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ORIGINAL ARTICLE

Landiolol does not enhance the effect of ischemic preconditioning in isolated rat hearts

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Abstract
Purpose To determine the effect of landiolol on ischemic preconditioned rat hearts.
Methods Isolated perfused rat hearts were divided into 8 groups. In the control group, there was no treatment before the 30-min global ischemia. In the landiolol infused groups, landiolol (100, 300, and 500 μM) was infused without ischemic preconditioning (IPC). In other groups, hearts were pretreated with 2 episodes of 5-min global ischemia and reperfusion before the 30-min ischemia. During the preconditioning, landiolol (0, 100, 300, and 500 μM) was infused.
Results Recoveries of coronary flow (CF) and myocardial oxygen consumption (MVO_2) at the 120th min after global ischemia to 86 ± 18 and 112 ± 19% of the baseline in the IPC group was, respectively, significantly greater than that to 65 ± 10 and 72 ± 10% in the control group. Landiolol 300 μM also increased the CF and MVO_2 significantly (97 ± 19 and 98 ± 39%) compared to the control. IPC + landiolol 500 μM reduced the increase in LV end-diastolic pressure significantly compared to the control. IPC, landiolol (100, 300, and 500 μM), and IPC + landiolol (100, 300, and 500 μM) all decreased infarct sizes significantly to 23.5 ± 15.2, 29.8 ± 12.1, 30.2 ± 13.3, 22.8 ± 14.8, 21.6 ± 7.8, 34.2 ± 14.7 and 25.5 ± 11.3% of the total left ventricular mass, respectively, compared to the control (53.3 ± 12.5%), but there were no significant differences among these groups.
Conclusion IPC and landiolol have cardioprotective effects on ischemia–reperfusion injury in isolated rat hearts, but pretreatment with landiolol does not enhance the cardioprotective effect of IPC.

Keywords Landiolol · Preconditioning · Ischemia

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Introduction

Ischemic preconditioning (IPC) is carried out by brief and repeated episodes of ischemia/reperfusion. IPC has been proven to have a protective effect on many tissues, as well as an effect on attenuating postischemic cardiac dysfunction [1–3]. In 1991, the adenosine A1 receptor was found to trigger ischemic preconditioning in rabbit hearts [4], and it has now been shown that this preconditioning protection is receptor mediated [5]. Ischemia-induced activation of the β-adrenergic signaling pathway during preconditioning should also be considered a trigger in eliciting preconditioning [6]. Mieno and his colleagues [7] found that activation of the β2-adrenergic receptor plays a pivotal role in generating the protective effect of ischemic preconditioning in rat hearts. Spear et al. [8] found that the β1-adrenergic receptor plays a dual role in myocardial ischemic damage: it contributes to ischemia–reperfusion damage as well as playing a role in ischemic preconditioning.

β blockade has also been reported to be effective in attenuating post-ischemic cardiac dysfunction [9, 10], so β blockade and preconditioning may both have an additional effect on ischemia–reperfusion injury. Wikström and colleagues [11] found no further improvement of ischemic myocardial metabolism by combining preconditioning with β blockade, whereas another study found

that pre-ischemic landiolol infusion may enhance the cardioprotective effect of ischemic preconditioning in isolated rabbit hearts [12].

Landiolol is a highly selective β1-blocker with an ultra-short acting time and a shorter half-time (4 min) than other β-blockers [13], and has also been proven to be a positive effector in the recovery from ischemia–reperfusion injury [9].

The present study was planned to clarify: (1) whether IPC has a cardioprotective effect on postischemic rat hearts, and (2) whether landiolol has an effect on IPC in isolated rat hearts, and, if yes, whether this effect is dose related.

Materials and methods

Fifty-six male Sprague–Dawley rats weighing 285–345 g were used in this study. All animals received humane care in accordance with the Guidelines for Animal Experimentation of Hamamatsu University School of Medicine, and the experimental protocols were approved by the Ethics Review Committee for Experimental Animals of this institution.

Rats (SLC, Shizuoka, Japan) were anesthetized with diethyl ether followed by thoracotomies. After that, the heart was rapidly excised and cannulated through the aorta on a Langendorff apparatus (WORKING L2; Primetech, Tokyo, Japan), where the heart temperature was maintained at 37°C by a warming heart chamber which was connected to a thermostatically controlled water circulator (Thermo minder; Taitec, Saitama, Japan). It was then perfused at 100 cmH_2O with Krebs–Henseleit bicarbonate (KHB) buffer solution (NaCl 119 mM, KCl 6.0 mM, $CaCl_2$ 1.24 mM, $NaHCO_3$ 20.1 mM, KH_2PO_4 1.24 mM, $MgSO_4$ 1.24 mM, glucose 11.2 mM at a PH of 7.4), which was oxygenated with 95% O_2 and 5% CO_2 at 37°C.

A saline-filled balloon was inserted into the left ventricle (LV) to measure left ventricular pressure (LVP) through a pressure transducer (MP5200; Edwards Lifesciences, Irvine, CA), at the same time LV end-diastolic pressure (LVEDP) was set to be 5–10 mmHg by initially adjusting the volume of the balloon, and the volume was kept constant throughout the experiment.

Coronary flow (CF) was measured with an electromagnetic flowmeter (MVF-3200; Nihon Kohden, Tokyo, Japan) that was placed directly into the aortic inflow line. Hemodynamic variances such as heart rate (HR), LV peak systolic pressure (LVSP), and LVEDP were measured via PowerLab Systems (ML840; AD Instruments, Colorado Springs, CO) pressure amplifier (AP-641G Blood Pressure Amplifier; Nihon Kohden). Left ventricular developed pressure (LVDP) was calculated as follows:

$$\text{LVDP} = \text{LVSP} - \text{LVEDP (mmHg)}$$

Hemodynamic variances and CF were monitored with PowerLab Systems. Data were acquired after 20 min of stabilization, before the 30 min of global ischemia, 30 min after reperfusion, 60 min after reperfusion, and 120 min after reperfusion. The exclusion criteria included LVDP of less than 40 mmHg or paced heart rate less than 290 beats/min. Five rats met the exclusion criteria and were excluded.

Hearts were paced from the beginning to the end of the experiment with a pacing rate set to be 110% of their own rates to eliminate the influence of heart rate.

As shown in Fig. 1, 56 rats were randomly divided into 8 groups: control (no treatment before ischemia), IPC (ischemic preconditioning), L100 (landiolol 100 μM infused), L300 (landiolol 300 μM infused), L500 (landiolol 500 μM infused), IPC + L100 (preconditioning with landiolol 100 μM infused), IPC + L300 (preconditioning with landiolol 300 μM infused), and IPC + L500 (preconditioning with landiolol 500 μM infused); the concentrations of landiolol were based on previous studies [14, 15]. After 20 min of stabilization, in the IPC, IPC + L100, IPC + L300, and IPC + L500 groups, hearts were treated with a 5-min perfusion of different concentrations of landiolol (0, 100, 300, and 500 μM) together with KHB solution, then with two episodes of 5 min global ischemia + 5 min reperfusion before the 30-min global ischemia. Also, during the 5-min reperfusions, different concentrations of landiolol were perfused together with KHB solution. Finally, there was a 120-min reperfusion.

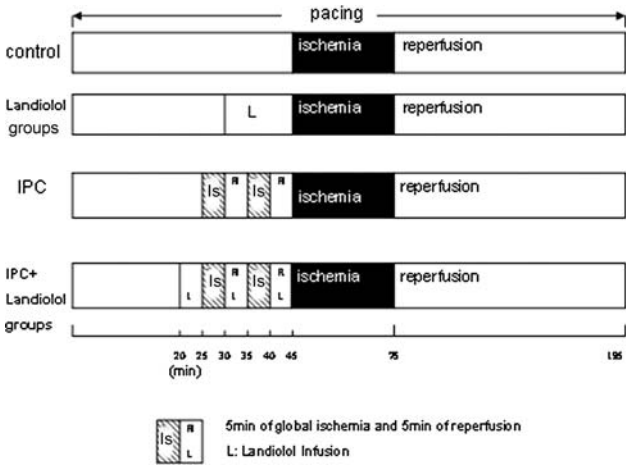

Fig. 1 Experimental protocol $n = 7$ each; pacing rate = 110% of its own rate. *IPC* Ischemic preconditioning, *Is* ischemia. *Landiolol groups*: 100, 300, and 500 μM of landiolol were infused with Krebs–Henseleit bicarbonate buffer solution. *IPC + Landiolol groups*: 100, 300, and 500 μM of landiolol were infused with Krebs–Henseleit bicarbonate buffer solution during preconditioning

Hearts without preconditioning received a 45-min stabilization (control) or a 15-min perfusion of landiolol (L100, L300, and L500 groups) alone, a 30-min global ischemia, and a 120-min reperfusion.

After 20 min of stabilization, before the 30-min global ischemia, at the 30th, 60th and 120th min of reperfusion, samples were collected from the inlet of the aortic cannulation and the outlet of the heart warming chamber, and then analyzed by blood gas analyzer (ABL77 series; Radiometer, Copenhagen). The MVO_2 was calculated as follows:

$$MVO_2(\mu l/min) = (PaO_2 - PVO_2) * \alpha' * CF$$

(As per the Flick principle with use of the Bunsen absorption coefficient $\alpha' = 0.036$ μl/mmHg/ml at 37°C)

After the 120-min reperfusion, the heart was removed from the Langendorff apparatus. The heart was then trimmed to leave only the left ventricular wall. After freezing slightly with nitrogen (N), the heart was sliced into cross-sections of 2 mm with a heart slicer (Rat Heart Matrix, RHM-4000C; ASI Instruments, Warren, MI), the cross-sections were then incubated at 37°C for 5 min in 1% 2,3,5-triphenyltetrazolium chloride in phosphate-buffered saline. After that, slices were fixed on a transparent plastic box, immersed in water, and a digital camera (Canon EOS Kiss Digital X) was used to take pictures with specific speed and iris. Finally, analysis software (programmed by co-author T.K.) was used to determine the ratio of infarct size according to the weights of the slices.

All values were expressed in mean ± SD. The infarct size was analyzed by one-way analysis of variance (ANOVA) followed by LSD post hoc test. Hemodynamic data and MVO_2 were analyzed by repeated measure ANOVA followed by the LSD post hoc test. Significant statistical differences were considered to be $P < 0.05$.

Results

At the baseline, as shown in Table 1, no significant differences were found among all groups in body weight, HR, CF, LVDP, LVEDP, or MVO_2.

IPC + L300 and IPC + L500 both had significant decreases in the elevation of LVEDP at the 30th and 60th min of reperfusion compared to the control. The elevation in LVEDP of IPC + L500 at the 120th min of reperfusion was significantly smaller than that of the control, L100, and L300 groups. IPC, IPC + L100, IPC + L300, and IPC + L500 all showed significant decreases in the elevation of LVEDP compared with L100.

Both L300 and L500 decreased CF significantly before ischemia compared to the control and IPC. Both IPC and L300 showed significantly increased recovery in CF compared to the control group during reperfusions. L500, IPC + L100, and IPC + L300 significantly decreased CF compared to L300. IPC + L500 resulted in an increased recovery in CF compared with the control group at the 30th and 60th min of reperfusion (Table 2).

MVO_2 of the IPC and L300 groups had significantly greater recoveries than that of the control group during reperfusions. IPC + L500 also caused similar changes at the 30th and 60th min of reperfusion, but finally no significant difference was observed compared to the control group in MVO_2. L300, L500, and IPC + L300 significantly decreased the MVO_2 before ischemia compared to the control and IPC groups. IPC + L100, IPC + L300, and IPC + L500 resulted in even worse recovery than that of the IPC group at the 120th min of reperfusion (Fig. 2).

With regard to infarct size, IPC, L100, L300, L500, IPC + L100, IPC + L300, and IPC + L500 significantly attenuated myocardial infarction sizes to 23.5 ± 15.2, 29.8 ± 12.1, 30.2 ± 13.3, 22.8 ± 14.8, 21.6 ± 7.8, 34.2 ± 14.7, and 25.5 ± 11.3%, respectively, compared to 53.3 ± 12.5% for the control group—but no significant

Table 1 Baseline

	Control	IPC	L100	L300	L500	IPC + L100	IPC + L300	IPC + L500	*P* value
LVDP (mmHg)	86 ± 11	81 ± 11	93 ± 16	83 ± 12	89 ± 26	82 ± 11	78 ± 21	86 ± 26	0.795
LVEDP (mmHg)	7.9 ± 2.1	8.1 ± 2.0	8.4 ± 1.2	7.6 ± 1.7	9.0 ± 1.6	8.7 ± 0.8	7.8 ± 1.5	6.9 ± 1.2	0.321
CF (ml/min)	16.5 ± 4.7	17.4 ± 1.9	14.7 ± 4.3	13.4 ± 4.1	14.3 ± 1.8	17.2 ± 3.8	17.0 ± 5.6	15.7 ± 5.0	0.472
HR (beat/min)	327 ± 10	331 ± 16	326 ± 10	314 ± 13	326 ± 19	327 ± 14	333 ± 18	331 ± 14	0.347
Weight (g)	310 ± 20	305 ± 10	307 ± 9	304 ± 8	308 ± 5	303 ± 4	301 ± 10	305 ± 12	0.783
MVO_2 (μl/min)	180 ± 36	173 ± 59	234 ± 54	192 ± 38	227 ± 50	199 ± 49	245 ± 67	204 ± 43	0.1

LVDP Left ventricular developed pressure, *LVEDP* left ventricular end-diastolic pressure, *CF* coronary flow, *HR* heart rate, *MVO_2* myocardial oxygen consumption, *IPC* ischemic preconditioning, *L100, 300, 500* landiolol (100, 300 or 500 μM) was perfused with Krebs–Henseleit bicarbonate buffer solution without ischemic preconditioning, *IPC + L (100, 300, 500)* landiolol (100, 300 or 500 μM) was perfused with Krebs–Henseleit bicarbonate buffer solution during ischemic preconditioning

Table 2 Hemodynamic changes

	Baseline	BeforeIS	Reper30	Reper60	Reper120
LVDP (% baseline value)					
Control	100	91 ± 14	86 ± 36	100 ± 16	84 ± 18
IPC	100	81 ± 10	103 ± 38	113 ± 9	98 ± 9
L100	100	74 ± 6	69 ± 50	96 ± 20	82 ± 18
L300	100	58 ± 5	101 ± 28	98 ± 22	79 ± 17
L500	100	52 ± 9	76 ± 64	111 ± 32	81 ± 28
IPC + L100	100	59 ± 22	95 ± 35	93 ± 28	87 ± 19
IPC + L300	100	62 ± 24	96 ± 20	92 ± 20	75 ± 18
IPC + L500	100	60 ± 26	122 ± 50	112 ± 33	85 ± 21
LVEDP (% baseline value)					
Control	100	112 ± 11	466 ± 180	371 ± 148	374 ± 147
IPC	100	142 ± 19	316 ± 219	269 ± 83	299 ± 89
L100	100	106 ± 6	553 ± 264 #	405 ± 97 #	438 ± 74 #
L300	100	107 ± 42	362 ± 162	357 ± 125	399 ± 130
L500	100	121 ± 26	483 ± 291	308 ± 100	316 ± 147
IPC + L100	100	156 ± 74	295 ± 158 ☆	296 ± 134	291 ± 95 ☆
IPC + L300	100	122 ± 27	236 ± 119 *,☆,⊙	228 ± 114 *,☆,†	246 ± 125 ☆,†
IPC + L500	100	143 ± 14	198 ± 72 *,☆,⊙	209 ± 106 *,☆,†	212 ± 135 *,☆,†
CF (% baseline value)					
Control	100	108 ± 20	77 ± 11	72 ± 9	65 ± 10
IPC	100	118 ± 20	103 ± 17 *	95 ± 17 *	86 ± 18 *
L100	100	86 ± 20 #	93 ± 10	80 ± 9 §	77 ± 9
L300	100	74 ± 12 *,#,§	113 ± 12 *,☆	109 ± 14 *,☆	97 ± 19 *,☆
L500	100	66 ± 18 *,#,§	93 ± 11 †,§	86 ± 10 †,§	68 ± 19 †
IPC + L100	100	90 ± 32 #	95 ± 12 §	82 ± 10 †,§	69 ± 13 †
IPC + L300	100	85 ± 42 #	86 ± 26 †,§	77 ± 23 #,†,§	59 ± 21 #,†,§
IPC + L500	100	107 ± 15	117 ± 30 *,☆	108 ± 23 *	82 ± 27

Symbols indicate significance: *$P < 0.05$ compared to control, #$P < 0.05$ compared to IPC, ☆$P < 0.05$ compared to L100, †$P < 0.05$ compared to L300, §$P < 0.05$ compared to IPC + L500, ⊙$P < 0.05$ compared to L500

LVDP Left ventricular developed pressure, *LVEDP* left ventricular end-diastolic pressure, *CF* coronary flow, *baseline* 20 min after stabilization, *beforeIS* before 30 min of ischemia, *reper30, 60, 120* 30, 60, 120 min of reperfusion, *IPC* ischemic preconditioning, *L100, 300, 500* landiolol (100, 300, or 500 μM) was perfused with Krebs–Henseleit bicarbonate buffer solution without ischemic preconditioning, *IPC + L(100, 300, 500)* landiolol (100, 300 or 500 μM) was perfused with Krebs–Henseleit bicarbonate buffer solution during ischemic preconditioning

difference was found among IPC, L100, L300, L500, IPC + L100, IPC + L300, and IPC + L500 (Fig. 3).

Discussion

In our study, we show: (1) IPC increased the recovery of CF and MVO_2 and reduced infarct size; (2) L300 increased the recovery of CF and MVO_2 and reduced infarct size; L100 and L500 also reduced infarct size; (3) IPC + landiolol groups caused some significant decreases in LVEDP (such as IPC + L500), but infarct sizes were similar to those of IPC and landiolol groups; and (4) landiolol did not enhance the postischemic cardioprotective effect of IPC.

Kurosawa et al. [14] showed in their study that 20 μM landiolol had no cardioprotective effect, but 100 and 500 μM landiolol did. Sakanashi et al. [15] reported that landiolol at 300 μM ameliorated myocardial ischemia–reperfusion injuries; in our study, the findings are similar to their reports.

To assess the effectiveness of preconditioning, there are some indexes to reference. The reduction of the infarct size is considered the gold standard [5]. Although IPC + L500 did cause a significant decrease in the elevation of LVEDP compared to the control, there was no significant difference in infarct size among the IPC, landiolol, and IPC + landiolol groups, which led us to conclude that in our study landiolol did not improve the effect of preconditioning.

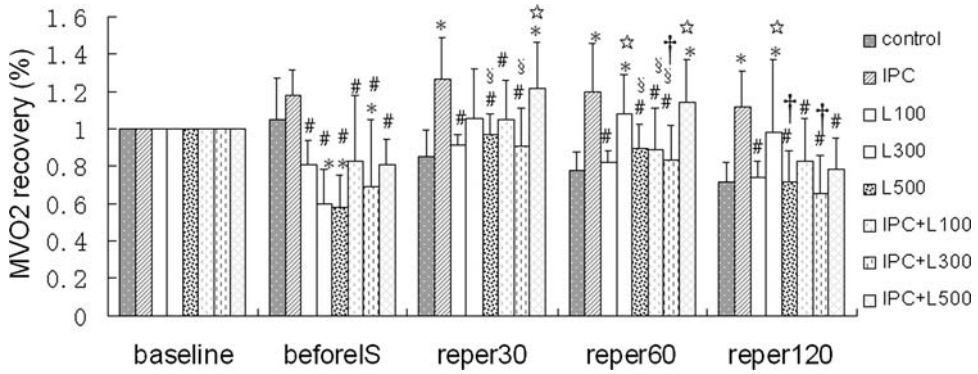

Fig. 2 Myocardial oxygen consumption (MVO_2) recovery of each group. *$P < 0.05$ compared to control, #$P < 0.05$ compared to IPC, ☆$P < 0.05$ compared to L100, †$P < 0.05$ compared to L300, §$P < 0.05$ compared to IPC + L500. *IPC* Ischemic preconditioning, *L(100, 300, 500)* 100, 300, or 500 μM of landiolol was perfused with Krebs–Henseleit bicarbonate buffer solution without ischemic preconditioning, *IPC + L(100, 300, 500)* 100, 300 or 500 μM of landiolol was perfused with Krebs–Henseleit bicarbonate buffer solution during ischemic preconditioning, *baseline* 20 min after stabilization, *beforeIS* before 30 min of ischemia, *reper30, 60, 120* 30th, 60th, 120th min of reperfusion

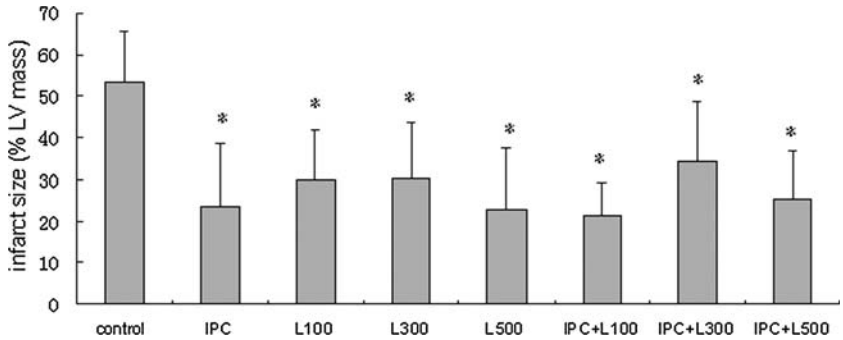

Fig. 3 Infarct size of left ventricle. *$P < 0.05$ compared to control, *IPC* ischemic preconditioning, *L(100, 300, 500)* 100, 300 or 500 μM of landiolol was perfused with Krebs–Henseleit bicarbonate buffer solution without ischemic preconditioning, *IPC + L(100, 300, 500)* 100, 300 or 500 μM of landiolol was perfused with Krebs–Henseleit bicarbonate buffer solution during ischemic preconditioning, *LV* left ventricular

It has been determined that there are indeed two phases in ischemic preconditioning: an early phase that develops within minutes and lasts for 2–3 h, and a late phase that occurs 12–24 h after ischemia and lasts for 3–4 days [16]. Although both the classic IPC and delayed IPC have the same stimulus of brief periods of ischemia and reperfusion, cellular mechanisms involved in the protection are different [17].

The early phase includes βAR-associated effects. Many studies have shown that, during preconditioning, the βAR is activated and the protection effect of preconditioning may be attributed to it [7, 8]. Frances et al. [18] found that cardioprotection provided by β-adrenergic stimulation is quite similar to IPC and mediated less by activation of β2-adrenoceptor than by β1-adrenoceptor. There are also some other viewpoints about the effect of preconditioning on β1 adrenergic receptor signaling. Tong and colleagues [19] reported that the protective effect of IPC could be induced by β-AR stimulation and that the effect was mediated via the β_2-AR subtype, and that preconditioning involves switching β_2-AR G-protein coupling from Gs to Gi.

Landiolol is a highly cardioselective β-blocker [13]. Compared to esmolol, it is 9 times more potent in β-blocking activity and 8 times more cardioselective ($\beta_1/\beta_2 = 255$). In myocardium, the β-adrenergic receptors are mainly the β1-receptor subtype [20], which plays a major role in regulating cardiac function. Landiolol alone has also been reported to be effective in attenuating cardiac dysfunction after warm cardioplegic arrest, and this effect may occur through adrenergic receptor-mediated action [9]. We also know that β-blockers exert some effects independently of β-receptor blockade, such as an anti-peroxidative effect [21], but how these effects interact with preconditioning is still unknown. The results of our study suggest that landiolol might act by blocking the β_1AR to attenuate the cardioprotective effect mediated by β_1AR activation which also mediates the cardioprotective effect of preconditioning, and only displays the cardioprotection of β-blocker, or the cardioprotective principle of IPC will interfere with the

same chain of events as β-blockade [11]. No additional effects were observed in our study.

In our study, neither IPC nor landiolol caused a decrease in the elevation of LVEDP (although IPC + L500 did cause a significant difference compared to the control) and neither had much effect on LVDP recovery. It is well known that not all the effects of β-blockers are beneficial. They may increase the LVEDP and they cause some cardiac dilatation, although they are very useful in the treatment of ischemia [22].In human, it is reported that landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure [23]. In rabbit, landiolol had slightly more potent negative chronotropic effect than esmolol with significantly less effect on blood pressure. Esmolol produced a dose-dependent decrease in mean arterial pressure that was not observed with landiolol [24]. Sakanashi et al. [15] reported that, whereas 300 μM landiolol ameliorated myocardial dysfunction, LVEDP was similar to that in the ischemic KHS group. The effect of landiolol on postischemic cardiac parameters was said to be concentration dependent. Yasuda and colleagues reported that, although the optimal concentration for maximum post-ischemic functional recovery was 2.5 mM, only improved recovery of aortic flow was observed [9]. In another report [25], although no significant difference was found in the recovery of cardiac parameters, a reduced infarct size was observed. In our study, although recovery of LVEDP with increasing landiolol concentrations improved, the differences were not significant.

The effect of preconditioning on post-ischemic myocardial performance is dependent on the duration of substantial ischemia. Efstathiou et al. [26] reported differential LVEDP and LVDP recovery as a function of ischemic time (15, 20, 30, and 45 min). After 30 min of ischemia, there was no strong correlation between infarct size limitation and contractile function improvement. It was also considered unlikely that reduction of contractile function plays a permissive role in the appearance of the cardioprotective effect of preconditioning [27]. Any post-ischemic improvement in global left ventricular function produced by preconditioning is secondary to reduced infarction, and preconditioning does not attenuate stunning [28]. As for ischemic preconditioning, infarct size is a more reliable endpoint than functional recovery [29].

A limitation of our study is that the lowest concentration of landiolol employed was somewhat high, and therefore was ineffectual for examining the concentration-related effect of landiolol on preconditioning. Furthermore, the implications of these data for potential clinical applications are unclear.

In conclusion, our study demonstrated that ischemic preconditioning has a cardioprotective effect after ischemia–reperfusion injury, and that the use of landiolol during preconditioning does not enhance the cardioprotective effect of preconditioning.

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