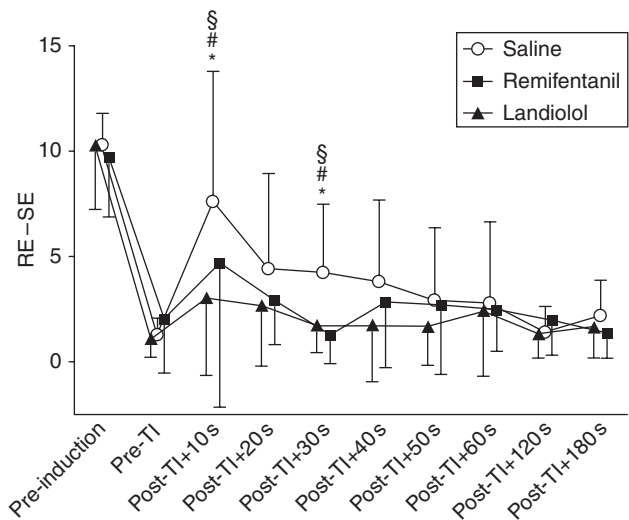
**Fig 3** SE before anaesthesia induction (Pre-induction), before tracheal intubation (Pre-TI), and after tracheal intubation (Post-TI+10, 20, 30, 40, 50, 60, 120, and 180 s). # $P < 0.05$  vs remifentanil group. § $P < 0.05$  vs landiolol group.

after tracheal intubation. RE, which includes EMG activity, increased significantly after tracheal intubation, and the increase in RE was abolished by remifentanil. Thus, the RE increase appears to be useful for estimating nociception during tracheal intubation. In the present study, although there was no significant increase in either BIS or SE after tracheal intubation in Group S, BIS and SE were slightly increased after tracheal intubation and there were significant differences between Group S and Groups R and L. These findings suggest that BIS and SE are both affected by EMG activity to some extent because the power spectrum of EMG overlaps that of EEG.

Noxious stimulation increases fEMG activity.<sup>17, 18</sup> SE reflects EEG activity and RE reflects both EEG and fEMG



**Fig 4** RE before anaesthesia induction (Pre-induction), before tracheal intubation (Pre-TI), and after tracheal intubation (Post-TI+10, 20, 30, 40, 50, 60, 120, and 180 s). \* $P < 0.05$  and \*\* $P < 0.01$  vs Pre-TI. # $P < 0.05$  vs remifentanil group. § $P < 0.05$  vs landiolol group.



**Fig 5** Difference between RE and SE (RE-SE) before anaesthesia induction (Pre-induction), before tracheal intubation (Pre-TI), and after tracheal intubation (Post-TI+10, 20, 30, 40, 50, 60, 120, and 180 s). \* $P < 0.05$  vs pre-TI. # $P < 0.05$  vs remifentanil group. § $P < 0.05$  vs landiolol group.

activity. Therefore, RE-SE reflects EMG activation<sup>8</sup> and this function may be useful for estimating the balance between nociception and antinociception.<sup>9, 11</sup> We previously reported that noxious stimulation (tetanic stimulation) increases RE-SE during sevoflurane anaesthesia without muscle paralysis.<sup>10</sup> In the present study, RE-SE increased significantly after tracheal intubation, and remifentanil, an antinociceptive agent, suppressed this increase. Therefore, an increase in RE-SE may reflect inadequate analgesia during general anaesthesia. Although the frequency band of RE-SE (32–47 Hz) also includes EEG gamma waves, which are associated with consciousness,<sup>19</sup> gamma wave activation may contribute little to the increase in RE-SE after tracheal intubation because another neuromuscular blocker, rocuronium, diminishes the increase in RE-SE after laryngoscopy.<sup>12</sup> Therefore, although it was uncertain whether gamma wave activity was absent after tracheal intubation in the present study, it was suggested that an increase in RE-SE in response to tracheal intubation mainly reflects fEMG activation rather than cortical arousal, such as EEG gamma wave activation.

RE-SE reflects the motor response to noxious stimulation.<sup>20</sup> Facial muscles are more resistant than other skeletal muscles to neuromuscular block,<sup>18, 21, 22</sup> and noxious stimulation increases RE before recovery from paralysis.<sup>9</sup> The dose at which neuromuscular block paralyses the facial muscles, however, can diminish the RE-SE response to noxious stimuli. Thus, the degree of facial muscle paralysis may affect the RE-SE. The increase in RE after laryngoscopy is abolished by the administration of rocuronium ( $0.6 \text{ mg kg}^{-1}$ ).<sup>12</sup> Although vecuronium ( $0.1 \text{ mg kg}^{-1}$ ) was used in the present study, RE-SE increased

**Table 2** Changes in MAP and HR. MAP, mean arterial pressure; HR, heart rate; pre-induction, values before anaesthesia induction; pre-intubation, values before tracheal intubation; post-intubation, values 60, 120, and 180 s after tracheal intubation. Values are mean (SD). \* and \*\* indicate  $P < 0.05$  and  $< 0.01$  vs pre-intubation. † $P < 0.05$  and ‡ $P < 0.01$  vs saline group at the same time point

	Pre-induction	Pre-intubation	Post-intubation		
			60 s	120 s	180 s
MAP (mm Hg)					
Saline	102 (12)	82 (15)	129 (20)**	106 (19)**	96 (17)**
Remifentanyl	100 (12)	65 (8)‡	86 (11)**‡	79 (9)**‡	73 (7)**‡
Landiolol	98 (9)	74 (12)	108 (15)**‡	97 (11)**	86 (10)**
HR (beats min <sup>-1</sup> )					
Saline	73 (12)	66 (11)	83 (13)**	77 (12)**	73 (12)*
Remifentanyl	67 (11)	54 (8)‡	67 (10)**‡	59 (10)**‡	57 (9)‡
Landiolol	75 (15)	63 (6)	72 (9)**‡	69 (8)†	67 (9)

after tracheal intubation in Group S. The degree of facial muscles paralysis is uncertain in the present study because facial muscle activity was not measured using objective neuromuscular monitoring. Nonetheless, neuromuscular blockers may affect the degree of RE–SE, and estimates of nociception using RE–SE should be interpreted carefully in different states of muscle paralysis during general anaesthesia.

We hypothesized that landiolol would suppress the entropy response to tracheal intubation because increased BIS after tracheal intubation was suppressed by landiolol in previous studies.<sup>4,5</sup> There are several reports regarding the antinociceptive effects of  $\beta_1$ -adrenoceptor antagonists. Esmolol significantly decreases the anaesthetic requirements for skin incision during balanced anaesthesia with propofol, nitrous oxide, and morphine.<sup>23</sup> A large dose of esmolol also enhances the decrease in isoflurane minimum alveolar concentration induced by alfentanil.<sup>24</sup> Perioperative administration of esmolol reduces the intraoperative use of fentanyl and the postoperative use of morphine.<sup>25</sup> In rats, systemic administration of esmolol<sup>26</sup> and intrathecal injection of landiolol<sup>27</sup> have antinociceptive effects. In the present study, landiolol and remifentanyl suppressed the increased entropy response to tracheal intubation, supporting the antinociceptive effect of  $\beta_1$ -adrenoceptor antagonists. Patient movement, a clinical sign of inadequate analgesia during or after tracheal intubation, was observed in patients receiving esmolol, whereas in a previous study no movement was observed in the patients receiving remifentanyl.<sup>13</sup> These findings suggest that the antinociceptive effect of  $\beta_1$ -adrenoceptor antagonists is weaker than that of remifentanyl or, because  $\beta_1$ -adrenoceptors are present in various parts of the reticular activating system, the effect-site of  $\beta_1$ -adrenoceptor-mediated antinociception may differ from that of remifentanyl.

As  $\beta_1$ -adrenoceptor antagonists reduce HR and cardiac output and low cardiac output increases the plasma propofol concentration,<sup>28</sup> it is possible that the suppressive effect of landiolol on RE and RE–SE is due to increased concentrations of plasma propofol. It was previously reported that esmolol reduced BIS and increased the suppression ratio during propofol and alfentanil TCI without

increasing serum propofol and alfentanil concentrations.<sup>29</sup> Furthermore, plasma propofol concentration does not increase until cardiac output decreases by approximately 31% in a swine shock model.<sup>30</sup> Therefore, it was suggested that the landiolol-induced decrease in cardiac output only weakly contributed to the suppressive effect of landiolol on RE and RE–SE response to tracheal intubation. Because the plasma propofol concentration was not measured, however, it is unclear whether landiolol increased the propofol concentration and suppressed the RE and RE–SE response to tracheal intubation in the present study.

The present study has some limitations. To avoid awareness during the study period, patients were excluded when the BIS was  $>65$  just before tracheal intubation (3, 4, and 3 patients in Groups S, R, and L, respectively). This may have biased our results because the patients included in this study may have been more sensitive to propofol. No intraoperative awareness or recall was reported, however, and an effect-site propofol concentration of more than  $3 \mu\text{g ml}^{-1}$  would be necessary to minimize the bias in our patients. The number of patients included in the present study was based on the means and standard deviation of the BIS response to intubation described by Oda and colleagues.<sup>5</sup> In the previous study, BIS increased from 39 (5) to 54 (10) after tracheal intubation, which is higher than the increase we observed [from 54 (6) to 58 (6) in Group S], probably because of the difference in anaesthesia (sevoflurane vs propofol). Therefore, it is possible that the lack of a significant increase in BIS in the present study was a result of inadequate sample size in our patients. Furthermore, because RE, SE, and BIS were computed in  $<1$  min (1.92–15.36, 15–60, and 15 s for RE, SE, and BIS, respectively), we recorded data within 1 min after tracheal intubation in addition to every 1 min after tracheal intubation. Significant increases in RE were observed 10, 20, and 30 s after tracheal intubation in the present study. It is also possible, however, that artifacts during tracheal intubation contaminated the data at 10 and 20 s after tracheal intubation. In addition, muscle paralysis was not monitored because electrical stimulation is noxious *per se* and may affect the interpretation of the nociceptive state

after tracheal intubation. Therefore, it is unclear whether the same degree of muscle paralysis was obtained in all patients.

In conclusion, RE increased in response to tracheal intubation, whereas BIS and SE did not. Landiolol and remifentanyl suppressed the increase in RE after tracheal intubation with significant inhibition of RE–SE.

## Funding

This study was funded by Department of Anaesthesia, National Defense Medical College, Tokorozawa, Saitama, Japan.

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