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ORIGINAL ARTICLE

The effect of landiolol on cerebral blood flow in patients undergoing off-pump coronary artery bypass surgery

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Abstract

Purpose To examine the effect of landiolol on cerebral blood flow in patients with normal or deteriorated cardiac function.

Methods Thirty adult patients who were diagnosed with angina pectoris and who underwent elective off-pump coronary artery bypass surgery were studied. Patients were divided into two groups, one with a preoperative left ventricular ejection fraction (EF) of 50% or higher (normal EF group; $n = 15$) and the other with an EF of less than 50% (low EF group; $n = 15$). The mean cerebral blood flow velocity (Vmca) and pulsatility index (PI) in the middle cerebral artery were recorded using transcranial Doppler ultrasonography (TCD). Individual hemodynamic data were obtained using a pulmonary arterial catheter.

Results In both groups, landiolol produced a significant decrease in heart rate (HR), which then returned to baseline 15 min after administration was completed. A significant decrease in mean arterial pressure occurred in the low EF group, but the decrease was within 30% of the baseline. In the normal EF group, there was no decrease in cardiac index (CI), whereas in the low EF group, CI significantly decreased along with the decrease in HR. There were no significant differences in Vmca and PI between the two groups.

Conclusion Continuous administration of landiolol at a dose of 0.04 mg/kg/min after 1 min rapid IV administration at a dose of 0.125 mg/kg/min decreases HR without causing aggravation of CBF during treatment of intraoperative tachycardia in patients with normal and deteriorated cardiac function.

Keywords Landiolol · Cerebral blood flow · Transcranial Doppler ultrasonography · Hemodynamics · Off-pump coronary artery bypass

Introduction

Intraoperative tachycardia in patients with coronary artery disease (CAD) is one of the major risk factors for intraoperative myocardial ischemia due to a reduction in oxygen supply, which is attributed to decreased coronary blood flow associated with shortening of the left ventricular diastole and increased oxygen demand [1–3]. β-Blockers can reduce myocardial oxygen consumption by promoting more efficient utilization of oxygen in the myocardium. Therefore, these drugs are considered useful for the perioperative management of patients with CAD [4–8]. Moreover, in cardiac surgery patients, β-blockers have been shown to result in a significant decrease in the incidence of postoperative neurologic complications [9]. However, some reports have recently raised questions about the perioperative use of β-blockers. In the Perioperative Ischemia Study Evaluation (POISE trial) published in The Lancet in 2008, the incidence of stroke, which was assumed to be associated with hypotension, increased despite the incidence of cardiac complications being reduced by the perioperative administration of metoprolol, and the prognosis was aggravated [10, 11]. Therefore, we investigated the cerebral effects of the β-blocker landiolol in cardiac surgery patients.

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Landiolol is an ultrashort-acting β_1-receptor-selective blocker for intravenous (IV) injection that was developed in Japan [12]. Landiolol is a derivative of esmolol, a typical short-acting β_1-receptor-selective β-blocker. Modifying the molecular structure of esmolol to produce landiolol resulted in augmented β_1-receptor affinity in the latter. Landiolol also has less of an effect on blood pressure compared with esmolol [13]. We previously investigated the influence of landiolol on hemodynamics and left ventricular function in patients with normal and deteriorated cardiac function, and found that the heart rate of intraoperative tachycardia could be reduced without aggravating hemodynamics in patients with normal cardiac function, but that attention should be paid to a decrease in blood pressure and a reduction in cardiac function in patients with a preoperative EF of less than 50% [12]. Accordingly, cerebral blood flow may decrease due to landiolol-induced aggravation of hemodynamics in patients with deteriorated cardiac function, but its influence has not yet been investigated. Therefore, we investigated the effects of landiolol on hemodynamics and cerebral blood flow in patients judged to have normal and deteriorated cardiac function, based on differences in preoperative EF using a thermodilution pulmonary artery catheter and transcranial Doppler ultrasonography (TCD).

Methods

Forty-two adults were recruited for this study; they were all patients who received a diagnosis of angina pectoris and underwent elective off-pump coronary artery bypass surgery at Oita University Hospital (Oita, Japan). After approval of the study by the hospital ethics review board, written informed consent was obtained from each of the patients. Patients were excluded from the study if they met one of the following criteria: age younger than 18 years, diabetes mellitus, uncontrolled hypertension, cerebrovascular disease, preoperative EF lower than 40%, recent myocardial infarction, continuous IV injection of catecholamines, or a need for mechanical assistance to breathe. Patients taking β-blockers as part of their regular therapeutic regimen were also excluded from the study.

All patients received morphine hydrochloride (0.1 mg/kg) and hydroxyzine (0.5 mg/kg) intramuscularly approximately 30 min prior to entering the operating room, and also underwent routine monitoring before off-pump coronary artery bypass surgery. Standard bedside measurements were used for coronary revascularization, including recording of a five-lead electrocardiogram, radial artery cannulation, pulse oximetry, capnography, and body temperature. Anesthesia was induced by midazolam (0.1 mg/kg) and fentanyl (5 μg/kg), and tracheal intubation was facilitated with vecuronium bromide (0.1 mg/kg).

After intubation, a central venous catheter and an 8 Fr thermodilution pulmonary arterial catheter (CCOmbo catheter; Edwards Lifesciences, Irvine, CA, USA) were inserted into the right external jugular vein and the right internal jugular vein, respectively. Right middle cerebral artery (MCA) mean flow velocity (Vmca) and pulsatility index (PI) were monitored from beat to beat using a 2 MHz pulsed Doppler probe (Multidop P; DWL, Sipplingen, Germany). The right MCA was insonated by the transtemporal approach at a depth of approximately 35–60 mm using standard criteria [14], and the probe was secured with a headband. The signal quality was determined based on both its characteristic high-pitched sound and the waveform of the displayed sonogram. The Vmca and PI were calculated automatically by tracing the waveforms every 5 s. Regarding the ventilation conditions, normal carbon dioxide partial pressure (about 40 mmHg) was maintained on end-tidal capnography under controlled respiration, and measurements were performed in the supine position. All TCD measurements were performed by one anesthesiologist and all images were videotaped for further analysis. The study was performed in a blinded manner, with the TCD practitioner unaware of the preoperative EF of the patients. Anesthesia was maintained with appropriate additional administration of fentanyl (total dose: 10–15 μg/kg), vecuronium bromide, and sevoflurane (not more than 2%). The sevoflurane concentration was adjusted to maintain the bispectral index (BIS) at 40–60, as measured by a BIS monitor (A-2000; Aspect Medical Systems, Newton, MA, USA). Nitroglycerine was also continuously administered at 0.5 μg/kg/min after inducing anesthesia.

The study was performed from the initiation of surgery to the completion of graft dissection during conditions in which the heart rate (HR) was 80 beats/min or higher, BIS was 40–60, and a sufficient depth of anesthesia was maintained [15]. Twelve patients who experienced heart rates of under 80 beats/min before the completion of the graft dissection were not given landiolol and were thus excluded from the study. We divided the remaining 30 patients into two groups according to cardiac function. Based on the preoperative EF (obtained from preoperative angiography or transthoracic echocardiography), a normal EF group ($EF \geq 50\%$, $n = 15$) and a low EF group ($EF < 50\%$, $n = 15$) were established for comparison. Landiolol was administered through the central venous catheter for 1 min at a rate of 0.125 mg/kg/min, followed by continuous infusion at 0.04 mg/kg/min. Administration of landiolol was terminated after a total of 5 min to assess hemodynamic changes. Measurements of hemodynamics, Vmca, and PI were made at three time points: before landiolol administration (T1), immediately before completion of landiolol administration (T2), and 15 min after completion of landiolol administration (T3) (Fig. 1). Neither an

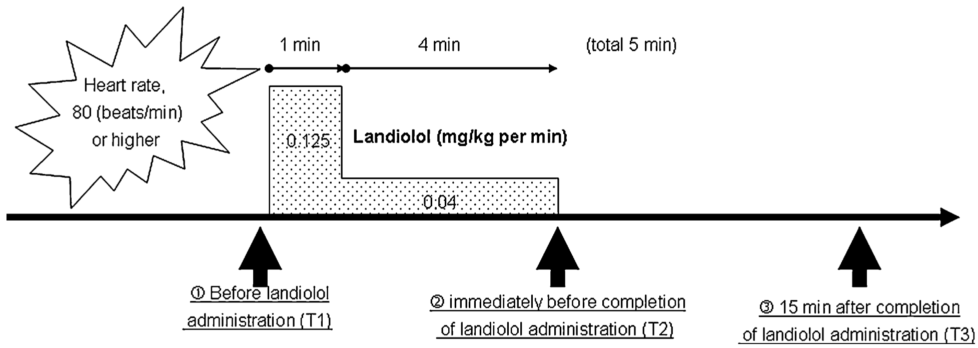

Fig. 1 Method of landiolol administration and time points when measurements were taken

additional dose of landiolol nor administration of other drugs that might affect hemodynamics were needed for any of the patients in the study. Phenylephrine was administered if the mean arterial pressure (MAP) decreased by 30% or more compared with the value at T1.

Heart rate, MAP, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), cardiac index (CI), and systemic vascular resistance index (SVRI) were measured using a catheter for open arterial pressure measurement and a thermodilution pulmonary artery catheter for cardiac output measurement (Vigilance Monitor; Edwards Lifesciences). The cardiac output was taken as the average of three measurements using 10 ml of cold (<10°C) 5% dextrose solution. $PaCO_2$ and hematocrit (Hct) were recorded at the same time.

Values are presented as the mean ± SD. Differences between groups were examined for statistical significance using unpaired *t*-tests for single comparisons and analysis of variance followed by Scheffé's post hoc test, using statistical software (StatView; Abacus Concepts Inc., Berkeley, CA, USA). A *P*-value of less than 0.05 was considered statistically significant.

Table 1 Demographic and operative data

	Normal EF group	Low EF group	*p* Value
Age (year)	65 ± 8	67 ± 7	0.49
Gender (male/female)	11/4	12/3	0.68
Body weight (kg)	60 ± 11	61 ± 12	0.91
Height (cm)	159 ± 7	158 ± 8	0.87
Body surface area (m^2)	1.61 ± 0.16	1.61 ± 0.18	0.98
Preoperative EF (%)	58 ± 5	46 ± 2	<0.05
Operation time (min)	241 ± 67	235 ± 49	0.79
Number of grafts	2.5 ± 0.6	2.7 ± 0.7	0.43

Left ventricular EF based on preoperative angiography or transthoracic echocardiography

Values are presented as the mean ± SD

Results

Demographic and operative data are shown in Table 1. The mean preoperative EF values of the normal EF and low EF groups were 58 ± 5% (range, 52–65%) and 46 ± 2% (range, 43–49%), respectively ($P < 0.05$). Heart rate, MAP, CI, and SVRI data are shown in Fig. 2. In both groups, landiolol produced significant decreases in HR ($P < 0.05$), but these values returned to their respective baseline levels at T3. No significant difference from baseline was found for MAP in the normal EF group, but MAP significantly decreased at T2 in the low EF group. There were no significant differences in HR and MAP between the two groups at each time point. None of the patients developed severe hypotension, and treatment with phenylephrine was not required. The cardiac index in the low EF group was significantly lower than that in the normal EF group at T1, T2 and T3. No significant changes in CI were observed in the normal EF group, but in the low EF group, the CI decreased significantly at T2 compared with the baseline level. No changes in SVRI from baseline occurred in either group. There were also no significant differences in PCWP and CVP between the two groups or among patients in each group (data not shown). No adverse effects occurred throughout the study. None of the patients developed stroke after surgery.

Transcranial Doppler ultrasonography data are shown in Fig. 3. No significant changes in Vmca and PI were observed between the two groups or among patients in each group. The $PaCO_2$, Hct and BIS data are shown in Table 2. No significant changes were noted in either group throughout the study.

Discussion

Our results show that landiolol can be used to rapidly decrease HR without an adverse influence on cerebral blood flow (CBF) in patients with normal cardiac function, as well as those with poor cardiac function (preoperative EF < 50%). We previously reported that attention should be paid to hypotension and cardiac dysfunction in patients

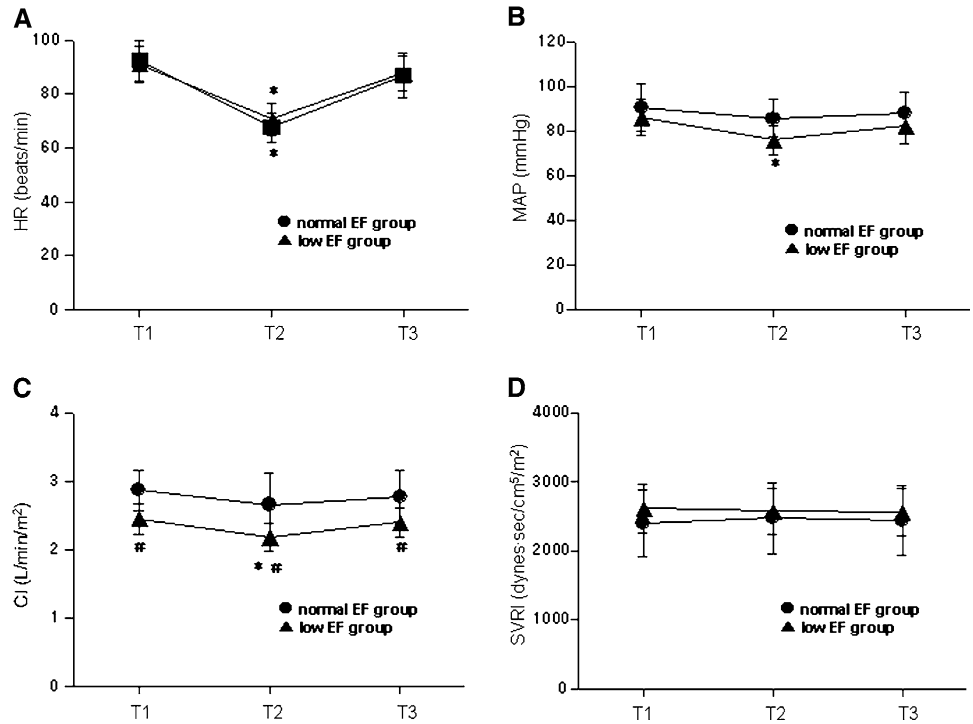

Fig. 2 Time course of changes in HR (**a**), MAP (**b**), CI (**c**), and SVRI (**d**). *HR* heart rate, *MAP* mean arterial pressure, *CI* cardiac index, *SVRI* systemic vascular resistance index, *T1*, before landiolol administration, *T2* immediately before completion of landiolol administration, *T3* 15 min after completion of landiolol administration. Values are presented as the mean ± SD. $^*P < 0.05$ versus T1; $^\#P < 0.05$ versus normal EF group

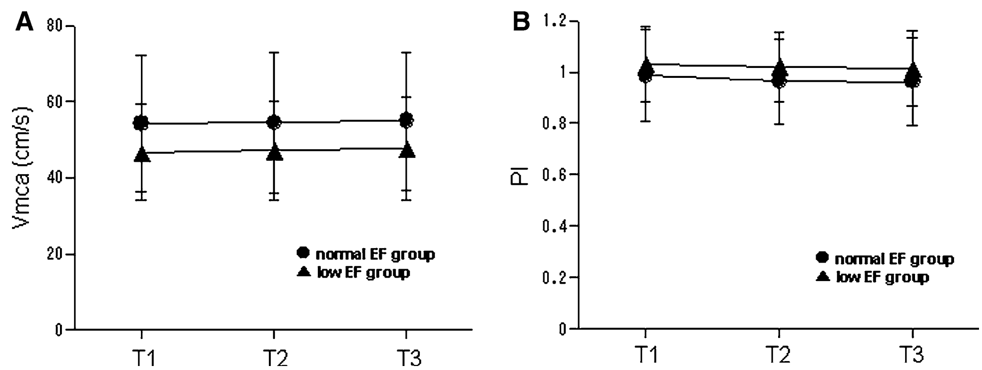

Fig. 3 Time courses of changes in Vmca (**a**) and PI (**b**) using TCD. *Vmca* right middle cerebral artery mean flow velocity, *PI* pulsatility index, *TCD* transcranial Doppler ultrasonography, *T1* before landiolol administration, *T2* immediately before completion of landiolol administration, *T3* 15 min after completion of landiolol administration. Values are presented as the mean ± SD

with poor cardiac function and a preoperative EF less than 50% [12]. In the present study, landiolol-induced hypotension and cardiac dysfunction were noted in patients with poor cardiac function, but CBF was not reduced on TCD. In the POISE trial, perioperative administration of metoprolol reduced the incidence of cardiac complications, but the incidence of stroke, assumed to be associated with hypotension, was increased, and the prognosis was aggravated [10, 11]. Since this report was published, active perioperative administration of β-blocker has been questioned, but our study showed that landiolol is a β-blocker that does not affect CBF. In another study of coronary artery bypass graft patients, Amory et al. reported that the use of β-blockers during the operation reduced postoperative cerebral complications [9]. In addition, the administration of β-blockers improved the survival rate of patients with cerebral injury [16–18]. Thus, β-blocker use during cardiac operation may have exerted a cerebral protective effect.

Landiolol was developed as an agent with highβ_1-receptor affinity and sensitivity by modifying the molecular structure of esmolol [19]. This agent has a much higher cardioselectivity ($\beta_1/\beta_2 = 225$) than esmolol ($\beta_1/\beta_2 = 32$) and is also shorter-acting: the elimination half-life of landiolol is 4 min, whereas that of esmolol is 9 min. The ultrashort-acting duration of landiolol is due to the rapid hydrolysis of its ester bond, which is primarily mediated by carboxylesterase and pseudocholinesterase in liver and plasma, respectively [20]. Landiolol has previously been reported to have no influence on changes in CBF in patients who underwent electroconvulsive therapy (ECT), similar to esmolol [21], but none of the previous reports investigated changes in CBF induced by perioperative administration of landiolol in patients with cardiac complications. In

Table 2 Values of $PaCO_2$, Hct and BIS

	T1	T2	T3
$PaCO_2$			
Normal EF group	38 ± 3	38 ± 3	38 ± 3
Low EF group	38 ± 3	37 ± 3	37 ± 3
Hct			
Normal EF group	35 ± 4	35 ± 4	34 ± 4
Low EF group	36 ± 5	36 ± 5	36 ± 5
BIS			
Normal EF group	47 ± 6	46 ± 6	47 ± 6
Low EF group	46 ± 6	46 ± 6	47 ± 6

Hct hematocrit, *BIS* bispectral index

Values are presented as the mean ± SD

addition, changes in CBF on landiolol administration to patients with deteriorated cardiac function have not been investigated, and thus the safety of landiolol in such patients is unclear. We performed a comparative study to examine the effects of landiolol on hemodynamics and CBF in patients with normal and deteriorated cardiac function.

CBF measurement methods include IV xenon, the Kety–Schmidt method, the Fick principle, and magnetic resonance imaging (MRI), but the procedures of these methods are complex, not readily applicable to the bedside, or expensive. Thus, the TCD method may be useful to estimate CBF changes under anesthesia for cardiac surgery [14]. The CBF rate is affected by $PaCO_2$ and hemodilution [22], but the influences of these on the findings of this study were likely small. The major cerebral arteries, such as the middle cerebral artery, were maintained at relatively constant vascular diameters, and the vascular diameters did not change in response to drug-induced changes in blood pressure and $PaCO_2$ [23]. Accordingly, changes in the blood flow rates in the main cerebral arteries reflected changes in CBF [24].

Heart rate decreased significantly at T2 compared with baseline, but then rapidly recovered at T3 in patients with normal and deteriorated cardiac function. This recovery of HR after completion of landiolol administration shows that landiolol is a highly controllable agent. MAP and CI did not change significantly from the baseline in the normal cardiac function group, nor were there significant changes in Vmca or PI. PI is widely used as an index of vascular resistance of regions below the measurement site [14, 25], suggesting that landiolol does not directly affect CBF or the vascular diameter of cerebral arterioles. In the deteriorated cardiac function group, MAP and CI decreased significantly from the baseline, but no significant changes were noted in Vmca or PI. The MAP at T2 in the deteriorated cardiac function group was approximately 75 mmHg, less than a 30% decrease from the baseline, and the CI was approximately 2.2 L/min/m^2, and was relatively well maintained, suggesting that the indirect reduction of CBF was avoided. Based on these findings, it was suggested that landiolol is a β-blocker that does not affect CBF, even when administered for intraoperative tachycardia during off-pump coronary artery bypass surgery. Vmca corresponds to the blood flow of one pulse, but cerebral blood flow per minute is influenced by pulse rate. Thus, landiolol not only reduced HR, but may also have reduced cerebral blood flow per minute in both groups. Bangalore et al. reported that treating tachycardia with β-blockers increased the risk of stroke [26], so we thought that reducing rapid HR with β-blockers required caution.

For maintenance anesthesia, fentanyl (total dose: 10–15 µg/kg) and sevoflurane (not more than 2%) were used. When opioids or volatile anesthetic agents are used, it is necessary to consider their influence on CBF, but it has been reported that moderate doses of opioids and sevoflurane do not significantly affect Vmca [14], suggesting that the influence is small. Nitroglycerine was used to maintain the coronary arterial blood flow, but its influence may have also been small because the dose was not changed throughout the study.

There are several limitations regarding the study design. First, the study was performed in a small patient population at a single medical facility. Second, the potential for bias was created by not blinding the investigators to the study group assignment. However, the TCD data should be unbiased since the preoperative EF data were not known by the TCD practitioner. Within these limitations, our data indicated different effects of landiolol on hemodynamics in patients with an EF of 50% or higher and lower than 50%. The mean HR and MAP measured before the administration of landiolol (T1) were approximately 90 beats/min and approximately 90 mmHg, respectively, in both groups; therefore, MAP was maintained, even in the low EF group. Because maintenance of LV volume was confirmed by transesophageal echocardiography and anesthetic depth was controlled with the BIS values used as an indicator in the study, it is unlikely that hypovolemia or light anesthesia affected HR and blood pressure at T1. However, when HR and blood pressure are maintained by compensated sympathetic activity in patients who have hypovolemia in addition to deteriorated cardiac function, care is required, because landiolol may induce greater aggravation of hemodynamics compared with those observed in this study. In such cases, attention should be paid to the potential for indirect reduction of CBF due to an excess blood pressure decrease and aggravation of cardiac function.

Our study population may have affected our results. We excluded patients with diabetes mellitus, uncontrolled hypertension, and cerebrovascular disease from this study because they exhibit altered cerebral blood responses to β-blockers. Thus, additional studies are needed to understand the response to β-blockers in patients with these complications. In this study, we examined the short duration effect of the β-blocker landiolol in patients undergoing off-pump coronary artery bypass surgery, specifically patients with EF under 50%. We determined cerebral blood flow and hemodynamics after a 5-min administration of the β-blocker landiolol. Thus, the long-term effect of β-blockers and the effects of the different β-blocker doses on cerebral blood flow require further study.

In conclusion, we have shown that continuous administration of landiolol at a dose of 0.04 mg/kg/min after 1 min rapid IV administration at a dose of 0.125 mg/kg/min decreases HR without causing aggravation of CBF during treatment of intraoperative tachycardia in patients with normal and deteriorated cardiac function.

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