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Original

Low Dose Landiolol Combined with Catecholamine Can Decrease Heart Rate without Suppression of Cardiac Contraction after Cardiopulmonary Bypass

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SUMMARY

Objective : Landiolol is a new ultra-short acting beta-adrenergic blocker that has potential for use in perioperative hemodynamic stabilization. The purpose of this study was to examine the effect of combined administration of landiolol and Catecholamine on regulation of heart rate in tachycardia after cardiopulmonary bypass.

Design : The study was performed as a prospective controlled trial.

Setting : A university hospital.

Participants : The subjects were 30 of 64 patients with heart rate ≥115 bpm after weaning from cardiopulmonary bypass.

Interventions : Fifteen of the patients (the landiolol group) were administered landiolol at a dose of 3-5 μg/kg/min without a decrease in the dose of Catecholamine. The other 15 patients (the control group) did not receive landiolol, but the Catecholamine dose of 1 μg/kg/min was decreased to reduce the heart rate.

Results : Mean arterial pressure, cardiac index and heart rate were measured 5, 10 and 15 min after drug administration and postoperatively. Mean arterial pressure and cardiac index were unchanged after drug administration, but heart rate was significantly lower after 15 min and postoperatively in patients administered landiolol compared with those who did not receive landiolol.

Conclusions : Combined administration of landiolol and Catecholamine is useful for stabilization of cardiovascular changes after cardiopulmonary bypass surgery.

Key Words : landiolol, Catecholamine, heart rate, cardiac index, cardiopulmonary bypass

INTRODUCTION

Cardiovascular impairment after weaning from cardiopulmonary bypass (CPB) is a major concern in cardiac surgery. To improve the cardiac status after CPB, anesthetic management in cardiac surgery is performed using Catecholamine, phosphodiesterase inhibitor and coronary dilator. Administration of these drugs

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requires precise management to moderate hemodynamic fluctuations in the perioperative period. However, there are differences among individuals in terms of responsiveness to Catecholamine and phosphodiesterase inhibitor, and these differences may cause tachyarrhythmia after weaning from CPB. Tachyarrhythmia also increases myocardial ischemia due to increased myocardial oxygen consumption, enhancing the incidence of perioperative ischemic heart diseases and heart failure.

Several recent reports have described the efficacy of beta blockers for hemodynamic stabilization and protection against myocardial ischemic dysfunction[1]. Landiolol (ONOACT, Ono pharmaceutical company, Osaka, Japan), a ultra-short acting beta adrenergic blocker, is particularly useful for perioperative hemodynamic stabilization[2,3]. However, the hemodynamic effects of combined administration of landiolol and Catecholamine for cardiovascular control during cardiac surgery have not been examined. In the current study, patients were continuously administered a low dose of landiolol to prevent tachycardia after weaning from CPB. The resulting decrease in heart rate suggests that landiolol is useful for maintenance of a stable heart rate under these conditions.

PATIENTS AND METHODS

Patients

This study protocol was approved by Dokkyo University Hospital Ethics Committee and written informed consent was obtained from all patients before the start of the study. The patients were allocated randomly to control and landiolol groups in equal numbers using randomly selected, mixed, sealed, opaque envelopes. The subjects were restricted to patients with heart rate ≥115 bpm after weaning from CPB. To avoid serious adverse effects including arrhythmia, hypotension and low cardiac output syndrome that may be induced by bradycardia and abnormal atrioventricular conduction, the exclusion criteria were a history of serious arrhythmia except sinus tachycardia and supraventricular tachycardia, and a cardiac index (CI) ≤2.2 L/min/m^2 (the lower limit of the normal range) at the start of drug administration.

Sampling procedure

No premedication was given in any cases. An electrocardiogram (ECG) was recorded and non-invasive blood pressure was measured before induction of anesthesia. Oxygen saturation was monitored continuously by pulse oximetry (Dynascope™, Fukuda Denshi, Tokyo) and arterial blood pressure was measured continuously at the left radial artery using a tonometric blood pressure monitor (Dynascope™). General anesthesia was induced with fentanyl (4 μg/kg), midazolam (0.5 mg/kg) and vecuronium (0.1 mg/kg). After tracheal intubation, a Swan-Ganz catheter was inserted into the right internal jugular vein for monitoring of cardiac output as the cardiac index (CI) with a volumetric monitor (Vigilance, Edwards Lifesciences, Irvine, CA, USA). Anesthesia was maintained with air-oxygen-sevoflurane inhalation (1-3%) and intermittent bolus injection of fentanyl and midazolam. During CPB, patients were given fentanyl (200 μg/h), midazolam (2 mg/h) and pancuronium (2 mg/h).

Continuous administration of dopamine and dobutamine was started before weaning from CPB in all patients. The dosage of Catecholamine was determined based on the preoperative cardiac condition of each patient. Noradrenaline was administered continuously to some patients as required. In patients with heart rate ≥115 bpm after weaning from CPB, those assigned to the landiolol group were administered landiolol at a dose of 3-5 μg/kg/min without a decrease of Catecholamine. Those in the control group were not administered landiolol, but the dose of Catecholamine was decreased to 1 μg/kg/min to reduce the heart rate. Heart rate and blood pressure were measured 3 times every five minutes after the start of heart rate regulation and at the completion of surgery, and CI was determined before and after heart rate regulation. Bradycardia (≤50 bpm), hypotension (systolic blood pressure ≤80 mmHg) and low cardiac output (CI ≤ 2.2 L/min/m^2) were monitored as potential adverse events.

Statistical analysis

Data are expressed as means ± SD. The difference in the dosage of Catecholamine between the control and landiolol groups was analyzed using Bonferroni test. Other data were analyzed by one-way ANOVA and

Table 1 Demographic characteristics of the patients (1)

	Landiolol	Control (catecholamine adjusted)
Number of subjects	N=11	N=11
Gender (M : F)	7 : 4	9 : 2
Age (years)	62±9.8	65±7.7
Height (cm)	159±9.8	159±7.9
Weight (kg)	61±9.9	57±12
Surgical method	CABG : 8AVR : 3	CABG : 7AVR : 3MVR : 1
Cardiopulmonary bypass time (minutes)	171±66	153±28

Data are shown as mean±SD except for gender and surgical method.
M=male ; F=female ; CABG=coronary artery bypass grafting surgery ; AVR=aortic valve replacement ; MVR=mitral valve replacement.

Table 2 Demographic characteristics of the patients (2)

	Landiolol	Control (catecholamine adjusted)
DOA (γ)	4.3±1.3	3.6±1.6
DOB (γ)	4.6±1.2	4.1±2.5
Number of subjects treated with NA	6	4
NA (γ)	0.04±0.08	0.02±0.03
Landiolol	5γ : 10 ／ 3γ : 1	0
Landiolol (γ)	4.8±0.6	0

Data are shown as the mean±SD, except for the number of subjects treated with noradrenaline.

intergroup comparison was performed by Mann-Whitney U test. Values of $P<0.05$ were considered statistically significant.

RESULTS

We obtained informed consent from 64 patients who underwent cardiac surgery during the study period, and of which 30 patients (22 men and 8 women ; age, 49-79 years old ; height, 145-173 cm ; weight, 39-76 kg), were selected as subjects in this study. Their heart rates were over 115 bpm after weaning from CPB and they were not included in our exclusion criteria.

The demographic characteristics of the 30 patients are presented in Table 1. There were no significant differences in age, height or weight between the landiolol and control groups. In the landiolol group, 10 patients underwent coronary artery bypass grafting (CABG) and 5 underwent aortic valve replacement (AVR). In the control group, 10 underwent CABG, 4 underwent AVR, and one patient had mitral valve replacement (MVR). The time of extracorporeal circulation was 171±63 min in the landiolol group and 161±39 min in the control group, with no significant difference between the groups.

The amounts of dopamine, dobutamine and noradrenaline administered to patients in both groups and the dose of landiolol given to patients in the landiolol group are shown in Table 2. The initial doses of dopamine and dobutamine were higher in the control group compared to the landiolol group, but with no significant difference between the groups. However,

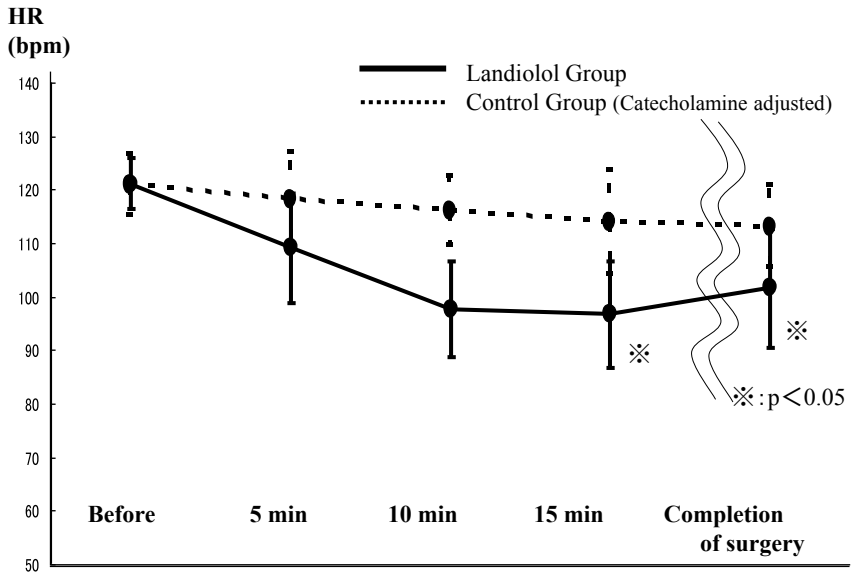

Figure 1 Changes in heart rate

Values are shown as means ± SD. Before = before control of heart rate ; 5 min, 10 min and 15 min = 5 min, 10 min and 15 min after hemodynamic stabilization with landiolol administration or Catecholamine adjustment. MBP = mean blood pressure.

※ p＜0.05 ; landiolol group vs. control group.

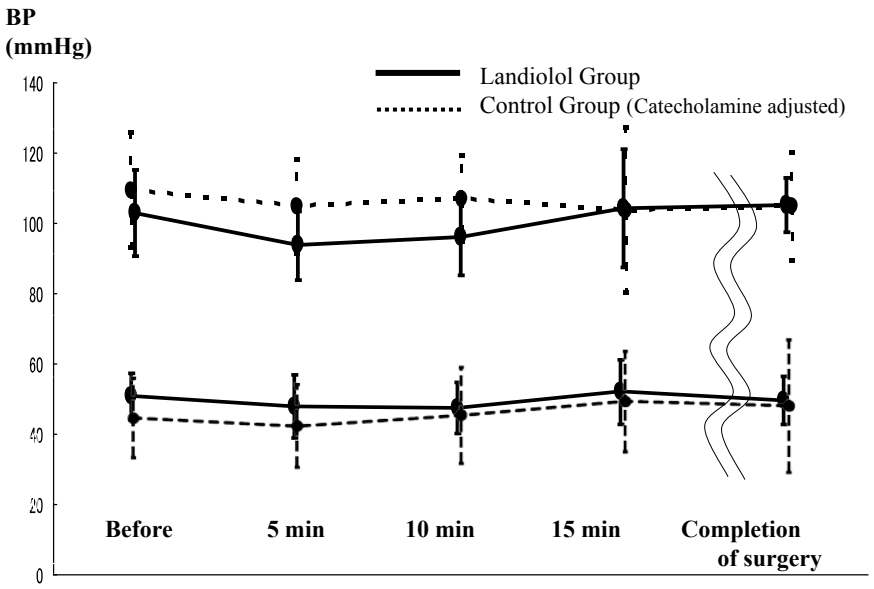

Figure 2 Changes in blood pressure

Values are shown as means ± SD. Before = before control of heart rate ; 5 min, 10 min and 15 min = 5 min, 10 min and 15 min after hemodynamic stabilization with landiolol administration or Catecholamine adjustment.

the doses of dopamine and dobutamine used to regulate heart rate were significantly lower in the control group compared to the landiolol group. There was no difference in the noradrenaline dose between the two groups.

Changes in heart rate and blood pressure determined every five minutes after the start of heart rate regulation and at the completion of surgery are shown in Figures 1 and 2, respectively. Changes in CI are shown in Figure 3. Heart rate (Figure 1) showed a

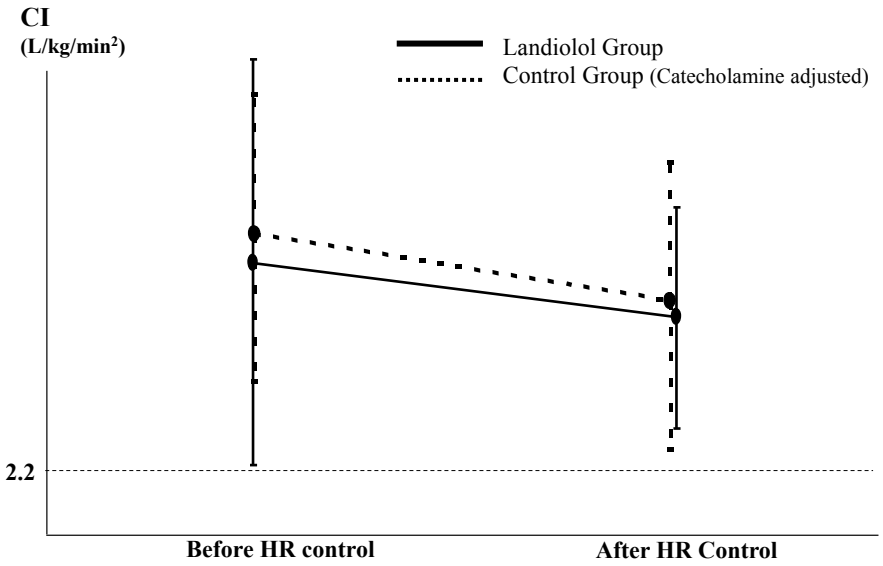

Figure 3 Changes in cardiac index
Values are shown are means ± SD. Before HR control = before control of heart rate with landiolol administration or Catecholamine adjustment ; After HR control = after completion of surgery in both groups. CI = cardiac index.

tendency to decrease from 5 min after the start of landiolol administration, but remained at around 110–120 bpm in the control group. At 15 min after the start of drug administration and at the completion of surgery, heart rate was significantly lower in the landiolol group (90–100 bpm) compared with the control group (※ $p<0.05$ VS control group). In contrast, there were no significant differences in blood pressure (Figure 2) and CI (Figure 3) between the groups throughout the study.

No adverse reactions of bradycardia (≤50 bpm), hypotension (systolic blood pressure ≤80 mmHg) or low cardiac output (CI ≤2.2 L/min/m^2) were observed in the study.

DISCUSSION

Tachycardia after weaning from CPB may be caused by a reduction in circulating blood volume, physical stimulus of the heart by surgical procedures, adventitious cardiogenic arrhythmia, or an adverse reaction to Catecholamines. The reduction in circulating blood volume can be treated by increasing fluid infusion and blood transfusion, and adventitious cardiogenic arrhythmia can be resolved by administration of appropriate antiarrhythmic agents. However, adverse effects of catechol amines administered to support cardiac circulation are more of a concern as a factor causing tachycardia after weaning from CPB. Catecholamine is useful for improving cardiac contraction, but common Catecholamine such as dopamine and dobutamine can induce perioperative tachyarrhythmia, rather than prompt pharmacological regulation of heart rate. Administration of a combination of dopamine and dobutamine in equal amounts or with a higher proportion of dobutamine has been shown to be effective in enhancing right ventricular performance[4]. However, Mayr et al. have proposed that the severity of cardiovascular dysfunction with tachyarrhythmia has a strong causal relationship with Catecholamine therapy[5]. Administration of these agents in weaning from CPB induces fluctuations in heart rate that are often difficult to regulate, and increased cardiac performance due to Catecholamine administration may induce intraoperative myocardial ischemia. Therefore, regulation of heart rate is required in weaning from CPB.

Landiolol is a recently developed beta-adrenergic receptor antagonist that can act as an antichronotropic agent. Landiolol has a greater specific beta-1 selectivity (beta-1/beta-2 = 277) and a shorter elimination half-life (4 min in healthy subjects) than esmolol, and has been used to treat tachyarrhythmia safely[6], including sinus tachycardia, tachycardiac atrial fibrilla-

tion and supraventricular tachycardia[7~11]. Landiolol has a protective effect of myocardial damage in cardiac surgery via intravenous administration at an initial recommended dose of 12.5μg/kg/min for 1 min and a subsequent dose in the range from 10-40μg/kg/min with monitoring of heart rate and blood pressure. Several studies reported the effectiveness of low dose landiolol administration without bolus injection[12,13]. Their reports suggested that the continuous intravenous administration of 0.03-0.06 or 0.05 mg/kg/min of landiolol might show the similar action of conventional administration of landiolol. Heart rate reduced approximately 10-20 bpm with landiolol administration in these reports. By using as the reference of the doses of landiolol in these manuscripts, we choose 3-5μg/kg/min (0.03-0.05 mg/kg/min) of the dosage of landiolol to avoid adverse effect in this study.

Goto et al[14] reported that administration of landiolol at this dosage causes a decrease in heart rate without aggravation of hemodynamics in patients with normal cardiac function, but may lead to further deterioration of cardiac function due to a decrease in heart rate in patients with a preoperative EF of lower than 50%. Moreover, landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts[15]. In the present study, combined administration of dopamine, dobutamine and landiolol decreased heart rate significantly without reducing blood pressure and CI. This is the first study to show that this combination improves cardiovascular stability during cardiac surgery.

We were concerned that the recommended dose of landiolol might have an adverse effect on cardiac contractility due to beta-1 blockage after weaning from CPB. Therefore, we administered landiolol at 3-5μg/kg/min, which is less than half of the minimum recommended dose[2,3] of 10μg/kg/min. Continuous administration of landiolol at this low dose significantly decreased heart rate without reducing blood pressure and CI and caused no adverse reactions in patients with tachycardia after weaning from CPB. Therefore, administration of landiolol at 3-5μg/kg/min with concomitant administration of Catecholamine does not inhibit inotropic effects on cardiac function and regulates heart rate, suggesting that landiolol at this dose should be administered before reducing the dosage of Catecholamine in patients with tachycardia after weaning from CPB. In a future study, it will be necessary to examine the effect of esmolol and other beta 1 blockers on the regulation of heart rate after weaning from CPB in cardiac surgery.

Common Catecholamine, such as dopamine or dobutamine, is usually initially administered at 3-5μg/kg/min or less for weaning from CPB. And, Catecholamine administration should be decreased when there is a risk of inducing of excessive cardiac function. Therefore, we decreased the dosage of both Catecholamines to 1μg/kg/min to avoid deterioration of cardiac function in the absence of use of landiolol. However, we conclude that combined continuous administration of landiolol at 3-5μg/kg/min with no reduction in both Catecholamines can decrease heart rate without reducing blood pressure and CI significantly. Therefore, this protocol can be used to stabilize cardiovascular reactions after cardiopulmonary bypass in cardiac surgery.

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