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Short communications

Effects of landiolol on the cardiovascular response during tracheal extubation

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Abstract
The objective of this study was to investigate the effect of landiolol on the cardiovascular responses to emergence from anesthesia and tracheal extubation. Fifty-nine patients without cardiovascular disorders who were scheduled for tympanoplasty were randomly allocated to receive a loading dose of landiolol at 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min, followed by an infusion at 0.01 $mg \cdot kg^{-1} \cdot min^{-1}$ (group L1), 0.02 $mg \cdot kg^{-1} \cdot min^{-1}$ (group L2), 0.03 $mg \cdot kg^{-1} \cdot min^{-1}$ (group L3), or 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$ (group L4). At the end of surgery, sevoflurane and nitrous oxide were discontinued, and landiolol was started. The mean arterial pressure (MAP), heart rate (HR), and rate pressure product (RPP) in the four groups were compared before anesthesia induction, just after extubation, 5 min after extubation, 10 min after extubation, and at discharge from the operating room. Just after extubation compared with the baseline, the MAP increased significantly in all groups; the HR increased in groups L1 and L2; and the RPP increased in all groups, except for group L4. Continuous administration of landiolol, at 0.03 or 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$, may prevent the increases in HR and RPP, respectively, that occur at the emergence from anesthesia and tracheal extubation.

Key words Landiolol · Extubation · Hemodynamic response

Laryngoscopy and tracheal intubation often provoke hypertension and tachycardia [1]. These hemodynamic changes are also observed at the end of anesthesia and just after endotracheal extubation [2]. These hemodynamic changes may cause a dangerous increase in myocardial oxygen demand in patients with coronary artery disease and arrhythmia. It is important to avoid tachycardia without reducing the blood pressure in these patients, because an adequate level of blood pressure is required to maintain coronary perfusion. However, clinically available β_1-adrenoceptor antagonists, including the ultrashort-acting, highly cardioselective antagonist, esmolol, appear to be insufficient to achieve these purposes because of their hypotensive effects [3]. In this regard, landiolol, a novel short-acting β_1-adrenoceptor antagonist, is eightfold more selective for cardiac β_1-adrenoceptors than esmolol and has a less significant effect on blood pressure than esmolol in animal models [4]. Some studies have reported that landiolol effectively inhibits the cardiovascular responses to tracheal intubation [5,6]. However, the effect of this β_1-adrenoceptor antagonist on hemodynamic changes in response to endotracheal extubation remains unknown.

In the present study, we examined the effect of landiolol on the hemodynamic changes resulting from the i.v. administration of atropine and neostigmine and tracheal extubation in patients undergoing elective tympanoplasty.

After the study protocol was approved by the Ethics Committee of our institution, each of 59 patients, of American Society of Anesthesiologists (ASA) physical status class 1, and age, 17–68 years, gave informed consent to participate in this study. The patients were randomly assigned to one of four groups: L1 group patients were given 0.01 $mg \cdot kg^{-1} \cdot min^{-1}$ landiolol (n = 14); L2 group patients were given 0.02 $mg \cdot kg^{-1} \cdot min^{-1}$ landiolol (n = 16); L3 group patients were given 0.03 $mg \cdot kg^{-1} \cdot min^{-1}$ landiolol (n = 14); and L4 group patients were given 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$ landiolol (n = 15). The dose of landiolol was blinded for the anesthesiologist. Patients who were receiving antihypertensive or vasoactive agents were excluded from the study.

Hydroxyzine hydrochloride (25 mg) was given orally 90 min before anesthesia induction. After the patient's arrival in the operating room, noninvasive monitoring of blood pressure, electrocardiogram, pulse oximetry, and end-tidal carbon dioxide was conducted. Before general anesthesia, three readings of the heart rate (HR) and blood pressure were taken; the mean values

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were used as the baseline. Anesthesia was induced with propofol at 2.0 mg·kg^{-1}, and tracheal intubation was facilitated with vecuronium at 0.1 mg·kg^{-1}. Anesthesia was maintained with 1.0%–2.0% sevoflurane and 60% nitrous oxide (N_2O) in oxygen and fentanyl at 0.1–0.2 mg. At the end of surgery, sevoflurane and nitrous oxide were discontinued, and a loading dose of landiolol (0.125 mg·kg^{-1}·min^{-1}) was administered for 1 min, followed by an infusion at 0.01–0.04 mg·kg^{-1}·min^{-1}. When spontaneous breathing was observed after surgery, 2.0 mg neostigmine and 1.0 mg atropine were given over a 1-min period before extubation. Extubation was performed when the patients could breathe spontaneously and open their eyes on command. In practice, this was between 5 and 12 min after the start of the injection of landiolol. Continuous infusion of landiolol was stopped at 2 min after the endotracheal extubation. The following drugs were administered as escape medications: ephedrine, at 4 mg, for hypotension (systolic blood pressure < 80 mmHg for 60 s) and atropine, at 0.5 mg, for bradycardia (HR < 50 for 60 s).

Hemodynamic measurements were made every minute until 10 min after extubation. The rate pressure product (RPP) was derived from the systolic blood pressure × HR·100^{-1}. All data values were expressed as means ± SD. Statistical analysis was made by using the χ^2 test or one-way or repeated-measures analysis of variance (ANOVA). When a significant difference was obtained using ANOVA, post-hoc analysis was performed with Scheffé's *F*-test. $P < 0.05$ was considered significant.

No escape medications were required for any patient during the study period. No statistically significant differences were observed between any of the four groups for sex, age, weight, height, duration of landiolol administration, or anesthesia (Table 1). The mean arterial pressure (MAP) increased significantly in all groups just after extubation compared with the baseline value (Fig. 1). An increase in MAP was also observed at 5 min after extubation in the L1 and L2 groups. The HR increased significantly in the L1 and L2 groups just after extubation (Fig. 2). An increase in HR was observed in the L1 group at 5 min after extubation. The RPP increased significantly in all groups, except for the L4 group, just after extubation (Fig. 3). In the L1 group, an increase in RPP was observed at discharge from the operating room.

Tracheal extubation is usually performed with the patient in a light stage of anesthesia, and the procedure produces significant increases in HR and BP, which persist into the recovery period [7]. The occurrence of significant increases in HR, MAP, and RPP, beginning immediately after extubation and continuing for at least until 2 min after it, has been demonstrated [8]. Furthermore, in our study, HR increased with the administration of 2.0 mg neostigmine and 1.0 mg atropine given in

Table 1. Demographic data, duration of landiolol administration, and duration of anesthesia

Group (landiolol mg·kg^{-1}·min^{-1})	0.01	0.02	0.03	0.04
n (Male:Female)	14 (9:5)	16 (7:9)	14 (7:7)	15 (8:7)
Age (years)	47 ± 12	54 ± 14	48 ± 19	52 ± 12
Weight (kg)	58 ± 18	58 ± 10	54 ± 9	59 ± 11
Height (cm)	158 ± 9	162 ± 9	157 ± 8	161 ± 8
Duration of landiolol administration (min)	14 ± 6	14 ± 8	15 ± 5	16 ± 7
Duration of anesthesia (min)	218 ± 83	214 ± 81	233 ± 85	262 ± 67

Data values are presented as means ± SD and as number of treatments (*n*). There were no significant differences between the groups

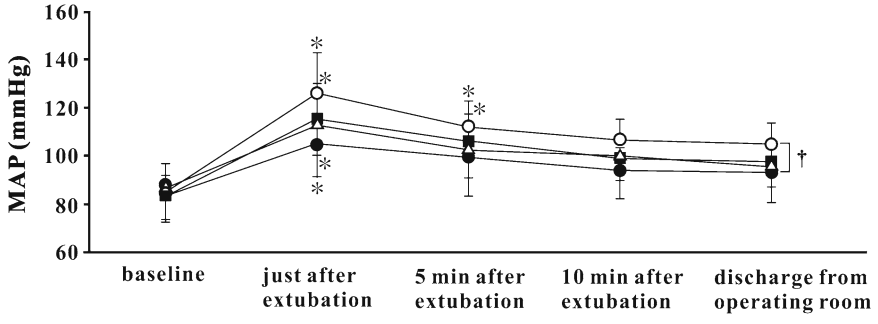

Fig. 1. Mean arterial pressure (*MAP*) changes during the study period. The values for the L1, L2, L3, and L4 groups are means ± SDs. *$P < 0.05$ vs each baseline value; †$P < 0.05$ L1 group vs L4 group. *Open circles*, L1 group (landiolol 0.01 mg·kg^{-1}·min^{-1}); *closed squares*, L2 group (landiolol 0.02 mg·kg^{-1}·min^{-1}); *open triangles*, L3 group (landiolol 0.03 mg·kg^{-1}·min^{-1}); *closed circles*, L4 group (landiolol 0.04 mg·kg^{-1}·min^{-1})

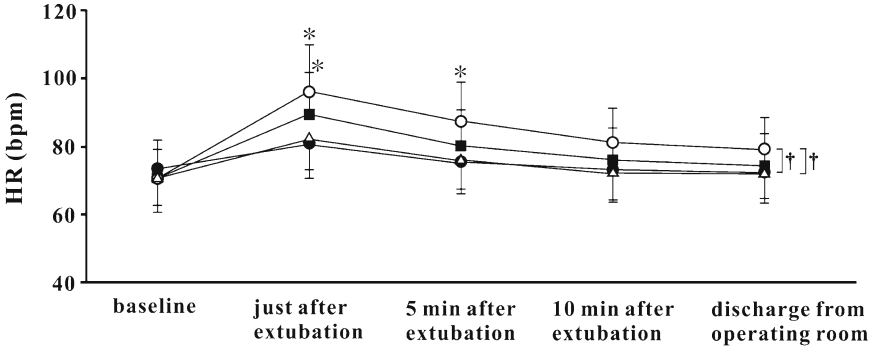

Fig. 2. Heart rate (*HR*) changes during the study period. The values for the L1, L2, L3, and L4 groups are means ± SDs. $^{*}P < 0.05$ vs each baseline value; $^{\dagger}P < 0.05$ L1 group vs L3 and L4 groups. *Symbols*, As in Fig. 1

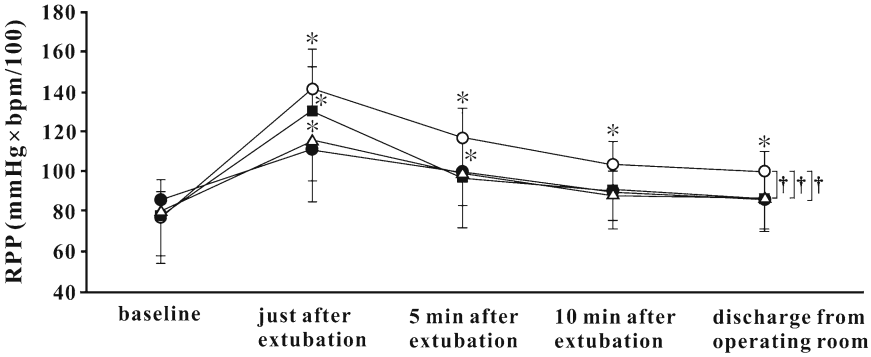

Fig. 3. Rate pressure product (*RPP*) changes during the study period. The values for the L1, L2, L3, and L4 groups are means ± SDs. $^{*}P < 0.05$ vs each baseline value; $^{\dagger}P < 0.05$ L1 group vs L2, L3, and L4 groups. *Symbols*, As in Fig. 1

order to reverse neuromuscular relaxation just before extubation.

The results of the current study indicate that landiolol, a novel beta-adrenergic blocker, given at a loading dose of 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min, followed by an infusion at 0.03 or 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$, attenuates the tachycardia accompanying emergence from anesthesia and extubation. The results also showed an inhibition of the increase in RPP induced by emergence from anesthesia and extubation with a loading dose of 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min, followed by an infusion at 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$.

The majority of patients are able to tolerate the hemodynamic responses to tracheal extubation without any significant consequences. In patients with coronary artery disease, however, the hemodynamic response to extubation may upset the balance between myocardial oxygen supply and demand, resulting in myocardial ischemia. Slogoff and Keats [9] have shown that perioperative myocardial ischemia is significantly related to episodes of tachycardia, but not to episodes of hypertension. We found that the HR increased significantly in the L1 and L2 groups just after extubation. There was a significant difference in HR between the L1 group and the L3 and L4 groups. Thus, landiolol appears to have a dose-related effect on HR. The occurrence of perioperative myocardial ischemia is associated with the subsequent development of postoperative myocardial infarction [9]. Our results suggest that a loading dose of landiolol at 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min followed by a continuous infusion of more than 0.03 $mg \cdot kg^{-1} \cdot min^{-1}$ may be effective to prevent myocardial ischemia during extubation as well as during the postoperative period.

We measured RPP as an index of myocardial oxygen consumption. It has been reported that patients who developed myocardial ischemia during extubation had a significantly greater RPP immediately before and 1 min after tracheal extubation than those patients who did not develop myocardial ischemia [10]. In our present study, a significant increase in RPP was observed in all groups except for the L4 group. These results suggest that a loading dose of landiolol at 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min followed by a continuous infusion of more than 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$ may be necessary to prevent an increase in myocardial oxygen consumption accompanying extubation.

A bolus administration of landiolol at 0.1 $mg \cdot kg^{-1}$ was effective against intubation-induced tachycardia in normotensive patients. However, 0.2 $mg \cdot kg^{-1}$ of landiolol was necessary to prevent tachycardia after intubation in hypertensive patients [6]. The limitations of our study include the fact that hypertensive patients were excluded from it. Our results suggest that a continuous infusion

of landiolol at 0.03 mg·kg^{-1}·min^{-1} or more may be necessary to prevent tachycardia during extubation in hypertensive patients. Another limitation of our study is that we did not evaluate myocardial ischemia. While some studies have assessed different methods of reducing the hemodynamic response to extubation [3,7,11,12], there have only been a few that examined the incidence of myocardial ischemia during extubation [10]. We feel that further studies in this area with regard to the methods of reducing the development of myocardial ischemia would be of value.

In conclusion, we have shown that the increases in HR and RPP that occur during extubation can be successfully attenuated by the continuous administration of landiolol, at 0.03 mg·kg^{-1}·min^{-1} and 0.04 mg·kg^{-1}·min^{-1}, respectively. The efficacy of landiolol given before extubation in patients with ischemic heart disease deserves further study.

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