

Beta-1 selective adrenergic antagonist landiolol and esmolol can be safely used in patients with airway hyperreactivity

Michiaki Yamakage, MD, PhD, Sohshi Iwasaki, MD, Seong-Wook Jeong, MD, PhD, Jun-Ichi Satoh, MD, and Akiyoshi Namiki, MD, PhD

This study was undertaken to clarify the effects of esmolol and landiolol, beta-1 selective adrenergic antagonists, on hyperreactive airways in both ovalbumin-sensitized guinea pigs and asthmatic patients. In the animal study, asthma was induced by ovalbumin. After control acetylcholine responses for total pulmonary resistance (Raw) and dynamic lung compliance (Cdyn) were obtained, the animals received propranolol, esmolol, or landiolol, and the same protocol was again performed. Sixty inpatients with coronary risk factors and asthma were enrolled in the human study. Under propofol anesthesia, the patients received saline, esmolol, or landiolol. To assess intubation-induced bronchoconstriction, the presence of wheezing was determined. The dose-response curves of Raw and Cdyn to acetylcholine were significantly elevated and declined in the ovalbumin-sensitized model compared with those in the control group. Neither esmolol nor landiolol had any effect on the acetylcholine-induced response curve in these sensitized animals. However, propranolol significantly enhanced Raw and reduced Cdyn in this model. Tracheal intubation increased the incidence of wheezing in asthmatic patients. However, there was no significant difference in the incidence of wheezing among these groups. The ultra-short-acting beta-1 selective adrenergic antagonists esmolol and landiolol can be safely used perioperatively in patients with airway hyperreactivity. (Heart Lung® 2009;38:48–55.)

Beta-blocker therapy has established benefits in the management of hypertension, acute myocardial infarction, and chronic heart failure.¹⁻³ Beta-adrenergic antagonists, such as propranolol, are therefore used to control tachyarrhythmias and hypertension perioperatively and in intensive care units. However, conventional beta-blockers are contraindicated in patients with airway hyperreactivity, such as patients with asthma and/or chronic ob-

structive pulmonary disease (COPD), because of its concomitant beta-2 blocking effect, which causes bronchoconstriction.⁴⁻¹¹ On the other hand, it was recently reported that cardioselective beta-blockers could be safely used for patients with airway hyperreactivity with concomitant heart failure or history of myocardial infarction.¹²⁻¹⁴ The ultra-short-acting beta-1 selective adrenergic antagonist esmolol is now widely used to control tachycardia/tachyarrhythmia perioperatively,¹⁵ and it has been established that this agent, because of its short duration of action and relative lack of effect on airway resistance, might be preferred over propranolol in awake patients with asthma¹⁶ and COPD¹⁷ who require treatment with an intravenous (IV) beta-blocking agent. Recently, the novel ultra-short-acting beta-1 selective adrenergic antagonist landiolol has also become available for control of tachycardia/tachyarrhythmia perioperatively¹⁸; however, the safety of this agent has not yet been confirmed in patients with airway hyperreactivity perioperatively.

From the Department of Anesthesiology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan.

Supported by a grant-in-aid (No. 15591648, 2003~2005) for research from the Ministry of Education, Science and Culture, Tokyo, Japan, and an incentive grant (No. B-15, 2003) for research from the Japan Medical Association, Tokyo, Japan.

Corresponding author: Michiaki Yamakage, MD, PhD, Department of Anesthesiology, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan.

0147-9563/\$ – see front matter
Copyright © 2009 by Mosby, Inc.
doi:10.1016/j.hrtlng.2008.01.002

Therefore, the present study was undertaken to clarify the *in vivo* effects of the ultra-short-acting and beta-1 selective adrenergic antagonist landiolol, as well as esmolol, on hyperreactive airway both in an ovalbumin-sensitized guinea pig model and in asthmatic patients with coronary risk factors who were scheduled for elective surgery.

MATERIALS AND METHODS

In vivo effects of esmolol and landiolol on total pulmonary resistance and lung dynamic compliance in ovalbumin-sensitized guinea pigs

The experimental protocol was approved by the Animal Care and Use Committee of our institution. The care and handling of the animals were in accord with National Institutes of Health guidelines (Department of Health and Human Services Publication No. 85-23, 1985). Young, male, pathogen-free Hartley guinea pigs (initial weight, approximately 350 g; $n = 48$) were randomly divided into two groups: a control group ($n = 24$) and an asthmatic group ($n = 24$). An experimental model of asthma was established by using the white-of-egg albumin ovalbumin (Ova) as an antigen.¹⁹⁻²¹ Briefly, the asthmatic group received Ova (1 mg/2 mL saline) intraperitoneally, and after 2 weeks the Ova sensitization was boosted by exposure to aerosolized Ova (10 mg, 1 mL saline) for 10 minutes. The control group received the same volume of sterilized .9% saline instead of Ova.

One day after the exposure to aerosol of Ova or saline for 10 minutes, guinea pigs were anesthetized with an intraperitoneal administration of urethane (1.5 g/kg), and supplemental doses of the anesthetic were administered whenever necessary to maintain abolition of corneal and withdrawal reflexes. The trachea was cannulated with a tracheal tube (5-cm length of polyethylene tubing; PE-240) just below the larynx via a tracheotomy. The animals were placed in the supine position and were ventilated with a respirator (Harvard model 683; South Natick, Mass) at a constant rate of 45 breaths/min and a tidal volume of approximately 6 to 8 mL/kg; the latter was adjusted in each animal to maintain the end-tidal CO_2 concentration (5250 RGM; Datex-Ohmeda Japan, Tokyo, Japan) at approximately 40 mm Hg. The right jugular vein and right carotid artery were cannulated for IV injections and arterial blood pressure/heart rate (HR) measurements, respectively. The intrapleural pressure was measured through a water-filled cannula (PE-240) that was placed in the lower third of the esophagus and

connected to one port of the differential pressure transducer. The transpulmonary pressure was determined by monitoring the difference between pressure in the external end of the tracheal cannula and the esophageal cannula using a Satham differential transducer (DP-45; Validyne Engineering, Northridge, Calif). A Fleisch pneumotachograph and a differential transducer were used to monitor respiratory flow rate (PULMOS-II system; M.I.P.S. Co, Osaka, Japan).²² All signals were recorded, and total pulmonary resistance (R_{aw}) and dynamic lung compliance (C_{dyn}) were analyzed continuously by an on-line computer on a breath-by-breath basis. A heating pad was placed under each animal, and the rectal temperature was kept at approximately 37°C during the study period.

To verify airway hyperresponsiveness, dose-response curves of R_{aw} and C_{dyn} to bolus IV injections (.2 mL vol) of acetylcholine (ACh) (1.0 to 6.0 $\mu\text{g/kg}$) were determined in each animal by successively increasing the concentration of ACh solution at 5-minute intervals. Injectants were flushed with .05 mL .9% saline (the dead space of the tubing was .02 mL). After the control ACh response for R_{aw}/C_{dyn} was obtained, each group was divided into three groups: a propranolol group, an esmolol group, and a landiolol group ($n = 8$ each). Each group received each beta-blocker at clinically relevant doses (.1 mg/kg bolus in the propranolol group, .15 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the esmolol group, and .04 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the landiolol group). At 15 minutes after the infusion of beta-blockers, the same protocol of ACh administration was again performed, and peak R_{aw} and C_{dyn} were also measured.

In vivo effects of esmolol and landiolol on wheezing in asthmatic patients during induction of anesthesia

This clinical study was approved by our institutional Ethics Committee on Human Research, and informed consent was obtained from each patient. We enrolled 60 in-patients in this randomized, double-blind, prospective study (age 59.8 ± 10.1 years [mean $\pm$ standard deviation]; 21 women and 39 men) who were scheduled to undergo elective surgery and had coronary risk factors (at least two of the following factors: ≥ 65 years of age, hypertension, history of smoking, serum cholesterol level ≥ 240 mg/dL, and diabetes mellitus).²³ Patients who had sinus bradycardia (<50 beats/min), atrioventricular block (degree II or III), and/or sick sinus syndrome were excluded from the study. All pa-

Table I

Demographic data

Variables	Control group (n = 20)	Esmolol group (n = 20)	Landiolol group (n = 20)
Gender (female/male)	8/12	6/14	7/13
Age (y)	59 ± 10	58 ± 9	61 ± 8
Weight (kg)	59 ± 10	60 ± 10	57 ± 9
Height (cm)	161 ± 12	162 ± 10	158 ± 9
Medications for asthma (n)	Xanthine derivatives (12) Steroid inhalation (8) Leukotriene antagonist (15) Beta-stimulant inhalation (8)	Xanthine derivatives (15) Steroid inhalation (7) Leukotriene antagonist (16) Beta-stimulant inhalation (5)	Xanthine derivatives (11) Steroid inhalation (10) Leukotriene antagonist (14) Beta-stimulant inhalation (6)

Each value is the mean ± standard deviation of 20 patients.
No statistical differences were found among the three groups.

tients enrolled in this study had already been diagnosed with asthma (apparent wheezing and an airway resistance > 180% of that predicted and a forced expiratory volume in 1 second of less than 70% of that predicted during asthmatic attack), and they showed reversible airway obstruction during preoperative investigations (improvement of FEV_{1,0} > 200 mL and %FEV_{1,0} > 12% by inhalation of beta-stimulants). The contents of medication for asthma depended on the physicians (Table I), but there was no significant difference in the type of medication.

The patients were randomly divided into three groups by use of an envelop technique: a control group, an esmolol group, and a landiolol group (n = 20 each). A propranolol group was not provided because of the detrimental results of an animal study and for ethical reasons. No premedication was given, and studies began at approximately 8:15 A.M. An IV catheter was inserted into a vein in the arm, and acetated Ringer's solution was infused at approximately 5 mL · kg⁻¹ · h⁻¹. Under routine monitoring and after preoxygenation, IV anesthetic propofol (2 mg/kg) was injected and then infused at 8 mg · kg⁻¹ · h⁻¹ continuously. After loss of consciousness, the patient's breathing was assisted with 100% oxygen, and vecuronium (.15 mg/kg) was injected. The patient then received either a bolus of esmolol (1 mg/kg) followed by continuous infusion at .25 mg · kg⁻¹ · min⁻¹ (esmolol group) or a bolus of landiolol (.125 mg/kg) followed by infusion at .04 mg · kg⁻¹ · min⁻¹ (landiolol group).²⁴ Normal saline

(5 mL) was injected in a control group instead of beta-blockers. At 3 minutes after vecuronium injection, the trachea was intubated. Infusion of propofol and beta-blocker was discontinued thereafter, and the anesthesia was maintained with 1% sevoflurane and 66% nitrous oxide. When ST changes were observed in an electrocardiograph monitor or the rate pressure product (systolic blood pressure × HR) was more than 16,000, the study was discontinued and appropriate medication for ischemic heart (ie, nitroglycerin and/or esmolol infusion) was started.

To assess bronchoconstriction in response to intubation, auscultation was always performed on either side of the chest at the fourth intercostal space in the midaxillary line, the fifth intercostal space in the midclavicular line, and the second intercostal space in the parasternal line before intubation and anesthesia and at 5 minutes after intubation.²⁵ The presence of wheezing was determined by a simple *yes* or *no* score by an anesthesiologist not involved in this study and blinded to the protocol. All patients were mechanically ventilated 10 times/min with a tidal volume of 10 mL/kg and an inspiratory flow of 40 L/min. Wheezing was defined as high-pitched expiratory rhonchi²⁶ that were audible in at least three of six auscultation sites.

Materials

The following drugs and chemicals were used in the animal study: ovalbumin, NaCl, propranolol hy-

drochloride, urethane (Sigma Chemical, St Louis, Mo), esmolol hydrochloride (Maruishi Pharmaceutical Co, Osaka, Japan), and landiolol hydrochloride (ONO Pharmaceutical Co, Osaka, Japan). In the subsequent clinical study, commercially available esmolol (Brevibloc; Maruishi Pharmaceutical Co) and landiolol (Onoact; ONO Pharmaceutical Co) were used.

Statistical analysis

Data are expressed as means $\pm$ standard deviation. Concentration or dose required to increase R_{aw} by 100% (ED_{200}) was calculated by linear interpolation. Changes in R_{aw} and C_{dyn} in the same groups and difference between groups with regard to wheezing after tracheal intubation were analyzed by one-way and two-way repeated-measurement analyses of variance followed by post hoc Fisher exact test. Differences between groups in R_{aw} and C_{dyn} were analyzed by the unpaired two-tailed t -test. In all comparisons, P less than .05 was considered significant.

RESULTS

In vivo effects of esmolol and landiolol on total pulmonary resistance and lung dynamic compliance in ovalbumin-sensitized guinea pigs

After sensitization by Ova, the average weight of the animals was 485 ± 14 g ($n = 24$), which was not significantly different from that of the control animals exposed to saline (492 ± 21 g; $n = 24$). In the nonsensitized animals under urethane anesthesia, mean arterial pressure (MAP) and HR were comparable in the beta-blocker groups. In the Ova-sensitized animals, MAP was slightly but significantly lower (by 6%) in the propranolol group than in the other two groups, but HRs in the groups were comparable (data not shown).

The effects of ACh and beta-blockers on changes in R_{aw} and C_{dyn} in the control nonsensitized groups are shown in Fig 1. ACh significantly increased R_{aw} and decreased C_{dyn} in a dose-dependent manner. In this nonsensitized model, neither esmolol nor landiolol had any effect on the ACh-induced changes in these parameters. Propranolol seemed to have a slight but not significant effect on these parameters. Fig 2 shows the effects of ACh and beta-blockers on changes in R_{aw} and C_{dyn} in the Ova-sensitized groups. There was no significant difference in the average baseline R_{aw} or C_{dyn} between the control and Ova-sensitized animals, but the

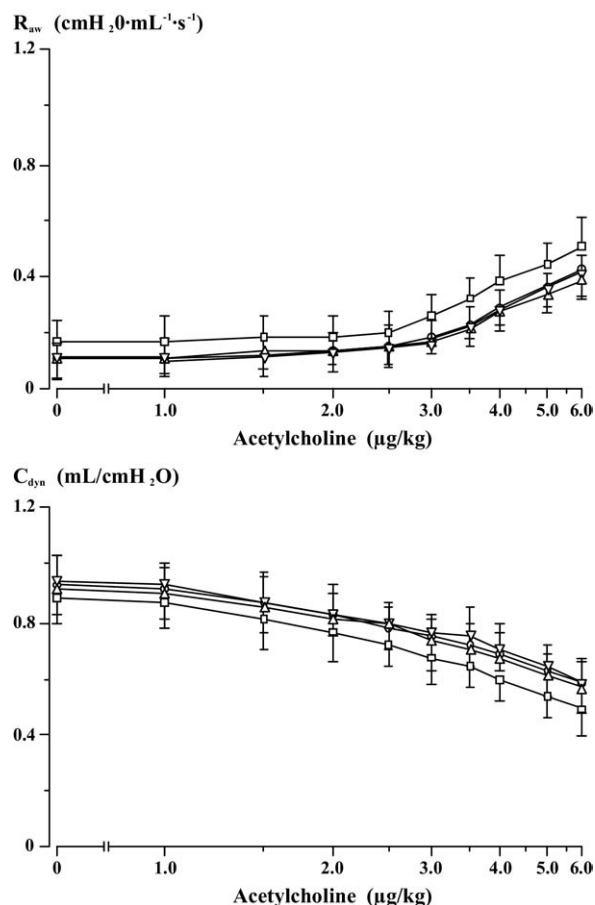


Fig 1 Dose responses of total pulmonary resistance (R_{aw}) and dynamic lung compliance (C_{dyn}) to IV injections of ACh in control nonsensitized guinea pigs. Peak response to each dose of ACh in each animal was averaged over three consecutive breaths that occurred within 10 breaths after the injection. ACh responses without any beta-blockers tested (open circles); ACh responses with esmolol (open upright triangles); ACh responses with landiolol (open inverted triangles), ACh responses with propranolol (open squares). Data are means $\pm$ standard deviation of eight guinea pigs in each group.

dose-response curves of R_{aw} and C_{dyn} to ACh were significantly elevated and declined in the latter, verifying the presence of nonspecific airway hyperresponsiveness in the Ova-sensitized group.²⁷ Ova sensitization significantly decreased ED_{200} of R_{aw} from $3.6 \pm .3$ $\mu\text{g/kg}$ to $2.3 \pm .4$ $\mu\text{g/kg}$ ($P < .05$). Similar to the data obtained in control nonsensitized animals, neither esmolol nor landiolol had any effect on the ACh-induced response curve in the sensitized animals. In contrast with these data, propranolol significantly enhanced R_{aw} and reduced C_{dyn} in the range of ACh tested.

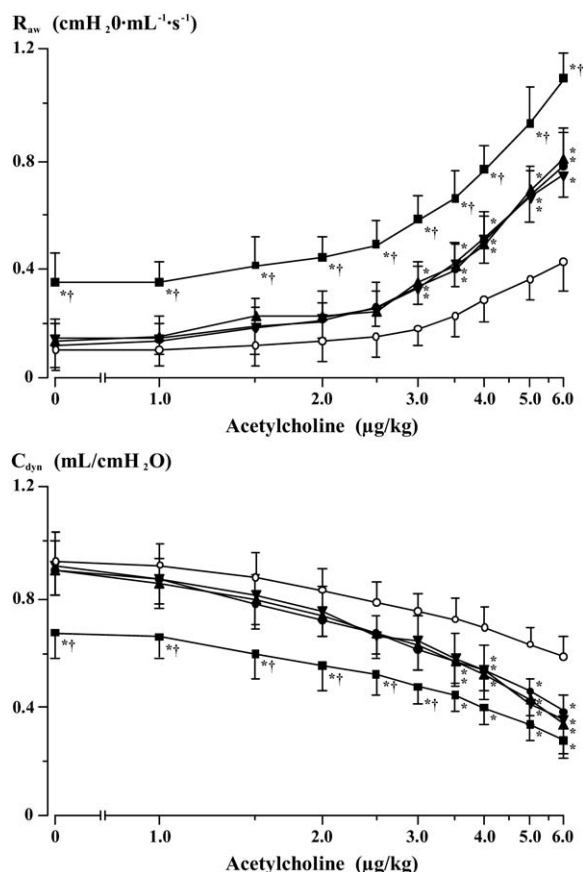


Fig 2 Dose responses of total pulmonary resistance (R_{aw}) and dynamic lung compliance (C_{dyn}) to IV injections of ACh in Ova-sensitized guinea pigs. ACh responses without any beta-blockers tested (closed circles); ACh responses with esmolol (closed upright triangles); ACh responses with landiolol (closed inverted triangles); ACh responses with propranolol (closed squares). Open circles represent ACh responses in control nonsensitized animals without any beta-blockers as reference. Data are means $\pm$ standard deviation of eight guinea pigs in each group. *+Significant differences comparing corresponding data between the control and Ova-sensitized groups and between the Ova-sensitized group with and without beta-blockers.

In vivo effects of esmolol and landiolol on wheezing in asthmatic patients during induction of anesthesia

All patients completed the study without any cardiac complications, and demographic characteristics (age, height, weight, gender, and American Society of Anesthesiologists physical status) were comparable between groups (Table I). In all groups, MAP decreased significantly just before the tracheal intubation and increased significantly after tracheal

intubation compared with the baseline. However, there were no differences in overall changes in MAP among the three groups (Table II). HR was not different at baseline between the groups. In the control group, HR was significantly increased by tracheal intubation and subsequently returned to the baseline. In comparison with the changes in HR in the control group, increases in HR in the esmolol and landiolol groups were inhibited significantly by the infusion of beta-blockers. Although HR increased significantly during tracheal intubation in these beta-blocker groups, it was comparable to baseline and was significantly less than that in the control group at 1 to 5 minutes after intubation.

We examined the incidence of wheezing in patients receiving these beta-blockers before and during tracheal intubation. No patient in any group experienced wheezing before intubation. As shown in Fig 3, tracheal intubation per se increased the incidence of wheezing in the enrolled subjects with asthma. However, there was no significant difference in the incidence of wheezing among these groups, indicating that the beta-1 selective adrenergic antagonists esmolol and landiolol have no adverse effect on hyperreactive airway during induction of anesthesia.

DISCUSSION

In vivo effects of esmolol and landiolol on total pulmonary resistance and lung dynamic compliance in ovalbumin-sensitized guinea pigs

In the former study, we first succeeded in making an Ova-induced hyperreactive airway model in guinea pigs. As shown in Figs 1 and 2, Ova sensitization significantly shifted the ACh-response curve of R_{aw} to the left, and ED_{200} was significantly decreased. In some previous studies, more complicated techniques were used to make asthmatic models to observe late airway response to Ova, as well as immediate airway response.^{28,29} However, our model seems to be adequate for perioperative bronchoconstriction because of the significant sensitization to IV ACh in this study.³⁰

We found that neither esmolol nor landiolol had an effect on the ACh-induced response curve in the control group or Ova-sensitized group. Previous studies revealed by using guinea pig atrial muscles (beta-1) and tracheal smooth muscles (beta-2) that selectivities for the beta-1 receptor of esmolol and landiolol were 137-fold and 302-fold higher, respec-

Table II

Changes in mean arterial blood pressure and heart rate

	Baseline	Before intubation	After intubation		
			1 min	3 min	5 min
Control (n = 20)					
MAP (mm Hg)	92 ± 10	70 ± 12*	145 ± 29*†	101 ± 16†	86 ± 16†
HR (bpm)	79 ± 15	76 ± 9	114 ± 15*†	97 ± 13*†	84 ± 14
Esmolol (n = 20)					
MAP (mm Hg)	97 ± 12	70 ± 13*	130 ± 25*†	96 ± 14†	90 ± 11
HR (bpm)	81 ± 14	65 ± 15*	88 ± 14*†‡	82 ± 12†‡	70 ± 9†‡
Landiolol (n = 20)					
MAP (mm Hg)	95 ± 12	68 ± 12*	140 ± 23*†	94 ± 11†	92 ± 10
HR (bpm)	82 ± 12	64 ± 14*	86 ± 13*†‡	76 ± 16†‡	71 ± 12†‡

MAP, Mean arterial pressure; HR, heart rate.

Each value is the mean ± standard deviation of 20 experiments.

*†‡P < .05 compared with baseline within the study group, with the value before intubation within the study group, and with the value at the same time point in the control group, respectively.

tively, than those of propranolol.^{31,32} Thus, the high beta-1 selectivity of these agents is considered to have a safe effect on adverse bronchoconstriction.

Propranolol, which has beta-2 and beta-1–blocking effects, showed a bronchoconstrictive effect in the Ova-sensitized animal model, although it had little effect on the ACh-induced response curve of R_{aw} in the control group. The reason for this is not known at present; however, the beta-2 adrenoceptor in airway smooth muscles could have been modified as well as the ACh receptor in this asthmatic model.^{33,34} On the basis of the apparent safety of esmolol and landiolol in the animal study, we next chose to assess their safety in human patients with hyperreactive airways.

In vivo effects of esmolol and landiolol on wheezing in asthmatic patients during induction of anesthesia

To verify that these novel beta-1 selective adrenoceptor antagonists can be safely used in humans with airway hyperreactivity, we tested these agents except for propranolol in asthmatic patients who had coronary risks. Because tracheal intubation per se is a major cause of bronchoconstriction perioperatively^{25,35} and sevoflurane has a strong bronchodilatory effect,³⁶ we observed bronchoconstriction by recognizing auscultatory wheezing during tracheal intubation with propofol anes-

thesia. Doses of the beta-blockers used in this study seem to be rather high,³⁷⁻³⁹ but these concentrations were selected by referring to previous reports on prevention of tracheal intubation-induced tachyarrhythmias.^{24,40-42}

The results of this study revealed that neither esmolol nor landiolol had a significant effect on the incidence of tracheal intubation-induced bronchoconstriction, and that the infusion of these beta-blockers during induction of anesthesia was beneficial for surgical patients with coronary risks by suppression of intubation-induced tachyarrhythmias. Sheppard et al¹⁶ and Gold et al¹⁷ demonstrated that esmolol had little effect on respiratory function in awake patients by measuring specific airway resistance and forced expiratory volume in 1 second/peak flow in awake patients with asthma and COPD, respectively, a finding that is consistent with the results of our study. In patients with bronchial hyperreactivity, airway instrumentation by tracheal intubation may evoke life-threatening bronchospasm and perioperative complications, resulting in the requirement of prolonged intensive care treatment.⁴³⁻⁴⁵ In particular, patients with active signs of obstructive airway disease are at a higher risk for perioperative complications.⁴⁵ Therefore, the use of drugs or anesthetics that have adverse effects on hyperreactive airway should be avoided, and the beta-1 selective adrenergic antagonists esmolol and landiolol can be safely used for these patients.

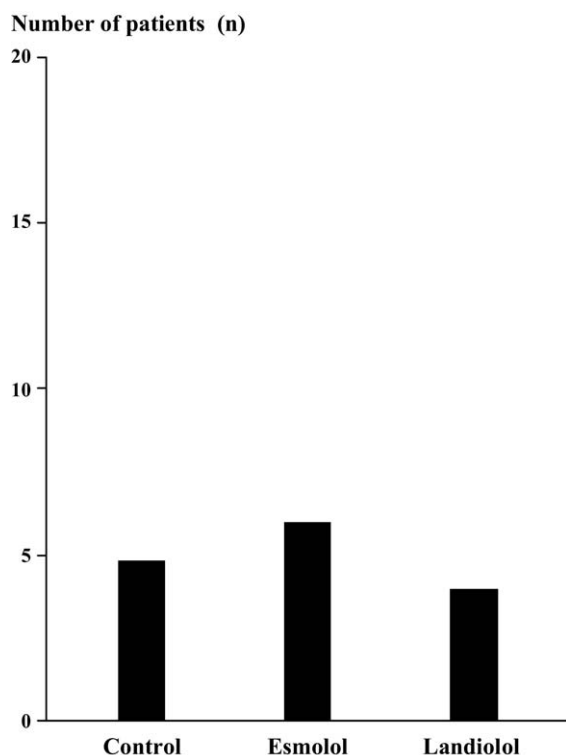


Fig 3 Incidence of airway obstruction (wheezing) in patients after intubation when pretreated with saline, esmolol, or landiolol. Tracheal intubation per se increased the incidence of airway obstruction; however, neither esmolol nor landiolol had any effect on the incidence.

Fernandez-Galinski et al⁴² reported that tracheal intubation-induced hemodynamic changes could be suppressed by the concomitant use of alfentanil, esmolol, or clonidine, and they found that esmolol was the best to control hemodynamic change during the induction of anesthesia. Opioids and α -2 agonists can also be used to suppress the changes in hemodynamics during induction of anesthesia. Opioids such as fentanyl, however, have a bronchoconstrictive effect, and the anesthetics are sometimes used for experimental asthma.⁴⁶ Although the α -2 agonist clonidine had little effect on intubation-induced change in hemodynamics in their study (Table II), it has been reported that the α -2 agonists clonidine and dexmedetomidine had some beneficial effect on airway contractility in animals.^{47,48} Further studies are needed to clarify in detail the effects of α -2 agonists on a hyperreactive airway model.⁴⁹

CONCLUSIONS

The results of the present animal and human studies revealed that the ultra-short-acting beta-1

selective adrenergic antagonists esmolol and landiolol, instead of propranolol, can be safely used perioperatively and in intensive care units in patients with airway hyperreactivity.

REFERENCES

1. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295-302.
2. Anonymous. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. Heart Failure Society of America. *Pharmacotherapy* 2000;20:495-522.
3. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;28:1328-428.
4. McMeill RS. Effect of a beta-adrenergic blocking agent, propranolol, on asthmatics. *Lancet* 1964;13:1101-2.
5. Raine JM, Palazzo MG, Kerr JH, Sleight P. Near-fatal bronchospasm after oral nadolol in a young asthmatic and response to ventilation with halothane. *Br J Med (Clin Res Ed)* 1981;282:548-9.
6. Williams IP, Millard FJ. Severe asthma after inadvertent ingestion of oxprenolol. *Thorax* 1980;35:160.
7. Harries AD. Beta-blockade in asthma. *Br J Med (Clin Res Ed)* 1981;282:1321.
8. Fraunfelder FT, Barker AF. Respiratory effects of timolol. *N Engl J Med* 1984;311:1441.
9. Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract* 1991;32:97-8.
10. Meeker DP, Wiedemann HP. Drug-induced bronchospasm. *Clin Chest Med* 1990;11:165-75.
11. August P. Initial treatment of hypertension. *N Engl J Med* 2003;348:610-7.
12. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol* 2001;37:1950-6.
13. Self T, Soberman JE, Bubla JM, Chafin CC. Cardioselective beta-blockers in patients with asthma and concomitant heart failure or history of myocardial infarction: when do benefits outweigh risks? *J Asthma* 2003;40:839-45.
14. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.
15. Menkhaus PG, Reves JG, Kissin I, et al. Cardiovascular effects of esmolol in anesthetized humans. *Anesth Analg* 1985;64:327-34.
16. Sheppard D, Distefano S, Byrd RD, et al. Effects of esmolol on airway function in patients with asthma. *J Clin Pharmacol* 1986;26:169-74.
17. Gold MR, Dec GW, Cocco-Spofford D, Thompson BT. Esmolol and ventilatory function in cardiac patients with COPD. *Chest* 1991;100:1215-8.
18. Iguchi S, Iwamura H, Nishizaki M, et al. Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull* 1992;40:1462-9.
19. Boskabady MH, Adel-Kardan S. Increased muscarinic receptor blockade by atropine in tracheal chains of ovalbumin-sensitized guinea pigs. *Pharmacology* 1999;58:300-8.

20. Wu Z-X, Zhou D, Chen G, Lee L-Y. Airway hyperresponsiveness to cigarette smoke in ovalbumin-sensitized guinea pigs. *Am J Respir Crit Care Med* 2000;161:73-80.
21. Toward TJ, Broadley KJ. Early and late bronchoconstrictions, airway hyperreactivity, leucocyte influx and lung histamine and nitric oxide after inhaled antigen: effects of dexamethasone and rolipram. *Clin Exp Allergy* 2004;34:91-102.
22. Giles RE, Finkel MP, Mazurowski J. Use of an analog on-line computer for the evaluation of pulmonary resistance and dynamic compliance in the anesthetized dog. *Arch Int Pharmacodyn* 1971;194:213-22.
23. Hollenberg M, Mangano DT, Browner WS, London MJ, Tubau JF, Tateo IM. Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *JAMA* 1992;268:205-9.
24. Oda Y, Nishikawa K, Hase I, Asada A. The short-acting beta₁-adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. *Anesth Analg* 2005;100:733-7.
25. Silvanus M-T, Groeben H, Peters J. Corticosteroids and inhaled salbutamol in patients with reversible airway obstruction markedly decrease the incidence of bronchospasms after tracheal intubation. *Anesthesiology* 2004;100:1052-7.
26. Murray JF. History and physical examination. In: Murray JF, Nadel JA, eds. *Textbook of respiratory medicine*. Philadelphia: Saunders; 1989:443.
27. Smith H. Animal models of asthma. *Pulm Pharmacol* 1989;2:59-74.
28. Kodani M, Sakata N, Takano Y, et al. Intratracheal administration of anaphylatoxin C5a potentiates antigen-induced pulmonary reactions through the prolonged production of cysteinyl-leukotrienes. *Immunopharmacol* 2000;49:263-74.
29. Abe M, Shibata K, Akatsu H, et al. Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats. *J Immunol* 2001;167:4651-60.
30. Hershenson MB, Aghili S, Punjabi N, et al. Hyperoxia-induced airway hyperresponsiveness and remodeling in immature rats. *Am J Physiol* 1992;262:L263-9.
31. Shiroya T, Ichioka Y, Yoshida K, et al. Pharmacological studies of ONO-1101 as a beta-blocking agent with high beta₁-selectivity and ultra-short duration of action. *KISO TO EINSHO* (written in Japanese) 1997;31:2913-23.
32. Iguchi S, Iwamura H, Nishizaki M. Development of a highly cardioselective ultrashort-acting beta-blocker, ONO-1101. *Chem Pharm Bull* 1992;40:1462-69.
33. Emala CW, Aryana A, Hirshman CA. Impaired activation of adenylyl cyclase in lung of the Besenji-greyhound model of airway hyperresponsiveness: decreased numbers of high affinity beta-adrenoceptors. *Br J Pharmacol* 1996;118:2009-16.
34. Emala CW, Clancy-Keen J, Hirshman CA. Decreased adenylyl cyclase protein and function in airway smooth muscle by chronic carbachol pretreatment. *Am J Physiol* 2000;279:C1008-15.
35. Pizov R, Brown RH, Weiss YS, et al. Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. *Anesthesiology* 1995;82:1111-6.
36. Volta CA, Alvisi V, Petrini S, et al. The effect of volatile anesthetics on respiratory system resistance in patients with chronic obstructive pulmonary disease. *Anesth Analg* 2005;100:348-53.
37. The Esmolol Research Group. Intravenous esmolol for the treatment of supraventricular tachyarrhythmia: results of a multicenter, baseline-controlled safety and efficacy study in 160 patients. *Am Heart J* 1986;112:498-505.
38. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anesth* 2001;48:985-9.
39. Nakashima M, Kanamaru M. Phase I study ONO-1101, a new ultra short acting beta₁-blocking agent in healthy volunteers. *RINSHO IYAKU* (written in Japanese) 2000;16:1531-56.
40. Hasuo H, Tomiyasu S, Hojo M. Effect of ONO-1101, a novel short-acting beta-blocker, on hemodynamic responses to isoflurane inhalation and tracheal intubation. *J Anesth* 1998;12:115-8.
41. Kitamura A, Sakamoto A, Inoue T, Ogawa R. Efficacy of an ultra-short-acting beta-adrenoceptor blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. *Eur J Clin Pharmacol* 1997;51:467-71.
42. Fernandez-Galinski S, Bermejo S, Mansilla R, Pol O, Puig MM. Comparative assessment of the effects of alfentanil, esmolol or clonidine when used as adjuvants during induction of general anesthesia. *Eur J Anaesthesiol* 2004;21:476-82.
43. Cheney FW, Posner KL, Caplan RA. Adverse respiratory events infrequently leading to malpractice suits. *Anesthesiology* 1991;75:932-9.
44. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia. A closed claims analysis. *Anesthesiology* 1990;72:828-33.
45. Warner DO, Warner MA, Barnes RD. Perioperative respiratory complications in patients with asthma. *Anesthesiology* 1996;85:460-7.
46. Wajima Z, Yoshikawa T, Ogura A. Intravenous colforsin darpate, a water-soluble forskolin derivative, prevents thiamylal-fentanyl-induced bronchoconstriction in humans. *Crit Care Med* 2002;30:820-6.
47. Manning MM, Broadstone RV. Effects of alpha₂-adrenergic receptor agonist and antagonist drugs on cholinergic contraction in bovine tracheal smooth muscle in vitro. *Am J Vet Res* 1995;56:930-5.
48. Groeben H, Mitzner W, Brown RH. Effects of the alpha₂-adrenoceptor agonist dexmedetomidine on bronchoconstriction in dogs. *Anesthesiology* 2004;100:359-63.
49. Yamakage M, Iwasaki S, Jeong S-W, Namiki A. Effects of alpha₂-adrenergic agonists clonidine and dexmedetomidine on enhanced airway tone in ovalbumin-sensitized guinea pigs. *Anesthesiology* 2004;101:A1585.