Landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure

[Le landiolol diminue la tachycardie en réponse à l'intubation endotrachéale sans affecter la tension artérielle]

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Purpose: Beta-adrenergic receptor antagonists (β -antagonists) have long been used to control perioperative tachyarrhythmias. The effects of a β_1 -antagonist, landiolol, on perioperative hemodynamics are unknown. We aimed to determine the appropriate dosage of landiolol for the treatment of hemodynamic changes in response to endotracheal intubation.

Methods: Sixty-four patients without heart disease or hypertension, were assigned to receive saline (group C) or landiolol (0.1 or 0.3 mg·kg⁻¹; groups L1 and L3). Anesthesia was induced with propofol (2 mg·kg⁻¹ iv) followed by saline or landiolol iv. After ventilation with facemask using 2% sevoflurane in 100% oxygen for 90 sec, endotracheal intubation was performed. After intubation, anesthesia was maintained using 1% sevoflurane in combination with 50% nitrous oxide. Values of heart rate and mean arterial blood pressure were recorded before induction to five minutes after intubation.

Results: In group C, heart rate and mean blood pressure increased simultaneously after tracheal intubation, compared with baseline values. Heart rate values were attenuated immediately before as well as after intubation in group L3, compared with groups C and L1. Heart rate did not increase after tracheal intubation in group L1, compared with baseline. In contrast, mean arterial blood pressure values did not differ among groups.

Conclusions: The newly developed β_1 -antagonist landiolol (0.1 and 0.3 mg·kg⁻¹) may help prevent tachycardia without affecting blood pressure during the induction of anesthesia.

Objectif : Les antagonistes des récepteurs bêta-adrénergiques (β -antagonistes) ont été longtemps utilisés pour contrôler les tachyarythmies périopératoires. Les effets d'un β_1 -antagoniste, le landiolol, sur l'hémodynamique périopératoire sont inconnus. Nous voulions déterminer le dosage approprié de landiolol pour traiter les changements hémodynamiques provoqués par l'intubation endotrachéale.

Méthode : Soixante-quatre patients sans cardiopathie, ni hypertension, ont reçu une solution saline (group C) ou du landiolol (0,1 ou 0,3 mg·kg⁻¹ ; groupes L1 et L3). L'anesthésie a été induite avec du propofol (2 mg·kg⁻¹ iv) suivi de la solution saline ou du landiolol iv. Après ventilation au masque, avec du sévoflurane à 2 % dans de l'oxygène à 100 pendant 90 s, l'intubation endotrachéale a été réalisée. Puis, l'anesthésie a été maintenue avec du sévoflurane à 1 % combiné à du protoxyde d'azote à 50 %. La fréquence cardiaque et la tension artérielle moyenne ont été enregistrées avant l'induction et jusqu'à cinq minutes après l'intubation.

Résultats : Dans le groupe C, la fréquence cardiaque et la tension artérielle moyenne ont augmenté simultanément après l'intubation endotrachéale, par rapport aux valeurs de base. La fréquence cardiaque a baissé immédiatement avant et après l'intubation dans le groupe L3 comparé aux groupes C et L1. La fréquence cardiaque n'a pas augmenté, sur les mesures de base, après l'intubation endotrachéale dans le groupe L1. Les valeurs de la tension artérielle moyenne étaient comparables entre les groupes.

Conclusion : Le nouveau β_1 -antagoniste landiolol (0,1 et 0,3 mg·kg⁻¹) peut aider à prévenir la tachycardie sans affecter la tension artérielle pendant l'induction de l'anesthésie.

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This work was presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, CA, October 11-15, 2003.

Accepted for publication August 17, 2004.

Revision accepted December 10, 2004.

BETA-ADRENERGIC receptor antagonists (β -antagonists) have long been used to decrease the incidence of perioperative tachyarrhythmias. The literature emphasizes the importance of β -adrenergic receptor blockade to prevent perioperative myocardial ischemia in patients with coronary artery disease.¹ It is crucial to avoid tachycardia without reducing blood pressure in these patients because an adequate level of blood pressure is required to maintain coronary perfusion.² However, clinically available β_1 -antagonists, including the short-acting antagonist esmolol, appear insufficient to achieve these objectives since they still have hypotensive effects.³⁻⁵ In this regard, the recently developed, selective short-acting β_1 -antagonist landiolol, which has less effect on blood pressure than esmolol in animal models, may be of interest.^{6,7} However, the effects of this β_1 -antagonist on perioperative hemodynamics remain largely unknown in humans.

The present study aimed to determine the appropriate dosage of landiolol for the prevention of hemodynamic changes in response to endotracheal intubation during the induction of anesthesia.

Materials and methods

The Institutional Investigation Committee of the Japanese Red Cross Society Wakayama Medical Center (Wakayama, Japan) approved this study, and a written informed consent was obtained from each patient enrolled. Patients with a history of cardiovascular disease, diabetes mellitus, disorders known to affect autonomic function, and those taking medications known to affect cardiovascular function were excluded. Sixty-four patients scheduled to undergo general anesthesia for elective non-cardiac surgery were randomly assigned to receive saline (control group; group C-, $n = 22$) or landiolol [0.1 or $0.3 \text{ mg}\cdot\text{kg}^{-1}$; groups L1 ($n = 22$) and L3 ($n = 20$)] in a double-blind fashion.

No premedication was administered. On arrival in the operating room, a 20-gauge *iv* catheter was inserted and acetate Ringer's solution was administered at a rate of $10 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ during the study period. Clinical monitoring included a three-lead electrocardiogram, non-invasive measurement of blood pressure, pulse oximetry and end-tidal carbon dioxide tension. Heart rate was determined as the average of four-second intervals recorded on the electrocardiogram.

General anesthesia was induced with propofol ($2 \text{ mg}\cdot\text{kg}^{-1}$, in 40 sec), and succinylcholine ($1 \text{ mg}\cdot\text{kg}^{-1}$) was administered to facilitate endotracheal intubation. Saline (group C) or landiolol (groups L1 and L3) was then administered intravenously in ten seconds. After

ventilation with a facemask using 2% sevoflurane in 100% oxygen for 90 sec, the trachea was intubated. After intubation, anesthesia was maintained using 1% sevoflurane in combination with 50% nitrous oxide, and vecuronium ($0.1 \text{ mg}\cdot\text{kg}^{-1}$) was administered to allow mechanical ventilation with a constant end-tidal carbon dioxide level ($30\text{--}35 \text{ mmHg}$). Values of heart rate and mean arterial blood pressure were measured at one-minute intervals, before induction, immediately before tracheal intubation and one to five minutes after intubation. When systolic blood pressure decreased to less than 80 mmHg or heart rate to less than $50 \text{ beats}\cdot\text{min}^{-1}$, a rescue medication was to be administered. However, no patient required rescue medication during the study.

Statistical analysis

Data are shown as mean $\pm$ SD. Statistical analysis was performed using repeated measures analysis of variance, followed by Fisher's PLSD test as post-hoc analysis. Differences were considered statistically significant when $P < 0.05$.

Results

There were no differences between groups for age, weight, height, and the duration of tracheal intubation, defined as the time from the insertion of the laryngoscope to inflation of the cuff and securing the endotracheal tube (Table).

In group C, heart rate and mean blood pressure increased simultaneously after tracheal intubation, compared with baseline values (Figure). Heart rate values were significantly attenuated immediately before as well as after intubation in group L3, compared with groups C and L1. Heart rate did not increase after tracheal intubation in group L1, compared with baseline (Figure). In contrast, mean arterial blood pressure values did not differ among groups during the study period. Mean arterial blood pressure increased similarly after tracheal intubation (Figure).

Prolonged bradycardia as well as hypotension were not observed in any patient.

TABLE Patient characteristics

	C group	L1 group	L3 group
Age (yr)	50.5 ± 16.4	49.0 ± 16.4	47.4 ± 14.5
Height (cm)	158 ± 7.1	159.5 ± 9.6	161 ± 8.6
Weight (kg)	55.8 ± 10.6	61 ± 12.7	58.4 ± 13.1
Duration of tracheal intubation (sec)	14.9 ± 4.8	14.2 ± 3.8	14.4 ± 4.2

Mean $\pm$ SD.

FIGURE Changes in heart rate (left) and mean arterial blood pressure (right) before anesthetic induction (Base), immediately before endotracheal intubation (Pre), and after intubation (one to five minutes). Statistically significant differences: *between groups C and L3, #between L1 and L3, and \$between base and after intubation.

Discussion

In patients with no known coronary risk factor or heart disease, landiolol (0.1 and 0.3 mg·kg⁻¹ *iv*) administered immediately after the induction of anesthesia completely inhibited tachycardia without producing hypotension or bradycardia after endotracheal intubation. Considering its short half-life of four minutes, the bolus administration of landiolol appears to be the best choice of β_1 -antagonist to prevent increases in heart rate after tracheal intubation without affecting blood pressure, at least in the group of patients we studied.⁶ Indeed, a recent case study has reported that approximately 0.1 mg·kg⁻¹ *iv* landiolol is effective to treat tachycardia in a patient with pheochromocytoma, indicating that the doses we used may have relevance to treat tachycardia induced by the release of catecholamines.⁸ Although induction of anesthesia with propofol reportedly impairs sympathetic response, resulting in hypotension and bradycardia,⁹⁻¹¹ our results suggest that the use of landiolol in combination with propofol does not result in hemodynamic instability, at least in healthy subjects. It is important to note that unlike the short-acting β_1 -antagonist esmolol which has a half-life of six minutes, landiolol within the dosage used in our study, does not affect blood pressure.⁶ A previous animal study documented that landiolol is a less potent negative inotropic agent than esmolol at equipotent chronotropic

doses, suggesting the lesser effect of landiolol on blood pressure.⁷ This property of landiolol may be beneficial to control heart rate in compromised patients with severe coronary artery or valvular heart disease.^{1,2,5} However, future clinical studies in patients with heart disease are warranted to support the beneficial effects of landiolol on hemodynamics.

In summary, we demonstrated that the newly developed β_1 -antagonist landiolol (0.1 and 0.3 mg·kg⁻¹) inhibited the increases in heart rate after tracheal intubation during the induction of anesthesia without decreasing blood pressure. Landiolol may help prevent tachycardia in compromised patients with heart disease.

References

- 1 Biccard BM. Peri-operative β -blockade and haemodynamic optimisation in patients with coronary artery disease and decreasing exercise capacity presenting for major noncardiac surgery. *Anaesthesia* 2004; 59: 60-8.
- 2 London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative β -adrenergic receptor blockade. Physiologic foundations and clinical controversies. *Anesthesiology* 2004; 100: 170-5.
- 3 Tan PH, Yang LC, Shib HC, Lin CR, Lan KC, Chen CS. Combined use of esmolol and nicardipine to blunt the haemodynamic changes following laryngoscopy and tracheal intubation. *Anaesthesia* 2002; 57: 1195-212.

- 4 Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br J Anaesth* 2002; 89: 857–62.
- 5 Deegan R, Wood AJ. β -Receptor antagonism does not fully explain esmolol-induced hypotension. *Clin Pharmacol Ther* 1994; 56: 223–8.
- 6 Muraki K, Nakagawa H, Nagano N, *et al.* Effects of ONO-1101, a novel beta-antagonist, on action potential and membrane currents in cardiac muscle. *J Pharmacol Exp Ther* 1996; 278: 555–63.
- 7 Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting β -blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anesth* 2001; 48: 985–9.
- 8 Nishina K, Mikawa K, Yonemoto Y, Sugimoto Y. The efficacy of bolus administration of landiolol for attenuating tachycardia in pheochromocytoma (Letter). *Anesth Analg* 2004; 98: 876–8.
- 9 Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *Br J Anaesth* 1988; 60: 3–9.
- 10 Sellgren J, Ejnell H, Elam M, Ponten J, Wallin BG. Sympathetic muscle nerve activity, peripheral blood flows, and baroreceptor reflexes in humans during propofol anesthesia and surgery. *Anesthesiology* 1994; 80: 534–44.
- 11 Horiguchi T, Nishikawa T. Heart rate response to intravenous atropine during propofol anesthesia. *Anesth Analg* 2002; 95: 389–92.