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Comparison of Remifentanil and Landiolol on Hemodynamic and Plasma Catecholamine Responses to Tracheal Intubation

Kazuyoshi Ishikawa, Kenshu Shirakawa, Masaru Nagao, Shigeki Yamaguchi

Department of Anesthesiology, Dokkyo Medical University School of Medicine

SUMMARY

The purpose of this study is to compare remifentanil with landiolol to examine the effects of hemodynamic and plasma catecholamine responses to tracheal intubation. Sixty patients scheduled for elective surgery were randomly divided into three groups, to receive either normal saline (group C), a 1-minute loading infusion of remifentanil 0.5 μg/kg followed by an infusion of remifentanil 0.25/μg/kg/min during the study (group R), or a 1-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min during the study (group L). After the 1-minute loading infusion of each drug, anesthesia was induced with intravenous injection of propofol 2 mg/kg, and vecuronium 0.1 mg/kg. Five minutes after the administration of each drug, tracheal intubation was performed within 30 seconds. Mean arterial pressure remained below the baseline value after tracheal intubation in group R, but not in groups L and C. Heart rate significantly increased after tracheal intubation in group C, but not in groups R and L. Plasma concentration of adrenaline remained below the baseline value after tracheal intubation in all groups, but it was significantly lower in group R, compared with other groups. Plasma concentration of noradrenaline significantly increased after tracheal intubation in groups L and C, but not in group R. Bispectral index in group R remained lower than that in groups L and C after tracheal intubation. Remifentanil may be preferable to landiolol to provide cardiovascular stability after tracheal intubation.

Key Words : remifentanil, landiolol, tracheal intubation, adrenaline, noradrenaline

INTRODUCTION

Larygoscopy and tracheal intubation increase activity of the sympathetic nervous system and release of catecholamine, resulted in adverse events, such as hypertension, tachycardia, cardiac arrhythmias, and coronary ischemia[1~5]. Many studies have been performed to prevent hyperdynamic responses induced by tracheal intubation. The mechanism by which laryngoscopy and tracheal intubation induce the hemodynamic changes are associated with systemic catecholamine release. Of various classes of drugs, narcotics or β_1-adrenoceptor antagonists have frequently been used to prevent such detrimental events. Since remifentanil has a shorter duration of action and suppresses autonomic and hemodynamic responses to noxious stimulation, it may be suitable to avoid adverse hemodynamic effects induced by tracheal intubation[7~11]. Landiolol, a newer, ultra-short-acting β_1-adrenoceptor antagonist, has recently been used to prevent hemodynamic responses induced by intubation[12~17]. However, little is

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Reprint requests to : Shigeki Yamaguchi, MD, PhD.
Department of Anesthesiology, Dokkyo Medical University School of Medicine, Mibu, Tochigi 321-0293, Japan

Table Demographic data

	saline (n=20)	remifentanil (n=20)	landiolol (n=20)	P
Age (yrs)	55±14	58±11	58± 8	n.s.
Height (cm)	158± 9	161± 9	158±10	n.s.
Weight (kg)	59±11	58± 8	58±11	n.s.
Gender (male/female)	8/12	8/12	9/11	n.s.
Duration of surgery (min)	91±37	92±48	96±41	n.s.
Duration of anesthesia (min)	157±45	151±42	161±40	n.s.

known about the effect of remifentanil versus landiolol on plasma catecholamines release during tracheal intubation.

In the present study, we examined the differential effects of remifentanil and landiolol on hemodynamic and plasma catecholamines responses during tracheal intubation.

MATERIALS AND METHODS

After approval of the ethics committee of Dokkyo Medical University School of Medicine and written, informed consent, 60 ASA physical status 1 or 2 patients aged 20-62 years, within 15% of ideal body weight, who were scheduled to undergo elective surgery under general anesthesia, were studied. Patients with predicted difficulty in tracheal intubation were excluded from the study. No patients were receiving any medication.

A 20-mL syringe containing an equivalent volume of either normal saline, landiolol or remifentanil was prepared in advance by an anesthesiologist not involved in the data collection. Patients were prospectively randomized via sealed envelope assignment, to one of three groups.

No premedication was given. After patient arrival at the operation room, the left radial artery was cannulated to measure systolic and diastolic blood pressure, and plasma adrenaline and noradrenaline levels. Pulse oximetry (Satlite ; Datex-Ohmeda, Madison, WI, USA), capnography (Capnomac ; Datex-Ohmeda) and the bispectral index (BIS ; model A1050, version 3.4, Aspect Medical Systems, USA) were monitored. Sixty patients were divided into three groups of 20 patients each to receive either 1) normal saline (saline group), 2) a 1-minute loading infusion of remifentanil 0.5 μg/kg followed by an infusion of remifentanil 0.25 μg/kg/min during the study (remifentanil group), or 3) a 1-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min using an automated infusion pump during the study (landiolol group). One minute after the start of administration of each drug, anesthesia was induced with intravenous injection of propofol 2 mg/kg. After loss of consciousness, vecuronium 0.1 mg/kg was administered intravenously. After mask ventilation with 100% oxygen, the trachea was intubated 5 minutes after the start of administration of saline, remifentanil, or landiolol. Each intubation was performed by an experienced anesthesiologist, who was blinded to the drug, and was accomplished within 30 seconds. After tracheal intubation, the ventilator was adjusted initially to deliver a tidal volume of 9 mL/kg and respiratory rate of 10 breaths/min. End-tidal carbon dioxide tension ($P_{ET\text{-}CO_2}$) was maintained at 35-40 mm Hg during the study. Anesthesia was maintained with 66% air in oxygen supplemented with sevoflurane 2% . All patients received a continuous infusion of acetate Ringer's solution at a rate of 5 mL/kg/h during the study.

Measurements of mean arterial pressure (MAP), heart rate (HR), and BIS values were performed before anesthesia (baseline), after induction of anesthesia, and one, 5 and 10 minutes after intubation.

Plasma adrenaline and noradrenaline were measured by high-performance liquid chromatography before anesthesia (baseline), after induction of anesthesia, and immediately, 5 and 10 minutes after intubation.

Data are presented as mean±SD. Intergroup differences were analyzed by two-way analysis of variance for the repeated-measures design. When a significant overall effect was detected, Scheffé's test was used for comparison of the mean values for the two variables. Comparison between both groups was made by apply-

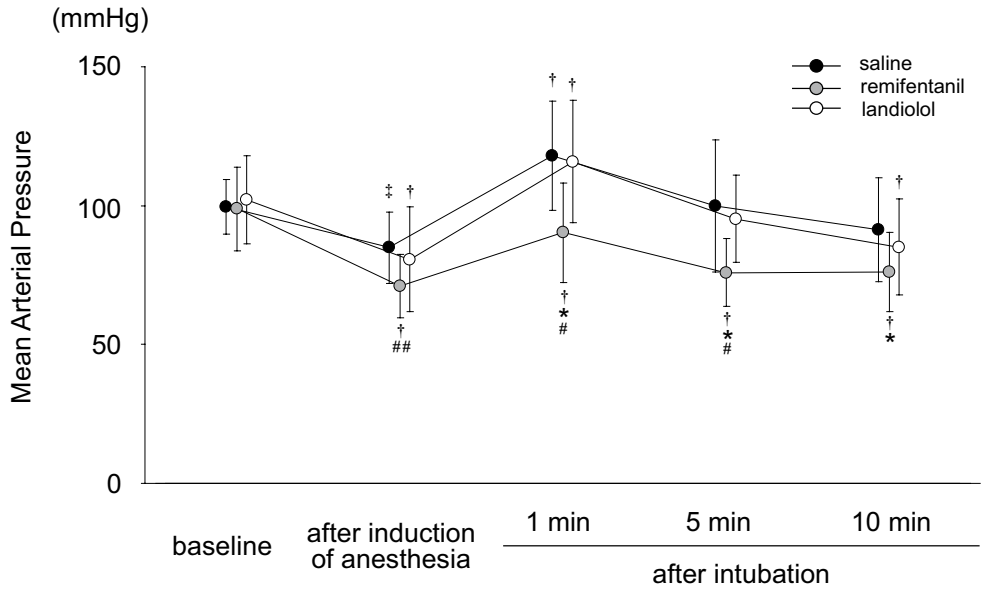

Figure 1 Changes in mean arterial pressure. $^{\dagger}P<0.01$ versus baseline. $^{\ddagger}P<0.05$ versus baseline. $^{*}P<0.01$ versus saline. $^{\#}P<0.01$ versus landiolol. $^{\#\#}P<0.05$ versus landiolol. Values are shown as mean ± SD.

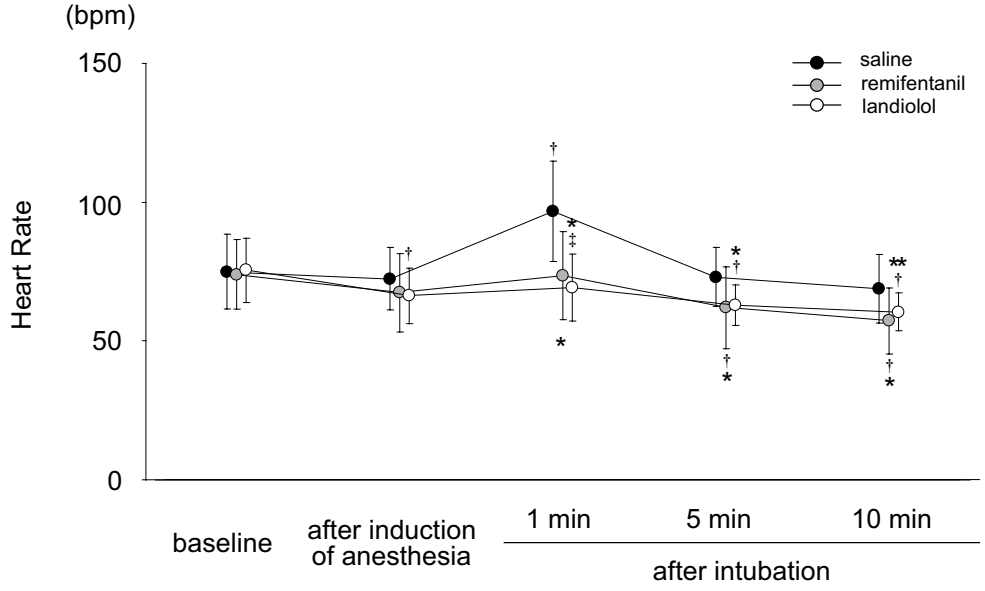

Figure 2 Changes in heart rate. $^{\dagger}P<0.01$ versus baseline. $^{\ddagger}P<0.05$ versus baseline. $^{*}P<0.01$ versus saline. $^{**}P<0.05$ versus saline. Values are shown as mean ± SD.

ing Scheffé's test. The threshold for statistical significance was $P<0.05$.

RESULTS

There were no significant differences in age, gender, body weight, height, and durations of surgery and anesthesia among the three groups (Table 1).

There was no significant difference in MAP at baseline among the three groups (Fig. 1). After induction of anesthesia, MAP decreased significantly compared with the baseline values in all groups. One minute after intubation, MAP increased significantly in the saline and landiolol groups, and those were significantly higher than that of the remifentanil group from one to 5 minutes after tracheal intubation. MAP in the remifentanil group remained lower than the baseline val-

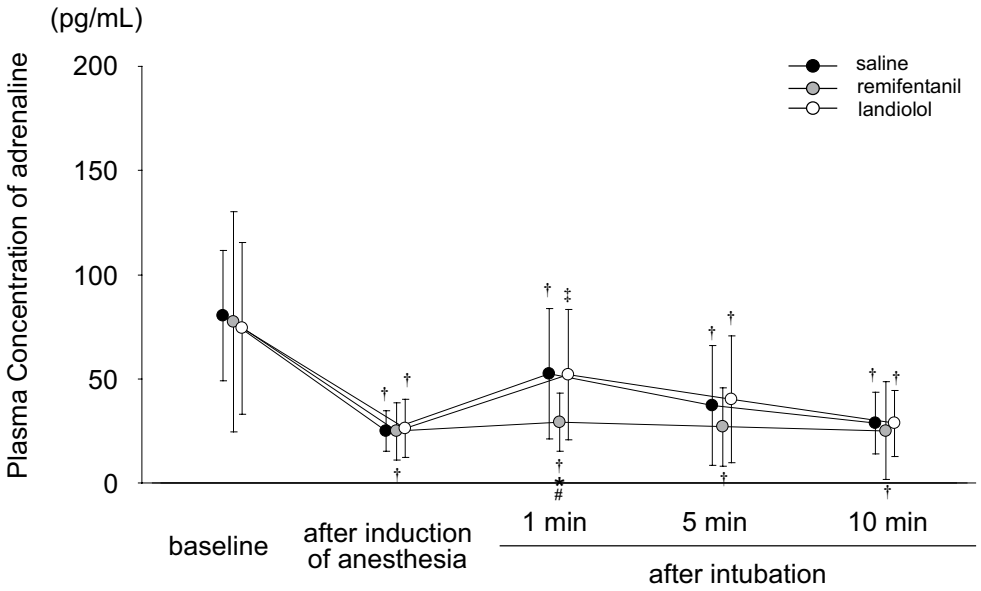

Figure 3 Changes in plasma concentration of adrenaline. $^{\dagger}P<0.01$ versus baseline. $^{\ddagger}P<0.05$ versus baseline. $^{*}P<0.01$ versus saline. $^{\#}P<0.01$ versus landiolol. Values are shown as mean ± SD.

ue during the study.

As shown in Fig. 2, there was no significant difference in HR at baseline among the three groups. One minute after tracheal intubation, HR increased significantly compared with the baseline value in the saline group, and decreased significantly in the landiolol group. HR in the saline group was significantly higher than those of the remifentanil and landiolol groups from one to 10 minutes after tracheal intubation. HR in the remifentanil and landiolol groups remained lower than the baseline values during the study.

No statistically significant difference was observed in plasma concentration of adrenaline at baseline among the three groups (80 ± 31 pg/mL in the saline group ; 77 ± 53 pg/mL in the remifentanil group ; 74 ± 41 pg/mL in the landiolol group) (Fig. 3). Plasma concentration of adrenaline decreased significantly during the study in all groups. One minute after tracheal intubation, adrenaline plasma level in the remifentanil group was significantly lower than those of the saline and landiolol groups (53 ± 31 pg/mL in the saline group ; 29 ± 14 pg/mL in the remifentanil group ; 52 ± 31 pg/mL in the landiolol group).

Changes of plasma concentration of noradrenaline are shown in Fig. 4. Plasma concentrations of noradrenaline increased significantly from one to 5 minutes after tracheal intubation in the saline and landiolol groups compared with the baseline values (baseline, 215 ± 69 pg/mL and 222 ± 65 pg/mL ; with the peak at immediately after tracheal intubation, 333 ± 151 pg/mL and 346 ± 112 pg/mL ; $P<0.01$). However, these of the remifentanil group decreased significantly compared with the baseline value during the study (baseline, 216 ± 92 pg/mL ; with the peak at immediately after tracheal intubation, 160 ± 82 pg/mL ; $P<0.05$), and were significantly lower than those of the saline and landiolol groups from one to 10 minutes after tracheal intubation.

BIS values decreased significantly compared with the baseline values during the study in all groups (Fig. 5). These of the remifentanil group were significantly lower than those of the saline and landiolol groups from one to 10 minutes after tracheal intubation.

$P_{ET}CO_2$ was maintained at 36 and 39 mm Hg during the study in three groups.

There were no severe adverse events, such as cardiovascular event, arrhythmia, hypoxemia, respiratory dysfunction, delayed recovery, anaphylactic reaction and others in all groups.

DISCUSSION

Tracheal intubation is a noxious stimulus which induces adverse hemodynamic responses. Many drugs have been used to attenuate adverse hemodynamic re-

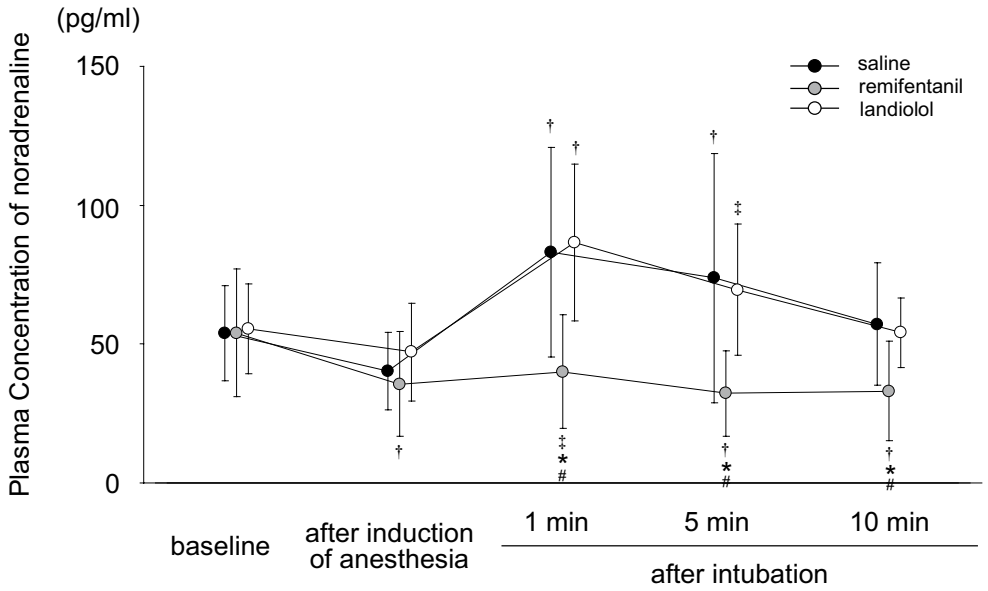

Figure 4 Changes in plasma concentration of noradrenaline. $^{\dagger}P<0.01$ versus baseline. $^{\ddagger}P<0.05$ versus baseline. $^{*}P<0.01$ versus saline. $^{\#}P<0.01$ versus landiolol. Values are shown as mean ± SD.

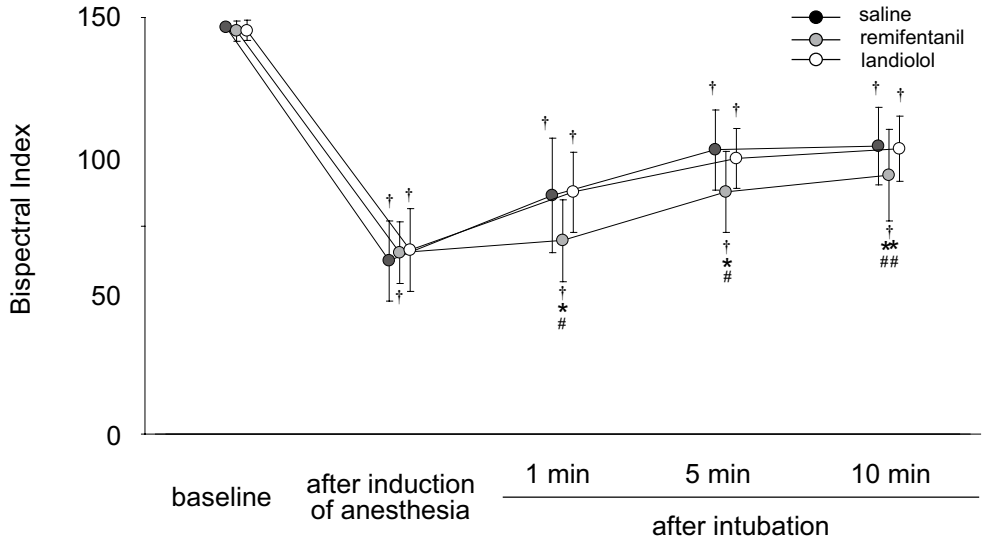

Figure 5 Changes in bispectral index. $^{\dagger}P<0.01$ versus baseline. $^{*}P<0.01$ versus saline. $^{**}P<0.05$ versus saline. $^{\#}P<0.01$ versus landiolol. $^{\#\#}P<0.05$ versus landiolol. Values are shown as mean ± SD.

sponses to laryngoscopy and intubation, but none is ideal[18]. Narcotics, such as fentanyl and remifentanil, have been used to prevent hyperdynamic responses induced by laryngoscopy and tracheal intubation. Remifentanil metabolized by tissue and plasma esterases has a more rapid onset of analgesic action than that of fentanyl which occurs within 1 to 1.5 minutes, and the elimination half-life is 8 to 20 minutes[19]. Its half-life is significantly shorter than that of fentanyl which has a half-life of approximately 3.7 hours. Therefore, remifentanil is preferable to fentanyl during tracheal intubation.

β-adrenoceptor antagonists, such as esmolol and labetalol, are also used to prevent hypertension and tachycardia induced by tracheal intubation because these agents have potent effects when activity of the sympathetic nervous system is increased. Landiolol, a newly developed ultra-short-acting β_1-adrenoceptor

antagonist, has recently been used to avoid adverse hemodynamic responses caused by intubation. Landiolol is rapidly hydrolyzed to an inactive metabolite M-1 by both pseudocholinesterase in the plasma and carboxylesterase in the liver, and excreted in the urine, resulting in an elimination half-life of approximately 3.5 minutes[20]. Its half-life is significantly shorter than that of esmolol which has a half-life of 9.2 minutes[21].

In the present study, we compared remifentanil with landiolol to examine the effects of hemodynamic responses to tracheal intubation. Plasma concentration of adrenaline decreased significantly after induction of anesthesia in all groups. The plasma adrenaline levels in the remifentanil group were unchanged after tracheal intubation, whereas that in the landiolol and saline groups increased after intubation. Although the plasma noradrenaline level increased after tracheal intubation in the landiolol and saline groups, that remained low level after tracheal intubation. No statistically significant differences were observed in plasma adrenaline and noradrenaline levels between the landiolol and saline groups after tracheal intubation. These results suggest that remifentanil is preferable to landiolol to prevent systemic catecholamines releases after tracheal intubation.

Mean arterial pressure in all groups decreased significantly after induction of anesthesia. However, MAP in the landiolol and saline groups increased significantly compared with that of the remifentanil group after intubation, and returned to the baseline value. No statistically significant difference was observed in MAP between the landiolol and saline groups after intubation. Heart rate in the remifentanil and landiolol groups decreased steadily after intubation. From these results, remifentanil suppresses increases in MAP and HR after intubation, whereas landiolol suppresses an increase in HR, not MAP. Increase in MAP after tracheal intubation may contribute to systemic catecholamine releases in the landiolol and saline groups. On the other hand, landiolol may have an only effect to reduce activity of the sympathetic nervous system after systemic catecholamine releases due to tracheal intubation. Our data suggested that remifentanil might be preferable to prevent noxious stimulus of tracheal intubation.

A 1-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min was used in this study because the dosage of landiolol was determined on the basis of its effectiveness in reducing the hemodynamic response to tracheal intubation under sevoflurane anesthesia[22,23]. The dosage of landiolol may affect our results. Further studies need to discuss about the action of landiolol to prevent cardiovascular changes after tracheal inbtubation.

BIS monitoring can currently be considered the accepted standard on depth of anesthesia. In the present study, the BIS values in the three groups decreased significantly after induction of anesthesia and these in the remifentanil group were significantly lower than those of the landiolol and saline groups after tracheal intubation because the antinociceptive effect of remifentanil blunted increases in BIS values after intubation[9,24]. However, previous studies have also shown that β_1-adrenoceptor antagonists blunt hemodynamic response to tracheal intubation and suppress increases of BIS values under propofol anesthesia although the mechanism is not fully elucidated[25,26]. The discrepancy between our results and the previous reports may be explained by the dosage of propofol and the duration from the induction of anesthesia to tracheal intubation. In the present study, anesthesia was induced with intravenous injection of propofol 2 mg/kg. Since propofol has been reported to suppress hemodynamic and plasma catecholamine responses[27~29], the agent affected decreases of MAP, HR and plasma adrenaline and noradrenaline levels after induction of anesthesia. Continuous infusion of propofol was not performed after the bolus injection in this study, but it was performed in the previous studies. Therefore, the total dosage of propofol in this study was less than those of the previous studies. Tracheal intubation was performed 5 minutes after induction of anesthesia in this study, but 7 minutes in the previous study. It is possible that continuous infusion of propofol for 7 minutes exerts an influence on hemodynamic responses during tracheal intubation in the previous studies. Additional studies are necessary to firmly establish whether β_1-adrenoceptor antagonists suppress hemodynamic response without anesthesia.

In conclusion, a 1-minute loading infusion of remifentanil 0.5 μg/kg followed by an infusion of remifentanil

0.25μg/kg/min suppresses hemodynamic and plasma catecholamine responses after tracheal intubation. However, a bolus of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min, which is used in clinical practice, may not suppress plasma catecholamine response during tracheal intubation.

REFERENCES

1) Manger WM, Frohlich ED, Gifford RW, et al : Norepinephrine infusion in normal subjects and patients with essential or renal hypertension : effect on blood pressure, heart rate, and plasma catecholamine concentrations. J Clin Pharmacol **16** : 129-141, 1976.
2) Chobanian AV, Gavras H, Gavras I, et al : Studies on the activity of the sympathetic nervous system in essential hypertension. J Hum Stress **4** : 22-28, 1978.
3) Schutz W, Hortnagl H, Magometschnigg D : Function of the autonomic nervous system in young, untreated hypertensive patients. Int JCardiol **10** : 133-140, 1986.
4) Low JM, Harvey JT, Prys-Roberts C, et al : Studies of anaesthesia in relation to hypertension. Br J Anaesth **58** : 471-477, 1986.
5) Oczenski W, Krenn H, Dahaba AA, et al : Hemodynamic and catecholamine stress responses to insertion of the combitube, laryngeal mask airway or tracheal intubation. Anesth Analg **88** : 1389-1394, 1999.
6) Bouvet L, Stoian A, Rimmelé T, et al : Optimal remifentanil dosage for providing excellent intubating conditions when co-administered with a single standard dose of propofol. Anaesthesia **64** : 719-726, 2009.
7) Yoo KY, Jeong CW, Park BY, et al : Effects of remifentanil on cardiovascular and bispectral index responses to endotracheal intubation in severe pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia. Br J Anaesth **102** : 812-819, 2009.
8) Albertin A, Casati A, Federica L, et al : The effect-site concentration of remifentanil blunting cardiovascular responses to tracheal intubation and skin incision during bispectral index-guided propofol anesthesia. Anesth Analg **101** : 125-130, 2005.
9) Guignard B, Menigaux C, Dupont X, et al : The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg **90** : 161-167, 2000.
10) Park KS, Park SY, Kim JS, et al : Effect of remifentanil on tracheal intubation conditions and haemodynamics in children anaesthetized with sevoflurane and nitrous oxide. Anaesth Intensive Care **37** : 577-583, 2009.
11) Crawford MW, Hayes J, Tan JM : Dose-response of remifentanil for tracheal intubation in infants. Anesth Analg **100** : 1599-1604, 2005.
12) Yamazaki A, Kinoshita H, Shimogai M, et al : Landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure. Can J Anesth **52** : 254-257, 2005.
13) Yoshida Y, Hongo T, Sakamoto A, et al : Successful management of tachycardiac atrial fibrillation in a septic patient with landiolol. Anesth Analg **100** : 294, 2005.
14) Goyagi T, Tanaka M, Nishikawa T : Landiolol attenuates the cardiovascular response to tracheal intubation. J Anesth **19** : 282-286, 2005.
15) Mayahara T, Goto M, Sato M, et al : Conversion of atrial fibrillation to sinus rhythm during landiolol infusion. J Anesth **18** : 304-306, 2004.
16) Ogata J, Yokoyama T, Okamoto T, et al : Managing a tachyarrythmia in a patient with pheochromocytoma with landiolol, a novel ultrashort-acting beta-adrenergic blocker. Anesth Analg **97** : 294-295, 2003.
17) Kaneko M, Yamaguchi S, Hamaguchi S, et al : Effects of landiolol on QT interval and QT dispersion during induction of anesthesia using computerized measurement. J Clin Anesth **21** : 555-561, 2009.
18) Henderson J : Airway management in the adult (chap 50). In : Miller RD, ed. Miller's Anesthesia. 7th ed., Philadelphia, Churchill Livingstone, pp1599, 2005.
19) Gutstein HB, Akil H : Opioid analgesics. (chap 23). In : Hardman JG, Limbird LE, eds. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 10th ed., McGraw-Hill, New York, pp596, 2001.
20) Murakami M, Furuie H, Matsuguma K, et al : Pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra short-acting beta 1-selective blocker, in a dose escalation regimen in healthy male volunteers. Drug Metab Pharmacokinet **20** : 337-344, 2005.
21) Sum CY, Yacobi A, Kartzinel R, et al : Kinetics of esmolol, an ultra-short-acting beta blocker, and of its

major metabolite. Clin Pharmacol Ther **34** : 427–434, 1983.

22) Oda Y, Nishikawa K, Hase I, et al : The short acting β_1–adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. Anesth Analg **100** : 733–737, 2005.

23) Goto K, Shingu C, Miyamoto S, et al : The effect of landiolol on hymodynamics and left ventricular function in patients with coronary artery disease. J Clin Anesth **19** : 523–529, 2007.

24) Dahaba AA, Lischnig U, Kronthaler R, et al : Bispectral-index-guided versus clinically guided remifentanil/propofol analgesia/sedation for interventional radiological procedures : an observer-blinded randomized study. Anesth Analg **103** : 378–384, 2006.

25) Menigaux C, Guignard B, Adam D, et al : Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. Br J Anaesth **89** : 857–862, 2002.

26) Kawaguchi M, Takamatsu I, Masui K, et al : Effect of landiolol on bispectral index and spectral entropy responses to tracheal intubation during propofol anaesthesia. Br J Anaesth **101** : 273–278, 2008.

27) Mustola ST, Baer GA, Toivonen JK, et al : Electroencephalographic burst suppression versus loss of reflexes anesthesia with propofol or thiopental : differences of variance in the catecholamine and cardiovascular response to tracheal intubation. Anesth Analg **97** : 1040–1045, 2003.

28) Mustola ST, Baer GA, Metsä-Ketelä T, et al : Haemodynamic and plasma catecholamine responses during total intravenous anaesthesia for laryngomicroscopy. Thiopentone compared with propofol. Anaesthesia **50** : 108–113, 1995.

29) NG A, Tan SS, Lee HS, et al : Effect of propofol infusion on the endocrine response to cardiac surgery. Anaesth Intensive Care **23** : 543–547, 1995.