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Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts

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Abstract
Purpose. We compared the negative chronotropic and inotropic effects of landiolol and esmolol, two clinically available short-acting β1-blockers with high β1-selectivity, using whole isolated rabbit heart preparations.
Methods. Tachycardia was induced by continuous perfusion of 10^{-7} M isoproterenol, and we used concentrations of landiolol or esmolol in ascending steps ($1 \cdot 10^{-6}$, $3 \cdot 10^{-6}$, $1 \cdot 10^{-5}$, $3 \cdot 10^{-5}$, and $1 \cdot 10^{-4}$ M). Heart rate (HR), left ventricular developed pressure (LVDP), the maximal rates of left ventricular force development ($LVdP/dt_{max}$), and myocardial oxygen consumption (MVO_2) were measured and compared.
Results. Both landiolol and esmolol produced dose-dependent decreases in HR, LVDP, $LVdP/dt_{max}$, and MVO_2. The HR lowering effects of the two agents were comparable. At concentrations of $3 \cdot 10^{-5}$ and $1 \cdot 10^{-4}$ M, esmolol produced more profound depression of LVDP (47 ± 26 and 12 ± 11 mmHg, respectively; mean ± SD) and reduction of $LVdP/dt_{max}$ (650 ± 287 and 120 ± 103 mmHg·s^{-1}) than landiolol (68 ± 20 and 64 ± 20 mmHg, and 897 ± 236 and 852 ± 240 mmHg·s^{-1}, respectively). At the same concentrations, esmolol caused more profound reduction in MVO_2 (40 ± 11 and 35 ± 10 μl·min^{-1}·g^{-1}) than landiolol (50 ± 8 and 48 ± 8 μl·min^{-1}·g^{-1}), respectively.
Conclusion. Our results indicate that in the isolated rabbit heart, landiolol and esmolol had equipotent negative chronotropic effects, however, landiolol had a less potent negative inotropic effect than esmolol.

Key words Landiolol · Esmolol · Negative inotropic effect

Introduction

β-Blockers have been used extensively in the treatment of hypertension and cardiac arrhythmias during the perioperative period. Previous clinical studies have demonstrated that perioperative β-blocker usage not only reduces the incidence of cardiac events [1] but also improves the 6-month survival rate [2]. The American College of Cardiology/American Heart Association guidelines have recommended (level I) the perioperative use of β-blockers in vascular patients with a positive stress test result [3]. The guidelines recommend commencement of medication with β-blockers days to weeks before elective surgery. During surgery, however, β-blockers are often used for urgent treatment of sudden rises in blood pressure and cardiac arrhythmias. Esmolol is effective for the treatment of sudden cardiac arrhythmias in the perioperative period because of its short action and high β1 selectivity [4]. However, in patients with poor cardiac function, care should be exercised with this agent because of the frequent occurrence of hypotension; hence, its application is sometimes prohibited [5–7].

Landiolol is a newly developed β-blocker that has been used clinically in Japan only since 2002. It is reported that landiolol has short-acting features with rapid onset and a short half-life, and higher β1-selectivity compared with other currently available β-blockers [8]. In addition, landiolol induces a milder fall in blood pressure than esmolol [9].

A number of studies have compared the negative chronotropic effects of landiolol and esmolol [10,11], but few have compared their negative inotropic effects. The purpose of this study was to compare both the negative chronotropic and inotropic effects of landiolol and esmolol, using whole isolated rabbit heart preparations.

Materials and methods

This study was approved by the Animal Research Committee of Osaka City University Graduate School of Medicine. Twenty-eight New Zealand white rabbits

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of either sex (1.8–2.2 kg) were anesthetized with isoflurane (5%) in oxygen in a polyethylene box. A tracheotomy was performed, and the animals were mechanically ventilated. The chest was opened, and after intravenous heparin injection, the heart was removed and quickly mounted on a nonrecirculating Langendorff apparatus. The coronary arteries were perfused via the aorta at a constant flow of 40 ml·min^{-1} with a modified Krebs-Henseleit buffer bubbled with a mixture of 95% O_2 and 5% CO_2. The buffer contained (in mM): 118 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 25 $NaHCO_3$, 5.5 glucose, and 2.0 Na pyruvate. The pH of the perfusate was maintained between 7.36 and 7.43, and the temperature of the preparation was kept at 37.0 ± 0.3°C throughout the experiment. A thin, saline-filled latex balloon was inserted into the left ventricle and was attached to a metal cannula. The connection of this cannula to a pressure transducer allowed the measurement of isovolumetric systolic left-ventricular pressure development. The balloon volume was adjusted to maintain an initial diastolic left ventricular pressure of 5–10 mmHg during the baseline period, and this remained constant throughout the experiment.

The pressure data were recorded on a biomedical research system (LEG-1000; Nihon-Kohden, Tokyo, Japan). Left ventricular developed pressure (LVDP) was obtained by subtracting diastolic left ventricular pressure from systolic pressure, and the maximal rate of left ventricular force development ($LVdP/dt_{max}$) was determined from the left ventricular pressure signal as an index of cardiac contractility. Spontaneous heart rate (HR) was monitored with bipolar electrodes placed in the right atrial and ventricular walls. Oxygen tension in the coronary inflow and outflow were measured offline, using a self-calibrating gas analyzer (ABL-4; Radiometer, Copenhagen, Denmark). Aortic inflow oxygen tension was maintained at 570 to 650 mmHg. Myocardial oxygen consumption (MVO_2; µl·min^{-1}·g^{-1}) was calculated as $(Pa_{O_2} - Pv_{O_2}) \cdot 24$ µl O_2 / ml at 760 mmHg·CF·g heart wet weight^{-1}, where $Pa_{O_2} - Pv_{O_2}$ is the difference in oxygen tension (mmHg) between the coronary inflow and outflow, and CF is coronary flow (ml·min^{-1}) [12]. The mean wet weight of all hearts was 9.5 ± 0.5 g (± SD). All measurements were taken during the last minute of each 10-min experimental period, and were subjected to statistical analysis.

The hearts were allowed to stabilize for at least 15 min before initial baseline measurements were taken. After stabilization, four hearts, in which contractility was low (LVDP < 50 mmHg), HR was slow (<120 beats·min^{-1}), or frequent ventricular arrhythmias occurred, were excluded from the study. Subsequently, the remaining hearts were continuously perfused with 10^{-7} M isoproterenol (Proternol-L injection; Nikken Chemicals, Tokyo, Japan) to induce tachycardia, which persisted throughout the experiment. In preliminary experiments, 10^{-7} M was found to be the submaximal dose of isoproterenol to induce tachycardia, in which the HR increased by 63 ± 22% of the baseline value. After stabilization for 10 min at tachycardia, the control values were determined.

The hearts were randomly assigned to two groups (12 hearts each) receiving either landiolol (Onoact; Ono Pharmaceutical, Osaka, Japan) or esmolol (Brevibloc; Maruishi Pharmaceutical, Osaka, Japan). The concentrations tested in our study (10^{-6} to 10^{-4} M), which are equivalent to 0.546–54.6 µg·ml^{-1} landiolol and 0.332–33.2 µg·ml^{-1} esmolol, corresponded to approximate therapeutic plasma free values (corrected for plasma protein binding, in percentages) of 1.94 µg·ml^{-1} (2.4%) landiolol [13,14] and 1.31 µg·ml^{-1} (56%) esmolol [15,16], respectively. Concentrations exceeding the estimated clinical plasma concentrations were also employed to compare drug responses. Each heart was perfused using concentrations, increased in steps, of $1 \cdot 10^{-6}$, $3 \cdot 10^{-6}$, $1 \cdot 10^{-5}$, $3 \cdot 10^{-5}$, and $1 \cdot 10^{-4}$ M with one of these drugs for a period of 10 min. After the last measurement, both β-blocker and isoproterenol were discontinued, and the hearts were allowed to stabilize for 15 min before recovery measurements were taken.

All data values were expressed as means ± SD. Raw data for each functional and metabolic variable were compared by analysis of variance with repeated measures (Sigma-Stat; SPSS, Chicago, IL, USA). Post-hoc analyses were performed with Holm-Sidak tests to compare absolute group means for each variable measured at the same drug concentration and individual drug concentrations against the control. Paired observations were analyzed with the paired *t*-test. A *P* value of less than 0.05 was considered statistically significant. The main results are summarized in the text, Table 1, and Figures.

Results

After the initial stabilization of the isolated hearts, there was no difference in baseline values between the two groups, and there was no difference in the control values after isoproterenol-induced tachycardia. All recovery values returned to baseline levels, with no significant differences between the two groups (Table 1).

Figure 1 illustrates HR changes induced by the administration of landiolol and esmolol under tachycardia induced by continuous perfusion of isoproterenol. HRs after the administration of landiolol at concentrations of $1 \cdot 10^{-6}$, $3 \cdot 10^{-6}$, $1 \cdot 10^{-5}$, $3 \cdot 10^{-5}$, and $1 \cdot 10^{-4}$ M were 263 ± 32, 196 ± 28, 177 ± 24, 162 ± 25, and 156 ± 26 beats·min^{-1}, respectively, while those after the administration of esmolol at concentrations of $1 \cdot 10^{-6}$, $3 \cdot 10^{-6}$,

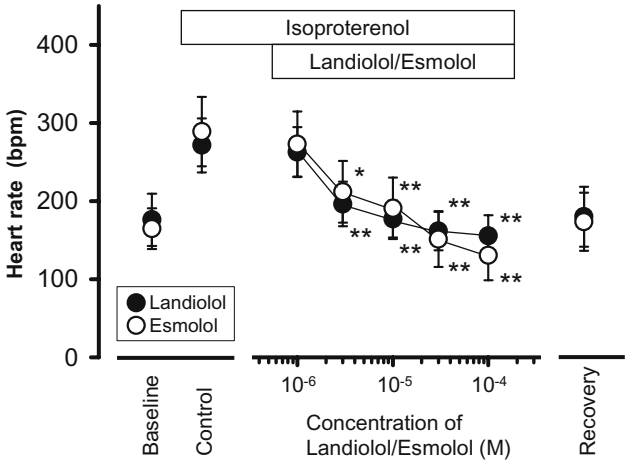

Fig. 1. Effects of landiolol and esmolol on heart rate (HR) in isolated heart constantly perfused with isoproterenol. *Baseline* values represent values after initial stabilization. *Control* denotes values after administration of 10^{-7} M isoproterenol. *Recovery* denotes values after withdrawal of both landiolol/esmolol and isoproterenol. Values are means ± SD; $n = 12$ in each group. $*P < 0.05$ and $**P < 0.01$ vs control within the group. Note the dose-dependent decrease in HR, and the lack of difference between the effects of the two agents

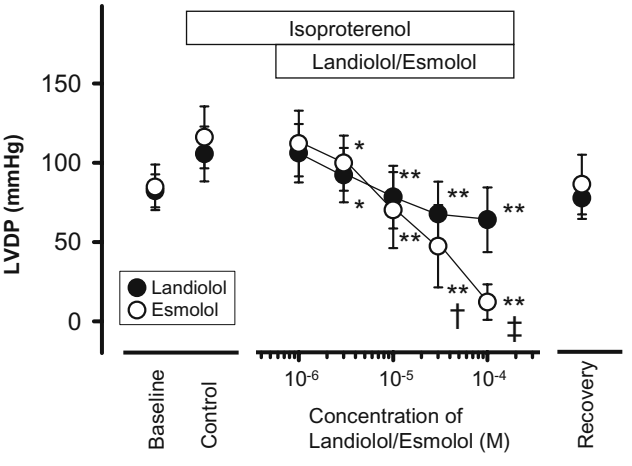

Fig. 2. Effects of landiolol and esmolol on left ventricular developed pressure (*LVDP*) in isolated heart constantly perfused with isoproterenol. *Baseline* values represent values after initial stabilization. *Control* denotes values after administration of 10^{-7} M isoproterenol. *Recovery* denotes values after withdrawal of both landiolol/esmolol and isoproterenol. Values are means ± SD; $n = 12$ in each group. $*P < 0.05$ and $**P < 0.01$ vs control within the group; $^{\dagger}P < 0.05$ and $^{\ddagger}P < 0.01$ vs landiolol. Note the dose-dependent depression of LVDP, and the greater severity of depression with esmolol than with landiolol at concentrations of $3{\cdot}10^{-5}$ M and $1{\cdot}10^{-4}$ M

Table 1. Baseline values after initial stabilization, control values after continuous infusion of 10^{-7} M isoproterenol, and recovery values after withdrawal of both landiolol/esmolol and isoproterenol

	Landiolol	Esmolol
Heart rate (beats·min^{-1})		
Baseline	176 ± 34	165 ± 26
Control	271 ± 35	289 ± 44
Recovery	180 ± 39	174 ± 37
LVDP (mmHg)		
Baseline	82 ± 3	85 ± 14
Control	106 ± 17	116 ± 20
Recovery	78 ± 13	86 ± 19
LVdP/dt$_{max}$ (mmHg·s^{-1})		
Baseline	1084 ± 173	991 ± 228
Control	1269 ± 180	1351 ± 222
Recovery	1049 ± 238	1087 ± 263
MVO$_2$ (µl·min^{-1}·g^{-1})		
Baseline	52 ± 9	53 ± 8
Control	67 ± 10	70 ± 9
Recovery	53 ± 12	56 ± 10

Data values are means ± SD; $n = 12$ rabbits in each group
LVDP, left ventricular developed pressure; LVdP/dt$_{max}$, maximal rate of left ventricular force development; MVO$_2$, myocardial oxygen consumption; baseline, value after initial stabilization; control, value after continuous administration of 10^{-7} M isoproterenol; recovery, value after withdrawal of both landiolol/esmolol and isoproterenol

$1{\cdot}10^{-5}$, $3{\cdot}10^{-5}$, and $1{\cdot}10^{-4}$ M were 273 ± 42, 212 ± 40, 191 ± 39, 151 ± 36, and 130 ± 32 beats·min^{-1}, respectively, indicating no significant difference at any concentration between the two groups. Although no significant difference in HR from the control values was found at $1{\cdot}10^{-6}$ M in both groups, a dose-dependent decrease was observed at concentrations of more than $1{\cdot}10^{-6}$ M for both agents. HRs recovered to baseline levels in both groups after discontinuation of the β-blocker and isoproterenol.

At concentrations of more than $1{\cdot}10^{-6}$ M, LVDP decreased dose-dependently in both groups (Fig. 2). At $3{\cdot}10^{-5}$ M, LVDP values were 68 ± 20 and 47 ± 26 mmHg in the landiolol group and the esmolol group, respectively, while at $1{\cdot}10^{-4}$ M, LVDP values were 64 ± 20 and 12 ± 11 mmHg, respectively, indicating that esmolol induced a significantly larger reduction in LVDP than landiolol. The LVDP value in the esmolol group at concentrations of more than $1{\cdot}10^{-5}$ M was markedly lower than the baseline value, while at $1{\cdot}10^{-4}$ M, it was close to zero. LVDP values also recovered to baseline levels in both groups after discontinuation of the β-blocker and isoproterenol.

In a similar manner, LVdP/dt$_{max}$ values were dose-dependently reduced at concentrations of more than $1{\cdot}10^{-6}$ M in both groups (Fig. 3). At $3{\cdot}10^{-5}$ M, the LVdP/dt$_{max}$ values were 897 ± 236 and 650 ± 287 mmHg·s^{-1} in the landiolol group and esmolol group, respectively, while at $1{\cdot}10^{-4}$ M, these values were 852 ± 240 and 120 ± 103 mmHg·s^{-1}, respectively. The LVdP/dt$_{max}$ values also recovered to baseline levels in both groups after discontinuation of the β-blocker and isoproterenol.

Finally, landiolol and esmolol dose-dependently decreased MVO$_2$ (Fig. 4). At a concentration of

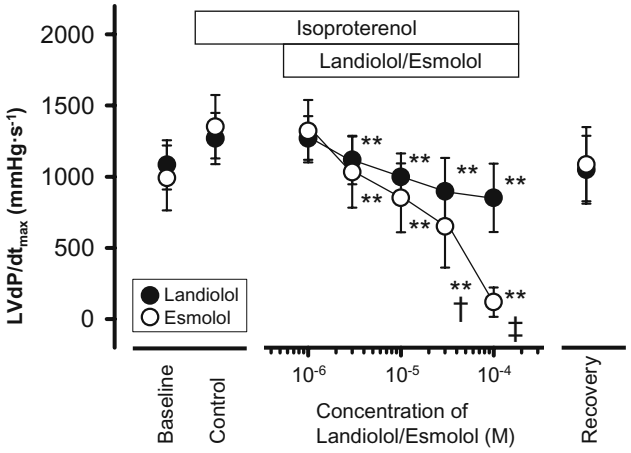

Fig. 3. Effects of landiolol and esmolol on the maximal rate of left ventricular force development ($LVdP/dt_{max}$) in isolated heart constantly perfused with isoproterenol. *Baseline* values represent values after initial stabilization. *Control* denotes values after administration of 10^{-7} M isoproterenol. *Recovery* denotes values after withdrawal of both landiolol/esmolol and isoproterenol. Values are means ± SD; $n = 12$ in each group. $^{**}P < 0.01$ vs control within the group; $^{\dagger}P < 0.05$ and $^{\ddagger}P < 0.01$ vs landiolol. Note the dose-dependent fall in $LVdP/dt_{max}$ and the greater depression with esmolol than with landiolol at concentrations of $3{\cdot}10^{-5}$ M and $1{\cdot}10^{-4}$ M

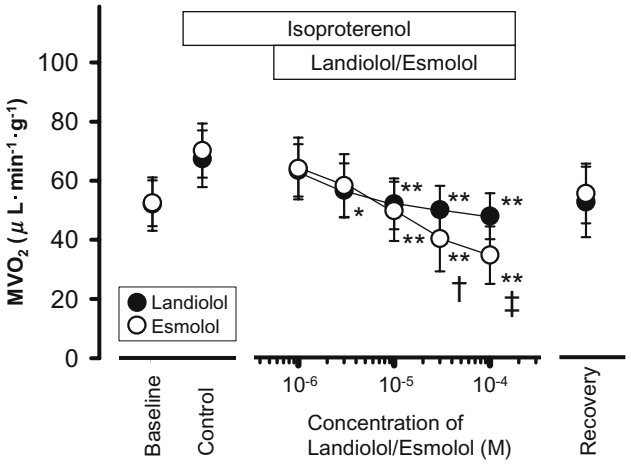

Fig. 4. Effects of landiolol and esmolol on myocardial oxygen consumption (MVO_2) in isolated heart constantly perfused with isoproterenol. *Baseline* values represent values after initial stabilization. *Control* denotes values after administration of 10^{-7} M isoproterenol. *Recovery* denotes values after withdrawal of both landiolol/esmolol and isoproterenol. Values are means ± SD; $n = 12$ in each group. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs control within the group; $^{\dagger}P < 0.05$ and $^{\ddagger}P < 0.01$ vs landiolol. Note the dose-dependent decrease in MVO_2 and the greater reduction with esmolol than with landiolol at concentrations of $3{\cdot}10^{-5}$ M and $1{\cdot}10^{-4}$ M

$3 \cdot 10^{-5}$ M, the MVO_2 values were 50 ± 8 and 40 ± 11 μl·min^{-1}·g^{-1} in the landiolol group and esmolol group, respectively, while at $1 \cdot 10^{-4}$ M, these values were 48 ± 8 and 35 ± 10 μl·min^{-1}·g^{-1}, respectively, indicating that esmolol induced a more significant reduction in MVO_2 than landiolol. MVO_2 values also recovered to baseline levels in both groups after discontinuation of β-blocker and isoproterenol.

Discussion

In this study, landiolol and esmolol showed equivalent negative chronotropic effects against isoproterenol-induced tachycardia. However, the negative inotropic effect induced by esmolol was stronger and myocardial oxygen consumption (MVO_2) was markedly reduced by esmolol. Our Langendorff preparation perfused at a constant flow allowed us to measure the effect of the two drugs on ventricular function (LVDP and $LVdP/dt_{max}$) and MVO_2. Because the preparation is infused with Krebs solution, the amount of drug in the perfusate corresponds to the free drug concentration when protein-bound drugs such as β-blockers are employed. In this study, rabbits were selected as the study animals because interspecies comparisons have revealed that rabbits are relatively closer to humans in terms of ventricular contractile functions; the order of the similarity is usually human, dog, rabbit, rat, and mouse, in this decreasing order [17].

Although esmolol is administered during the perioperative period, its use has been limited because of its notable inhibitory effects on the circulation [5–7]. In the present study, esmolol demonstrated a strong inhibitory effect on cardiac function. Specifically, following the perfusion of esmolol at $1 \cdot 10^{-6}$-$3 \cdot 10^{-6}$ M, i.e., close to the concentration used clinically, LVDP, a parameter that reflects cardiac contractility, was dose-dependently diminished, but was still beyond the baseline value; these findings can be accounted for by the β-blocking effects of esmolol. However, when esmolol was administered at higher concentrations ($3 \cdot 10^{-5}$–$1 \cdot 10^{-4}$ M), it produced a much stronger effect on LVDP and reduced it to a level less than the baseline value. The same was true for $LVdP/dt_{max}$. To our knowledge, the mechanism of the inhibitory effects of esmolol on the circulation is still unknown [7]; however, the results of various studies make it unlikely that its circulatory inhibitory effects are due to its β-blocking effects, leading us to consider the possible involvement of other mechanisms, such as inhibition of the calcium current [18] or sodium current [19]. Esmolol has been used during cardiac surgery to induce minimal myocardial contraction while maintaining continuous normothermic perfusion to avoid ischemia, and the agent has been shown to provide myocardial protection equivalent to cardioplegia [20]. The exact mechanism(s) of the effects of cardioprotective agents is/are not fully understood, but β-blockers are thought to exert beneficial effects on the ischemic heart by low-

ering MVO_2 consequent to reduced contractility and HR. The results of the present study also confirm the reported features of esmolol; i.e., esmolol inhibits MVO_2 dose-dependently and has myocardial protective effects. Furthermore, myocardial contraction in the presence of esmolol at $1 \cdot 10^{-4}$ M was almost zero in the present study, whereas at higher concentrations (approximately 1.0 mM), esmolol was reported to induce cardiac arrest [21].

Despite the numerous reports on esmolol, only a few studies have examined the effects of landiolol. Landiolol was developed by modifying the chemical structure of esmolol to attain more remarkable cardioselectivity and higher potency as a β-blocker, without increasing the half-life [8]. Landiolol is an injectable ultra-short-acting β1-selective blocker with a potency ratio (β1/β2) of 255, compared with 33 for esmolol [8]. Landiolol is rapidly hydrolyzed to an inactive form by both carboxylesterase in the liver and pseudocholinesterase in the plasma, resulting in the shortening of its elimination half-life to about 4 min [8]. In the present study, we compared the potencies of landiolol and esmolol based on their molar concentrations. Our results indicated that the negative chronotropic effects of the two drugs were comparable. In many studies, landiolol and esmolol have been compared from various aspects, and the results obtained have shown that the former is stronger than the latter. However, marked variability was noted in their potencies, from slightly more potent [10] to several times more potent [11,22], or sometimes to nine times more potent [8]. It is postulated that these differences between studies might be due to several factors, including methodological differences, differences in species, and the presence or absence of isoproterenol-induced tachycardia. However, in in vivo studies, it is necessary to take into consideration the large differences in the protein-binding ratios of the two drugs (2.4% for landiolol [14] and 56% for esmolol [16]).

The present study showed that landiolol had a weaker negative inotropic effect than esmolol. Perfusion of landiolol at higher concentrations in isoproterenol-induced tachycardia resulted in reductions of both LVDP and $LVdP/dt_{max}$ to slightly below baseline. These results indicate that the negative inotropic effects of landiolol, unlike those of esmolol, could be explained by its β-blocking activity. It has been documented that landiolol has a less potent effect on blood pressure in animal models than esmolol [9,11,22]. Our results are in agreement with these findings. In clinical studies, patients treated with landiolol were reported to be less vulnerable to hypotension [23].

The administration of β-blockers plays an important role in preventing perioperative myocardial ischemia in patients with coronary artery diseases [24]; however, tachycardia should be avoided without reducing blood pressure, because an adequate blood pressure level is required to maintain coronary perfusion [25]. In the present study, we used a denervated rabbit model, and there are several potential limitations in explaining the clinical effectiveness of landiolol in such a model. However, if tachycardia can be controlled by landiolol with minimal reduction of blood pressure, this agent could be effective especially in patients with poor cardiac function or in procedures such as off-pump coronary artery bypass grafting surgery, in which blood pressure control is essential.

In conclusion, using a whole-organ preparation, we have demonstrated that landiolol and esmolol, two clinically available short-acting β1-blockers with high β1-selectivity, have equipotent negative chronotropic effects; however, landiolol exhibited a less potent negative inotropic effect than esmolol. We believe that landiolol is effective in the treatment of tachycardia during the perioperative period. These findings, however, should be confirmed in clinical settings.

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