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Landiolol attenuates the cardiovascular response to tracheal intubation

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Abstract
Purpose. The objective of this prospective study was to compare the cardiovascular responses with or without landiolol to the induction of general anesthesia and tracheal intubation.
Methods. Twenty-two patients were randomly allocated to receive a loading dose of landiolol 125 μg kg^{-1} min^{-1} for 1 min followed by an infusion at 40 μg kg^{-1} min^{-1} for 4 min, or placebo. Four minutes after landiolol or placebo was started, propofol and succinylcholine were administered. Laryngoscopy and tracheal intubation were performed 1 min after the administration of succinylcholine. Heart rate and blood pressure were measured noninvasively every minute.
Results. A significant attenuation of the heart rate and blood pressure response were seen in the landiolol group for 3 min after intubation. Heart rate and systolic blood pressure in the landiolol group were decreased for 2 min before intubation and just before intubation compared with baseline, srespectively.
Conclusion. Continuous administration of landiolol before tracheal intubation results in the attenuation of cardiovascular response for tracheal intubation.

Key words Landiolol · Intubation · Hemodynamics

Introduction

Hypertension and tachycardia caused by tracheal intubation lead to cardiac ischemia, increase of intracranial pressure, and adverse effects in some patients. Various studies reported attenuation of hemodynamic responses to tracheal intubation. Of various classes of drugs, β-adrenoceptor antagonists, such as esmolol [1–10], labetalol [11,12], and landiolol [13], are widely used to prevent detrimental events. Landiolol, a newly developed, commercially available agent, is an ultrashort-acting β-adrenoceptor antagonist with a half-life of 3 min and is eight times more cardioselective than esmolol [14–16]. Although landiolol was used as a bolus dose before intubation to prevent detrimental events in a previous study [13], landiolol is recommended to be used by continuous infusion because of the ultrashort-acting property. The present study was designed to compare the cardiovascular responses with or without the continuous administration of landiolol during induction of anesthesia and tracheal intubation.

Materials and methods

After the study protocol was approved by the Ethical Committee of our institution, each of 22 patients, American Society of Anesthesiologists (ASA) physical status I or II, aged 20–60 years, gave informed consent to participate in this study. The patients were randomly allocated to receive either landiolol or placebo before induction via sealed envelope assignment. We excluded those patients with unstable coronary artery disease or heart failure, atrial or ventricular tachyarrhythmia, 2° or 3° A-V block, controlled and uncontrolled hypertension, and those who were pregnant.

Premedication consisted of diazepam 5 mg and roxatidine acetate 75 mg orally 90 min before induction of anesthesia. After the baseline blood pressure (BP) and heart rate (HR) were recorded noninvasively, landiolol or placebo infusion was started. The patients in the landiolol group received landiolol 125 μg kg^{-1} min^{-1} for 1 min followed by 40 μg kg^{-1} min^{-1}, whereas, in the control group the same volume of saline was administered. Four minutes after the start of infusion, propofol 1.5 mg kg^{-1} and succinylcholine 1 mg kg^{-1} were administered. Laryngoscopy and tracheal intubation were performed 1 min after the administration of succinylcholine. Intratracheal or oropharyngeal topical

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lidocaine was not given to any patient before laryngoscopy. Then, anesthesia was maintained with 67% nitrous oxide and 33% oxygen until 5 min after intubation, and controlled ventilation was started immediately after tracheal intubation. The infusion of the landiolol or the placebo was discontinued 2 min after tracheal intubation. Hemodynamic measurements were made every minute until 5 min after intubation.

All data are presented as mean ± standard deviation (SD). Demographic and hemodynamic data were analyzed by unpaired Student's *t* test. The incidence of tachycardia (>100 beats min^{-1}), hypertension (systolic BP >160 mmHg), bradycardia (<50 beats min^{-1}), and hypotension (systolic BP <90 mmHg) were analyzed by chi square test. A two-way analysis of variance for repeated measures was used to analyze changes over time. When statistical significance was found, the difference between two different data for each variable was analyzed by post hoc test (Scheffe's *F* test). $P < 0.05$ was considered significant.

Results

The two study groups studied were similar with respect to age, weight, height, ASA physical status, and gender, as well as preoperative BP and HR values. Also, the duration of laryngoscopy was similar between the two groups (Table 1).

The administration of landiolol did not affect BP compared with the control group except the time course from consideration ($F = 3.720$, $P = 0.0681$). However, there were significant differences in BP of time course ($F = 18.292$, $P < 0.0001$) and in the interaction between the administration of drugs and the time course ($F = 6.250$, $P < 0.0001$). No change in BP occurred after the injection of landiolol or saline in both groups until intubation. Systolic BP at 1, 2, 3, 4, and 5 min after tracheal intubation in the control group were significantly greater than those in the landiolol group (Table 2). Compared with baseline values (T_0), systolic BP at 1 and 2 min after tracheal intubation in the control group significantly increased, while in the landiolol group systolic BP at in 4 and 5 min after tracheal intubation significantly decreased (Table 2). Increases in systolic BP 1, 2, 3, and 4 min after tracheal intubation in the control group were significantly greater than those in the landiolol group (Fig. 1).

Diastolic BP before intubation and 1 min after intubation in the control group were significantly greater than those in the landiolol group (see Table 2). Compared with baseline values (T_0), diastolic BP at 1 and 2 min after tracheal intubation in the control group significantly increased.

There were significant differences in HR response to tracheal intubation, not only excepting the time course from consideration between the two groups ($F = 4.647$, $P = 0.0435$), but also with the time course ($F = 14.735$, $P < 0.0001$) and the interaction between administration of drugs and the time course ($F = 5.171$, $P < 0.0001$). Similarly, HR at 1, 2, and 3 min after tracheal intubation in the control group were significantly greater than those in the landiolol group (see Table 2). Also, changes in HR at intubation and 1, 2, 3, and 4 min after intubation in the control group were significantly greater than those in the landiolol group (Fig. 2). HR at 1 and 2 min after intubation increased significantly above baseline value (T_0) in the control group. In the landiolol group, heart rate 4 and 5 min after landiolol administration (T_3, T_4) significantly decreased compared with the baseline (T_0).

The incidences of tachycardia, hypertension, bradycardia, and hypotension during the study period are shown in Table 3. None of the patients developed a HR <50 beats min^{-1} except for one patient in the control group who developed 47 beats min^{-1} 5 min after tracheal

Table 1. Demographic data, time of laryngoscopy, blood pressure (BP), and heart rate (HR)

Factor	Control group ($n = 11$)	Landiolol group ($n = 11$)
Age (years)	55 ± 18	51 ± 16
Weight (kg)	62 ± 13	57 ± 7
Height (cm)	162 ± 12	159 ± 9
ASA status (I/II)	10/1	10/1
Sex (male/female)	5/6	4/7
Time of laryngoscopy (s)	11 ± 2	12 ± 3
Preoperative SBP (mmHg)	135 ± 30	137 ± 25
Preoperative DBP (mmHg)	74 ± 15	73 ± 9
Preoperative HR (beats min^{-1})	72 ± 13	70 ± 8

Data are presented as mean ± standard deviation
n, sample size; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate
There were no significant differences between groups

Table 2. Changes in systolic and diastolic blood pressure and heart rate before and after tracheal intubation in patients with or without landiolol

Time	T_0	T_1	T_2	T_3	T_4	T_5	I_1	I_2	I_3	I_4	I_5
SBP (mmHg)											
Control group	139 ± 20	136 ± 22	136 ± 19	134 ± 19	132 ± 22	133 ± 19	177 ± 18*,**	167 ± 21*,**	154 ± 25*	145 ± 26*	137 ± 24*
Landiolol group	137 ± 25	129 ± 22	134 ± 22	129 ± 20	126 ± 19	123 ± 13	143 ± 20	137 ± 28	127 ± 23	120 ± 20**	117 ± 17**
DBP (mmHg)											
Control group	74 ± 15	71 ± 15	72 ± 15	70 ± 14	72 ± 13	70 ± 11	100 ± 16*,**	90 ± 15**	84 ± 21	79 ± 18	72 ± 19
Landiolol group	73 ± 9	72 ± 13	70 ± 8	68 ± 8	67 ± 7	67 ± 6	81 ± 15	78 ± 18	70 ± 12	66 ± 16	64 ± 11**
HR (bpm)											
Control group	72 ± 13	72 ± 12	71 ± 13	70 ± 12	69 ± 11	69 ± 10	94 ± 11*,**	85 ± 14*,**	80 ± 12*	76 ± 12	69 ± 10
Landiolol group	70 ± 8	72 ± 11	69 ± 11	64 ± 9	62 ± 9**	62 ± 8**	72 ± 12	69 ± 12	69 ± 13	68 ± 12	67 ± 13

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; T_0, baseline; T_1, 1 min after infusion; T_2, 2 min after infusion; T_3, 3 min after infusion; T_4, 4 min after infusion; T_5, 5 min after infusion; I_1, 1 min after tracheal intubation; I_2, 2 min after tracheal intubation; I_3, 3 min after tracheal intubation; I_4, 4 min after tracheal intubation; I_5, 5 min after tracheal intubation
* $P < 0.05$ vs. landiolol group; ** $P < 0.05$ vs. T_0

intubation. Also, there was no patient who developed bronchospasm and increased airway resistance.

Discussion

This randomized, controlled study demonstrated that landiolol, a novel short-acting β-adrenergic antagonist, attenuated cardiovascular responses (blood pressure and heart rate) to tracheal intubation.

Kitamura et al. [13] reported that a bolus dose of landiolol 0.1, 0.25, or 0.5 mg kg^{-1} attenuated cardiovascular responses to laryngoscopy and tracheal intubation but that the largest dose caused hypotension (SBP <90 mmHg) 5 min after tracheal intubation. They concluded that landiolol 0.25 mg kg^{-1} was a suitable dose for tracheal intubation to prevent hypertension (SBP >160 mmHg) and tachycardia (HR >100 beats min^{-1}) without adverse effects. In the present study, we administered landiolol continuously to maintain an effective plasma concentration during tracheal intubation, and the results were consistent with those obtained by Kitamura et al. Although HR before tracheal intubation decreased transiently compared with the baseline value in the landiolol group, we did not observe severe bradycardia caused by landiolol throughout the study.

On the other hand, systolic BP (SBP) at intubation and 4 and 5 min after tracheal intubation decreased significantly compared with baseline (T_0) in the landiolol group. However, no patient developed SBP <90 mmHg (see Table 3). Sasao et al. [17] reported that both landiolol and esmolol reduced HR in a dose-dependent fashion but that the reduction of HR was more rapid with landiolol. Although mean arterial pressure was decreased in a dose-dependent fashion by esmolol, only a high dose of landiolol administration decreased the mean arterial pressure. Sasao et al. gave the drugs as a bolus dose. These results suggest there is a possibility of different potency against blood pressure in the β-adrenergic antagonists. Further investigation is required to explicate the effects of landiolol on blood pressure at various doses.

In the clinical setting, it is useful and convenient to administer the bolus dose. However, we used the continuous infusion of landiolol to minimize the adverse effects of a bolus dose, which are severe hypotension and bradycardia. According to the meta-analysis, although esmolol is effective in the attenuation of the adrenergic response to tracheal intubation, to minimize its adverse effects it should be administered as a continuous infusion [1].

The time required for tracheal intubation was 11–12 s in this study; systolic BP after intubation was elevated by 38 mmHg from the baseline (T_0) and HR increased by 21 beats min^{-1} from the baseline value in the control

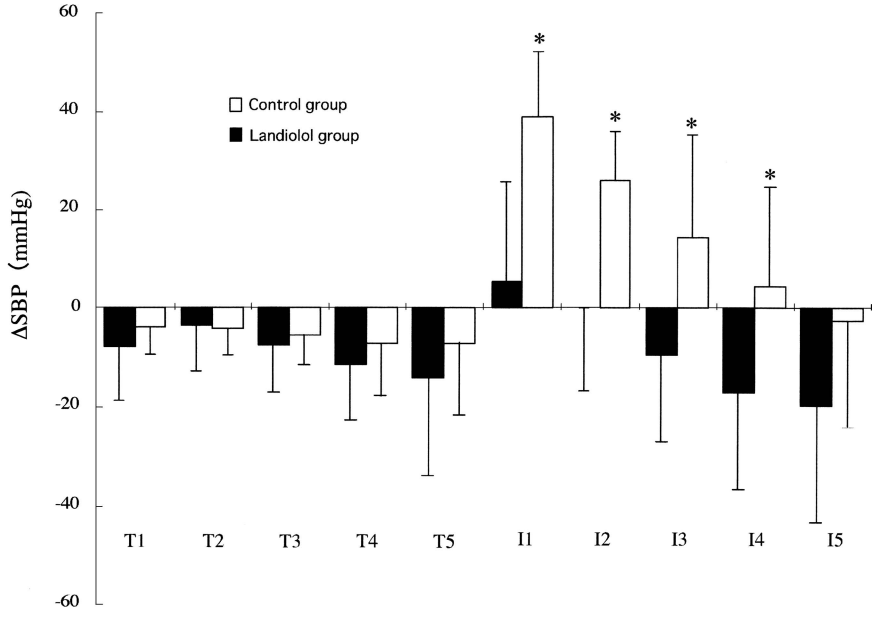

Fig. 1. Changes in systolic blood pressure (ΔSBP) from the baseline values (T0). Blood pressure was recorded before induction (baseline, T0), 1 min after infusion (*T1*), 2 min after infusion (*T2*), 3 min after infusion (*T3*), 4 min after infusion (*T4*), 5 min after infusion (*T5*), 1 min after tracheal intubation (*I1*), 2 min after tracheal intubation (*I2*), 3 min after tracheal intubation (*I3*), 4 min after tracheal intubation (*I4*), and 5 min after tracheal intubation (*I5*). Values are mean ± SD. **P* < 0.05 vs. landiolol group

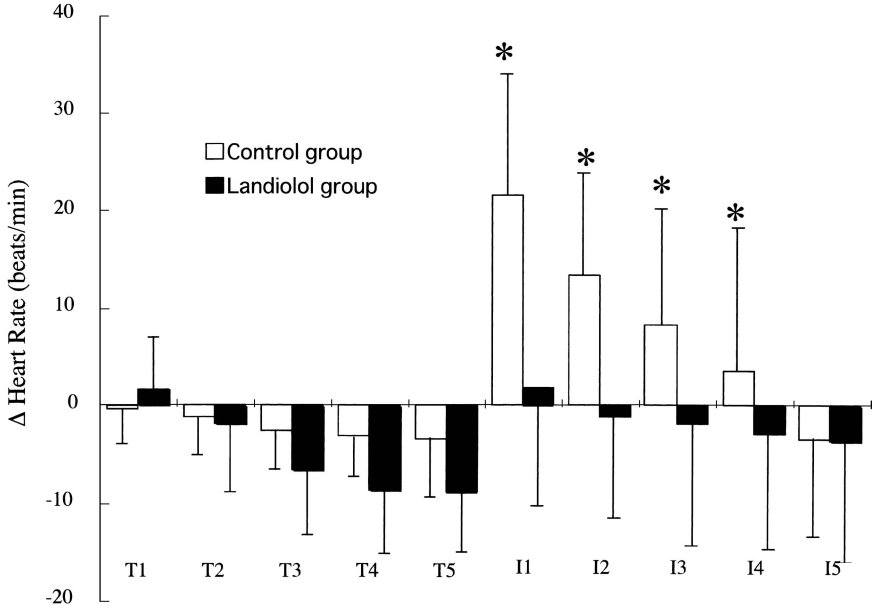

Fig. 2. Changes in heart rate (ΔHR) from the baseline value (T0). Heart rate were recorded before induction (baseline, T0), 1 min after infusion (*T1*), 2 min after infusion (*T2*), 3 min after infusion (*T3*), 4 min after infusion (*T4*), 5 min after infusion (*T5*), 1 min after tracheal intubation (*I1*), 2 min after tracheal intubation (*I2*), 3 min after tracheal intubation (*I3*), 4 min after tracheal intubation (*I4*), and 5 min after tracheal intubation (*I5*). Values are mean ± SD. **P* < 0.05 vs. landiolol group

Table 3. Incidence of sinus tachycardia, hypertension, hypotension, and bradycardia (case %)

	Tachycardia (%) (HR >100 beats min^{-1})	Hypertension (%) (SBP >160 mmHg)	Bradycardia (%) (HR <50 beats min^{-1})	Hypotension (%) (SBP <90 mmHg)
Control group (n = 11)	5 (45.5)	8 (72.7)	1 (9.0)	0 (0)
Landiolol group (n = 11)	0 (0)*	1 (9.1)*	0 (0)	0 (0)

HR, heart rate; SBP, systolic blood pressure
* $P < 0.05$ vs. control group

group. The intubation time is an important determinant for HR and BP responses to tracheal intubation [18]. Thus, the short duration of laryngoscopy could have minimized hemodynamic effects in this study.

In patients who have coronary artery disease, hypertension, or cerebrovascular disease, an increase of HR or BP may precipitate myocardial ischemia, arrhythmias, infarction, and cerebral hemorrhage. Therefore, the hemodynamic depression of landiolol following tracheal intubation is helpful for these patients. In this study, we used clinically healthy patients. Because the cost of landiolol is relatively high, the use of landiolol to depress hemodynamic effects after intubation may be suitable for these high-risk patients rather than healthy patients. Further study needs to address the effect of landiolol for patients with cardiac or cerebrovascular complications.

In conclusion, our results indicate that continuous administration of landiolol before intubation attenuates cardiovascular responses to tracheal intubation. Further studies are required to optimize this effect in high-risk patients.

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