Postoperative administration of landiolol hydrochloride for patients with supraventricular arrhythmia: the efficacy of sustained intravenous infusion at a low dose

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Abstract

The purpose of this study was to investigate the efficacy of landiolol hydrochloride, a short-acting β_1 blocker, by initiating its administration at a low dose (5 μg • kg^{-1} • min^{-1}) in patients with postoperative supraventricular arrhythmia. The efficacy of landiolol was evaluated in 38 patients who, after developing postoperative atrial flutter or fibrillation, with sinus tachycardia and 2 patients who had a history of paroxysmal atrial fibrillation with frequent atrial extrasystole. The heart rate and blood pressure before and 2 hours after the administration of landiolol were compared. A return to the sinus rhythm from supraventricular arrhythmia was noted in 89%. The heart rate was reduced from 137 ± 26 bpm (before landiolol administration) to 93 ± 18 bpm (2 hours after the start of the medication, $P < 0.01$). As an agent to correct an arrhythmic condition, landiolol successfully raised the systolic blood pressure from 108 ± 24 mmHg (before medication) to 120 ± 19 mmHg (2 hours after the medication was started, $P < 0.05$). Continuous intravenous infusion of landiolol at a low dose was found to be effective for postoperative supraventricular arrhythmia.

Keywords: β blocker, landiolol hydrochloride, postoperative care, supraventricular arrhythmia

1. Introduction

The perioperative care is necessarily conducted under unique conditions, such as excitation of the sympathetic nervous system, administration of agents to stimulate the circulatory system and systemic inflammatory responses [1,2] It has been found that β blockers are not only effective in controlling myocardial ischemia and arrhythmia but also in suppressing inflammatory cytokines and stabilizing intravascular plaques, [3-5] thus attracting further attention to their efficacy during perioperative care. In Japan, however, propranolol hydrochloride (hereafter abbreviated to propranolol) is the only β blocker that is currently available for intravenous administration, which was not always convenient for perioperative care because of its relatively long half-life [6]. Landiolol hydrochloride (hereafter abbreviated to landiolol) is a short-acting β_1 blocker that has been developed in Japan [7] Because of its extremely short half-life in blood (approximately 4 minutes), [8] it appears to be highly promising as an agent in adjusting the timing of intravenous administration.

In view of the efficacy of β blockers in the management of postoperative supraventricular arrhythmia, the current study was conducted employing landiolol. Based on the clinical results, administration at a low dose was initiated.

2. Patients and Method

The subjects were 40 patients (mean age, 70 ± 9, range, range, 41 to 84 years; 30 men and 10 women) who underwent continuous infusion of landiolol at a low dose during postoperative care at the Kochi University Hospital that started between April 2004 and December 2007. The group comprised those with: ischemic heart disease (12), valvular diseases (5), aortic diseases (9), respiratory tract diseases (5), digestive system diseases (7) and others (2) (Table 1).

Among those individuals who suffered from atrial flutter or fibrillation during the postoperative period, the following were selected as the subjects of the present study: 38 who failed in an attempt to correct the water-electrolyte balance and resisted the treatment of 50 mg of pilsicainide hydrochloride (hereafter abbreviated to pilsicainide) and 2 who had a history of paroxysmal atrial fibrillation and had began to develop frequent bouts of atrial extrasystole. Based on the clinical experience in the use of landiolol, a continuous intravenous infusion was started at a dose of 5 $\mu g \bullet kg^{-1} \bullet min^{-1}$ for defibrillation; and depending on the heart rate and blood pressure, it was adjusted to approximately 2 $\mu g \bullet kg^{-1} \bullet min^{-1}$ every 5 to 10 minutes. These patients suffered from the following clinical conditions: atrial fibrillation (28, with 2 maintaining the sinus rhythm after MAZE operation), atrial flutter (5), sinus tachycardia (5) and prophylaxis for paroxysmal atrial fibrillation (2).

The heart rate and blood pressure before and 2 hours after the administration of landiolol were compared.

Prior to medication, the expected outcome and the need of the treatment were fully explained to those 2 patients who were scheduled for the prevention of paroxysmal atrial fibrillation.

The age, dosages, heart rate and blood pressure of the patients were recorded as a mean ± standard deviation. For statistical analysis, the Student's-*t*-test was used with the significance level set at $P < 0.05$.

3. Results

For the most patients, landiolol administration was started between days 2 and 5 after surgery (Fig. 1). Restoration of the normal sinus rhythm from supraventricular arrhythmia was noted in 34 of the 38 patients (89%). This effect was noted in 24 of the 28 patients (86%) of

those with atrial fibrillation and all of those with atrial flutter or sinus tachycardia. Subsequently, the heart rate was reduced from 137 ± 26 bpm (before the start of landiolol administration) to 93 ± 18 bpm (2 hours after the start of the medication, $P < 0.01$) (Fig. 2). As a consequence of antiarrhythmic treatment, the systolic blood pressure rose from 108 ± 24 mmHg (before the start of landiolol administration) to 120 ± 19 mmHg (2 hours after the start of the medication, $P < 0.05$) (Fig. 3). The maximum dosage given was 7.5 ± 7.6 $\mu g \bullet kg^{-1} \bullet min^{-1}$. Reductions in the heart rate were noted even in the 2 patients who were treated for tachycardia associated with chronic atrial fibrillation. In one patient who developed an electrical storm in addition to postoperative atrial fibrillation, a complete atrioventricular block developed even at the dosage of 1 $\mu g \bullet kg^{-1} \bullet min^{-1}$ but cessation of medication restored the previous state.

In both of the 2 patients who were treated to prevent paroxysmal atrial fibrillation, it was possible to maintain the sinus rhythm when landiolol administration was started when atrial extrasystoles repeatedly developed.

4. Discussion

Landiolol is outstanding in its immediate efficacy and adjustability [8]. Because of its high selectivity with β_1 receptors, [6] it is readily administered to patients with respiratory tract diseases. Recently there have been occasional reports in which landiolol, with its outstanding adjustability, was found to be effective in the treatment of not only arrhythmia due to supraventricular tachycardia, [9] but also for correction of a left ventricular outflow tract obstruction [10,11] and amelioration of myocardial infarction [12]. In this country, the application of landiolol has been approved by National Health Insurance for the emergency treatment of intraoperative and postoperative arrhythmia due to supraventricular tachycardia

[13,14]. More recently, however, its clinical efficacy at a low dosage has been recognized. For the management of supraventricular arrhythmia, which is caused by surgical stress, the application of landiolol, a β blocker with an outstanding modulatory effect, is effective and therefore should be considered for inclusion in the therapeutic modalities. One of the reason why landiolol is advantageous to use is that in the advent an atrioventricular block, an adverse effect of the medication develops, the condition can be swiftly corrected by simply withdrawing the medication.

As evidenced in the current study, landiolol restores the sinus rhythm at a very high frequency in cases of supraventricular arrhythmia. Combined with nicardipine, the efficacy of landiolol has also been reported for the antihypertensive therapy of aortic aneurysms and aortic dissection, perioperative care in left ventricular outflow tract obstruction and perioperative care of cases with myocardial ischemia [15]. Further increase in the indications for landiolol over wide clinical areas is expected.

5. Conclusion

Continuous intravenous infusion of landiolol at a low dose was found to be effective for postoperative supraventricular arrhythmia. Because it is a short-acting agent, the early treatment to suit to each clinical finding was possible.

Table 1

Table 1 shows the background of patients who underwent continuous infusion of landiolol at a low dose during postoperative care

Age (Years)	70±9
Men/Women	30/10
Primary disease	
Ischemic heart disease	12
Valvular diseases	5
Aortic diseases	9
Respiratory tract diseases	5
Digestive system diseases	7
Others	2

References

[1] Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135: 1061-73.

[2] Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995; 60: 1709-15.

[3] Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997; 349: 375-80.

[4] Prabhu SD, Chandrasekar B, Murray DR, Freeman GL. β-adrenergic blockade in developing heart failure: effects on myocardial inflammatory cytokines, nitric oxide, and remodeling. Circulation 2000; 101: 2103-9. Erratum in: *Circulation* 2000; 102:141

[5] Ohtsuka T, Hamada M, Saeki H, Ogimoto A, Hiasa G. Comparison of effects of carvedilol versus *metoprolol on cytokine levels in patients with idiopathic dilated cardiomyopathy*. *Am J Cardiol* 2002; 89: 996-9.

[6] Shiroya T, Ichioka Y, Yoshida K. Nishijima K, Omawari N. Pharmacological studies of ONO-1101 as a β-blocking agent with high β_1-selectivity and ultra-short duration of action. Kiso To Rinsho 1997; 31: 2913-23. (in Japanese)

[7] Atarashi H, Kuruma A, Yashima M, Saitoh H, Ino T. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting β-blocker, in patients with cardiac arrhythmias. Clin Pharmacol Ther 2000; 68: 143-50.

[8] Nakashima M, Kanamaru M. Phase I study of ONO-1101, a new ultra short acting β_1-blocking agent in health volunteers. Rinsho Iyaku 2000; 16: 1531-56. (in Japanese)

[9] Tsunezuka Y, Shimizu Y, Tanaka N. Significance of administration of landiolol hydrochroride for tachyarrythmia after lung surgery. Prog Med 2007; 27: 2236-8. (in Japanese)

[10] Matsuda S, Fumisawa K, Hirashima K. Experience of anesthesia using landiolol hydrochroride for cases with gastorectomy complicated with hypotrophic cardiomyopathy. Shinyaku To Rinsho 2003; 52: 242-3, 2003. (in Japanese)

[11] Kushikata T, Hashimoto H, Hashiba E, Fukui K, Ito K. A case in which landiolol hydrochloride improved left ventricular outflow tract obstruction with systolic anterior motion of the mitral valve following the mitral valve plasty. Masui 2006; 55: 96-9. (in Japanese)

[12] Kobayashi Y, Osone J, Kiya T, Tsujiguchi N, Yoshikawa O. Low dose landiolol for the treatment of intraoperative tachyarrhthmias in four patients with cardiovascular complications. Rinsho Masui 2004; 28: 877-9. (in Japanese)

[13] Murakami M, Furuie H, Matsuguma K, Wanibuchi A, Kikawa S. Pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra short-acting β_1-selective blocker, in a dose escalation regimen in healthy male volunteers. Drug Metab Pharmacokinet 2005; 20: 337-44.

[14] Harasawa R, Hayashi Y, Iwasaki M, Kamibayashi T, Mashimo T. Bolus administration of landiolol, a short-acting, selective β_1-blocker, to treat tachycardia during anesthesia: a dose-dependent study. J Cardiothorac Vasc Anesth 2006; 20: 793-5.

[15] Wariishi S, Nishimori H, Fukutomi T, Sasaguri S. Landiol-based perioperative management: efficacy of continuous intravenous administration. Jpn J Cardiovasc Surg 2008; 37(Suppl): 307. (in Japanese)

Figure legends

Fig. 1: The number of days after surgery when the medication was started (n=36)

After the 7th day

Op: surgery; POD: number of days after surgery.

Fig. 2: Changes in heart rate (n=38)

Before the start of landiolol administration

2 hours after the start of landiolol administration

○: heart rate; *: comparison with the data before landiolol administration, $P < 0.05$.

Fig. 3: Changes in blood pressure (n=38)

Before the start of landiolol administration

2 hours after the start of landiolol administration

△ : systolic blood pressure; □: diastolic blood pressure;

*: a comparison with the value before landiolol administration, $P < 0.05$.

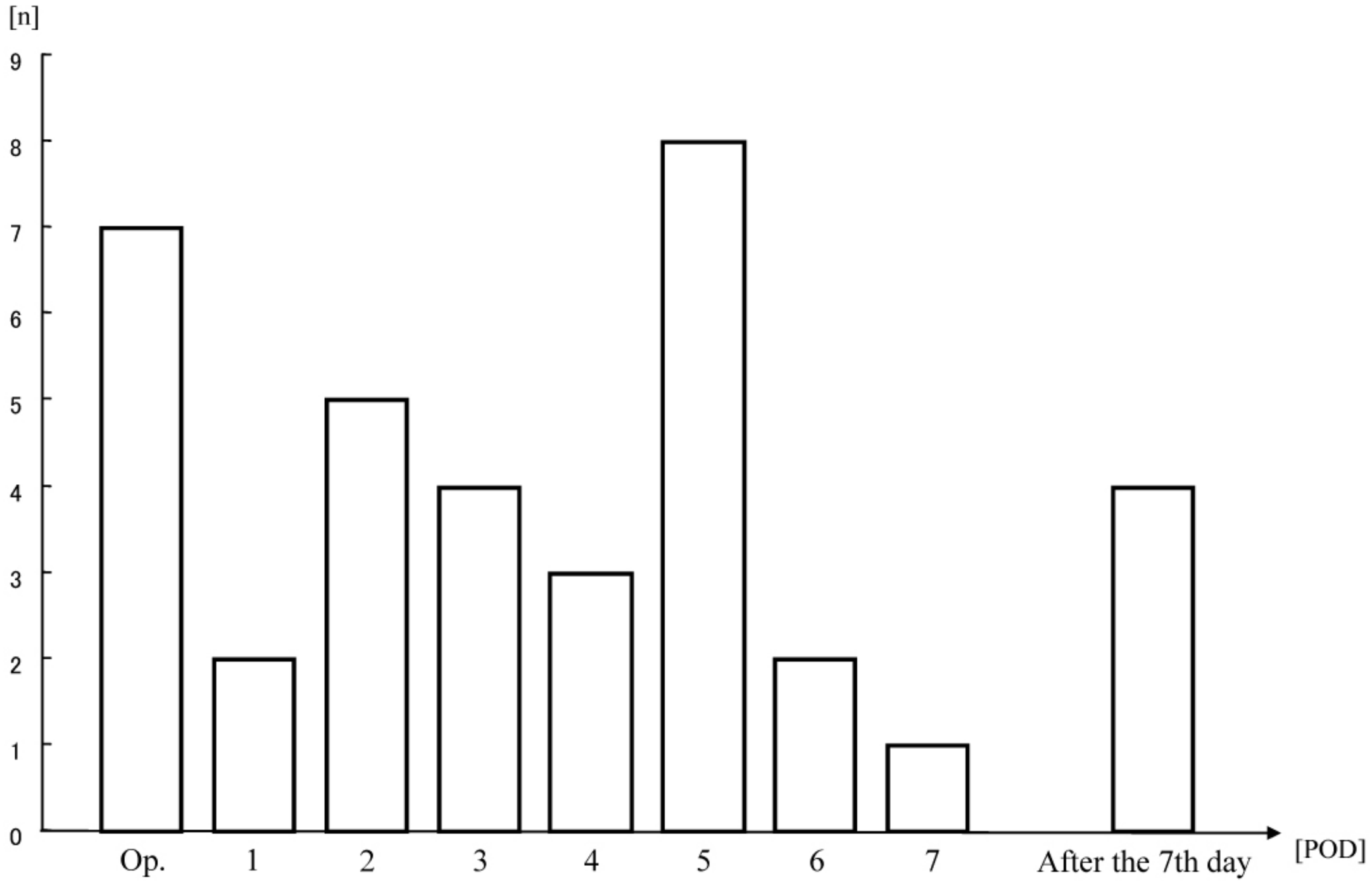

Fig. 1. The number of days after surgery when the medication was started (n=36)

Op.: surgery; POD: number of days after surgery

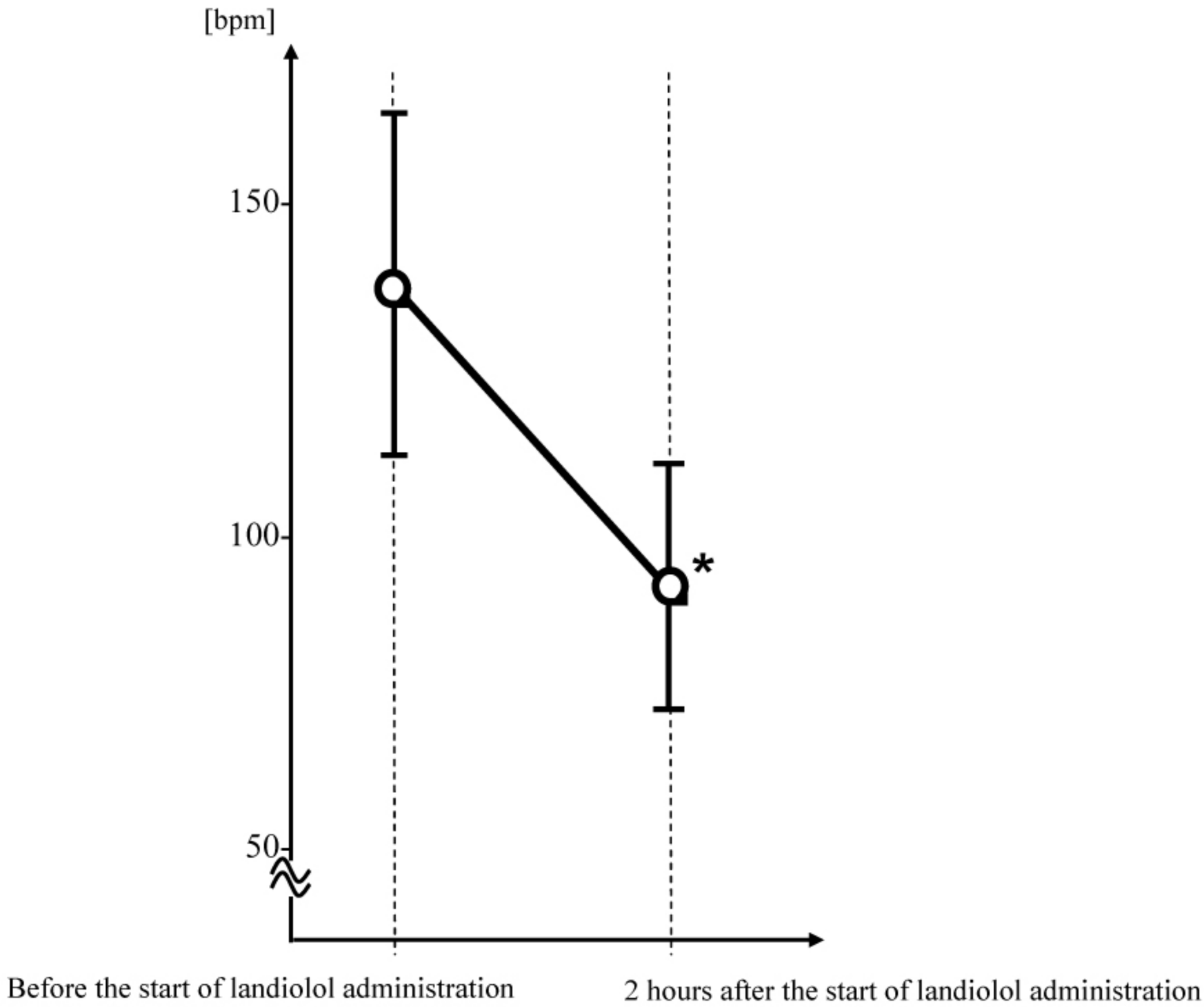

Fig. 2. Changes in heart rate (n=38)

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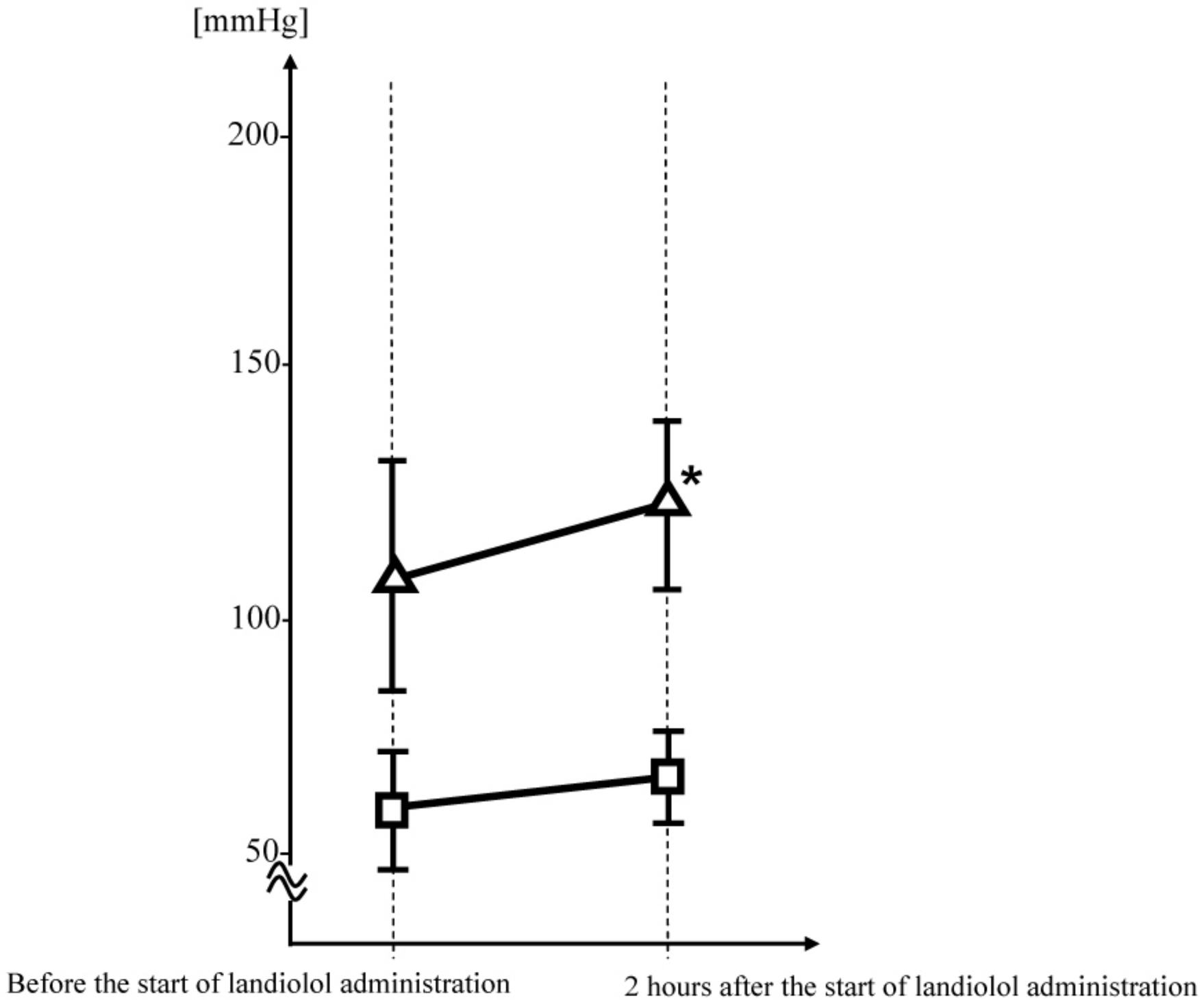

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△: systolic blood pressure; □: diastolic blood pressure;

*: a comparison with the value before landiolol administration, $P < 0.05$.