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

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Background. β1-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), remifentanil (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 remifentanil, 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 remifentanil suppressed the increase in RE after tracheal intubation with significant inhibition of RE−SE difference.

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Tracheal intubation during anaesthesia induction is one of the most intensive noxious stimuli and can induce haemodynamic responses and increase the bispectral index (BIS).[1–3] Opioids or β1-adrenoceptor antagonists[4 5] 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.[6 7] 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.[8] 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.[8] Noxious stimulation increases RE, and RE−SE increases after noxious stimulation.[9 10] Furthermore, RE−SE is suggested to be a potential surrogate marker of the adequacy of

antinociception.[11] Tracheal intubation also increases entropy indices during propofol anaesthesia.[12]

Although the mechanism is unknown, β1-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[5] or propofol[2] anaesthesia. Little is known, however, about the effect of β1-adrenoceptor antagonists on the entropy index responses to tracheal intubation.[13] 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 β-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), remifentanil (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 μg ml^{-1}) using a Diprifusor TCI pump (Terumo Corporation, Tokyo, Japan) based on the kinetic set of Marsh and colleagues.[14] Ventilation was controlled to maintain end-tidal CO_2 at 35–40 mm Hg with a fresh gas flow of 6 litre min^{-1} (100% oxygen) via a facemask. Target concentration of propofol was reduced to 3 μg ml^{-1} 90 s after anaesthesia induction. Two minutes after anaesthesia induction, vecuronium bromide (0.1 mg kg^{-1}) was administered and an infusion of remifentanil, landiolol, or saline was initiated. In Group R, remifentanil was infused at a rate of 0.8 μg kg^{-1} min^{-1} for 1 min and then decreased to 0.2 μg kg^{-1} min^{-1}. According to the pharmacokinetic sets published by Minto and colleagues,[15] the infusion rate of remifentanil produced an effect-site concentration of approximately 5 ng ml^{-1} at tracheal intubation, which can suppress the BIS response to tracheal intubation.[16] In Group L, landiolol was infused at a rate of 0.125 mg kg^{-1} min^{-1} for 1 min and then decreased to 0.04 mg kg^{-1} min^{-1}, which can suppress the BIS response to tracheal intubation.[5] 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 CO_2 monitoring were performed with an S/5™ 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™) and an Entropy Sensor™ (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.[5] 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