

## Clinical Trials Study

## Landiolol, an ultra-short-acting $\beta$ 1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis

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### Abstract

**AIM:** To investigate whether landiolol, an ultra-short-acting  $\beta$ 1-antagonist, can safely and effectively control heart rate in septic patients with supraventricular tachyarrhythmias.

**METHODS:** We reviewed all patients with sepsis who admitted to our intensive care unit between January 2006 and December 2011. Sixty one septic patients suffered from supraventricular tachyarrhythmias (heart rate  $\geq$  120 bpm for  $>$  1 h). Among 61 patients, 39 patients were treated with landiolol (landiolol group) and 22 patients were not treated with landiolol (control group). Arterial pressure, heart rate, cardiac rhythm, pulmonary arterial pressure and cardiac output (if a pulmonary arterial catheter was inserted) were compared between the 2 groups at 1, 8 and 24 h after the initiation of tachyarrhythmias.

**RESULTS:** Mean age and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were similar between the 2 groups. Paroxysmal atrial fibrillation/flutter (87%), paroxysmal atrial tachycardia (10%), and paroxysmal supraventricular tachycardia (3%) were observed. The initial landiolol dose administered was  $6.3 \pm 5.8$  g/kg per minute. Rapid and substantial reduction of heart rate was observed in the landiolol group without any

deterioration of hemodynamics. Landiolol significantly reduced heart rate (from  $145 \pm 14$  bpm to  $90 \pm 20$  bpm) compared to the control group (from  $136 \pm 21$  bpm to  $109 \pm 18$  bpm,  $P < 0.05$ ). The conversion to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point ( $P < 0.01$  at 8 h;  $P < 0.05$  at 1 and 24 h).

**CONCLUSION:** Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmias.

**Key words:** Landiolol; Supraventricular tachyarrhythmias; Sepsis; Rate control; Conversion to sinus rhythm

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**Core tip:** The management of tachyarrhythmia is important but it is often difficult because of unstable hemodynamics in septic patients. Landiolol is an ultra-short-acting  $\beta_1$  selective adrenoceptor antagonist. It exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other  $\beta$  blockers. In fact, landiolol significantly reduced heart rate without any deterioration of hemodynamics in this study. The most impressive finding is high conversion rate to sinus rhythm immediately after landiolol administration. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias. Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

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## INTRODUCTION

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The incidence of paroxysmal atrial fibrillation/flutter (PAF) has been reported to be 31% in critically ill patients with sepsis<sup>[1]</sup>. Tachyarrhythmias have been identified as a major source of morbidity in critically ill patients<sup>[2,3]</sup>. Therefore, controlling tachyarrhythmia should be important in such patients.

Measurements of serum catecholamine level and direct measurements of renal sympathetic nerve activity have revealed that severe infection activates the sympathetic nervous system<sup>[4-9]</sup>. This activation may trigger supraventricular tachyarrhythmias in the presence of severe infection<sup>[10]</sup>. Therefore, we believed

that  $\beta$  blockers can be used to control heart rate (HR) in patients with severe infection. However, it is difficult to use  $\beta$  blocker in patients with severe sepsis because of hemodynamic instability.

Landiolol (ONOACT; Ono Pharmaceutical, Osaka, Japan), a newly developed commercially available agent, is an ultra-short-acting  $\beta$ -adrenoceptor antagonist with a half-life of 4 min in healthy subjects. Landiolol also has high  $\beta_1$  selectivity ( $\beta_1/\beta_2 = 255$ ) and is 8 times more cardioselective than esmolol<sup>[11-14]</sup>. Moreover, landiolol exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol in rabbits<sup>[15,16]</sup>. In clinical situations, landiolol has been used to treat perioperative tachyarrhythmias in Japan. Landiolol reduced HR significantly without reducing blood pressure and stabilized hemodynamics in postsurgical patients<sup>[11,17-20]</sup>.

Considering these characteristics, landiolol could be valuable and suitable for managing tachyarrhythmias in patients with severe infection. Therefore, we investigated whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in patients with severe sepsis.

## MATERIALS AND METHODS

### Study design and patients selection

This historical cohort, single-center, interventional, and inter-subjective comparison study was approved by the Institutional Review Board of the Kanazawa University Hospital and was registered under ISRCTN number 70831305. Informed consent was obtained from all patients.

Medical records of all patients were screened and followed for sepsis with supraventricular tachyarrhythmia by a single intensivist in the intensive care unit (ICU) of the Kanazawa University Hospital from January 2006 to December 2011, were reviewed. Patients were included in this study if they met the following criteria: (1) systemic inflammatory response syndrome score  $\geq 2$  with infection; (2)  $\geq 18$  years of age; (3) supraventricular tachyarrhythmias with HR  $\geq 120$  bpm for  $>1$  h; (4) no history of chronic supraventricular tachyarrhythmias; and (5) no supraventricular tachyarrhythmias at the time of ICU admission. Patients were divided into 2 groups: those treated with landiolol (landiolol group) and those not treated with landiolol (control group) to control HR of supraventricular tachyarrhythmias.

### Measurements

Arterial pressure and HR were compared between the 2 groups at 1, 8, and 24 h after the initiation of tachyarrhythmia. We also investigated heart rhythm and the conversion to sinus rhythm. Pulmonary arterial pressure, central venous pressure (CVP), cardiac output, and cardiac index (CI) were measured if a pulmonary arterial catheter was inserted. Systemic vascular resistance index (SVRI) was calculated as follows: SVRI

Table 1 Patients' characteristics

	Landiolol	Control
<i>n</i>	39	22
Age, yr	70.7 ± 12.3	70.8 ± 12.5
Underlying disease		
Cardiovascular disease	16 (41.0%)	11 (50.0%)
Malignancy	11 (28.2%)	3 (13.6%)
Immunological disorder	3 (7.7%)	2 (9.1%)
Others	9 (23.1%)	6 (27.2%)
Infected site		
Respiratory tract	17 (43.6%)	14 (63.6%)
Intra-abdominal	13 (33.3%) <sup>a</sup>	2 (9.1%)
Blood	5 (12.8%)	0 (0%)
Skin/soft tissue	2 (5.1%)	0 (0%)
Urinary tract	1 (2.6%) <sup>a</sup>	4 (18.2%)
Others	1 (2.6%)	2 (9.1%)
APACHE II	22.8 ± 5.4	22.1 ± 7.7
SOFA	8.8 ± 4.0	9.1 ± 3.9

<sup>a</sup>*P* < 0.05 vs control. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

(dyne·s/cm<sup>5</sup> per square meter) = 80 (mean arterial pressure-CVP)/CI.

### Endpoints

The primary endpoint was HR reduction of the supraventricular tachyarrhythmias without a decrease in arterial pressure. The secondary endpoint was the frequency of conversion to sinus rhythm.

### Statistical analysis

Continuous variables are expressed as mean ± SD. Patient characteristics and hemodynamics of the 2 groups were compared using an independent *t* test for continuous variables and with either Fisher's exact test or a chi-square test for categorical variables. Differences of conversion rates were analyzed with Fisher's exact test or the chi-square test as appropriate. Other data were analyzed by repeated-measures analysis of variance. In all analyses, *P* < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Masayuki Takamura, PhD from Kanazawa University Graduate School of Medicine.

## RESULTS

A total of 188 septic patients were admitted to the ICU in this period. Among them, 23 patients were excluded from analysis because of less than 18 years of age. Two patients were excluded because of atrial fibrillation at the time of ICU admission. Supraventricular tachyarrhythmias occurred in 61 patients (37.4%) in leaving 163 septic patients. Among 61 patients, 39 patients were treated with landiolol and 22 patients were not treated with landiolol.

Patient characteristics are indicated in Table 1. There were no significant differences between the 2 groups with respect to age, underlying disease, Acute Physiology and Chronic Health Evaluation II score and

Table 2 Hemodynamics

	Landiolol	Control
Heart rate, bpm	145 ± 14 <sup>a</sup>	136 ± 21
Systolic arterial pressure, mmHg	113 ± 34 <sup>a</sup>	137 ± 39
Diastolic arterial pressure, mmHg	60 ± 17	66 ± 13
Mean arterial pressure, mmHg	78 ± 21	86 ± 28
Diastolic pulmonary arterial pressure, mmHg	19 ± 6	20 ± 7
Cardiac output, L/min	3.9 ± 1.7	5.8 ± 1.5
Cardiac index, L/min per square meter	2.5 ± 1.1 <sup>a</sup>	4.0 ± 1.3
SVRI, dyne·s/m <sup>5</sup> per square meter	2068 ± 795	1615 ± 399
Arrhythmia		
Paroxysmal atrial fibrillation/flutter	34 (87%)	13 (60%)
Paroxysmal atrial tachycardia	4 (10%)	8 (36%)
Paroxysmal supraventricular tachycardia	1 (3%)	1 (5%)
Concomitant drugs to control arrhythmia		
Calcium-channel blocker	3 (8%)	5 (22%)
Other β blockers	0 (0%)	3 (14%)
Disopyramid phosphate	0 (0%)	1 (5%)
Amiodarone	0 (0%)	1 (5%)

<sup>a</sup>*P* < 0.05 vs control. SVRI: Systemic vascular resistance index.

Sequential Organ Failure Assessment. Intra-abdominal infection was more (*P* < 0.05) and urinary tract infection was less (*P* < 0.05) in landiolol group than in control group. Respiratory tract infection was the most frequent disease in both groups.

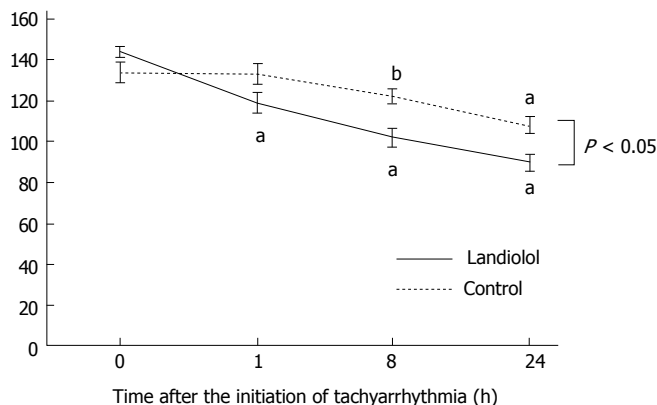
Baseline hemodynamics are summarized in Table 2. Baseline HR was higher in the landiolol group. Systolic arterial pressure and CI were lower in the landiolol group. PAF was the most frequent observation in both groups. Calcium channel blockers and antiarrhythmic agents were used to control HR or cardiac rhythm in the control group.

The initial dose of landiolol was 6.3 ± 3.3 g/kg per minute. Landiolol significantly reduced HR from 145 ± 14 bpm to 119 ± 28 bpm (*P* < 0.01) without reducing arterial pressure at 1 h after the initiation of tachyarrhythmia (Figures 1 and 2). At that time, HR did not change significantly in the control group (from 136 ± 21 bpm to 135 ± 21 bpm) (Figure 1). The conversion rate to sinus rhythm was 25.6% in the landiolol group but 0% in the control group (Figure 1, *P* < 0.05).

After that, a substantial reduction in HR was observed in the landiolol group without any deterioration of hemodynamics. At 24 h after the initiation of tachyarrhythmia, landiolol reduced HR dramatically from 145 ± 14 bpm to 90 ± 20 bpm (Figure 1). A lesser degree of HR reduction was seen in the control group (from 136 ± 21 bpm to 109 ± 18 bpm) than in the landiolol group (Figure 1). The conversion from to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point (Figure 1, *P* < 0.01 at 8 h; *P* < 0.05 at 24 h).

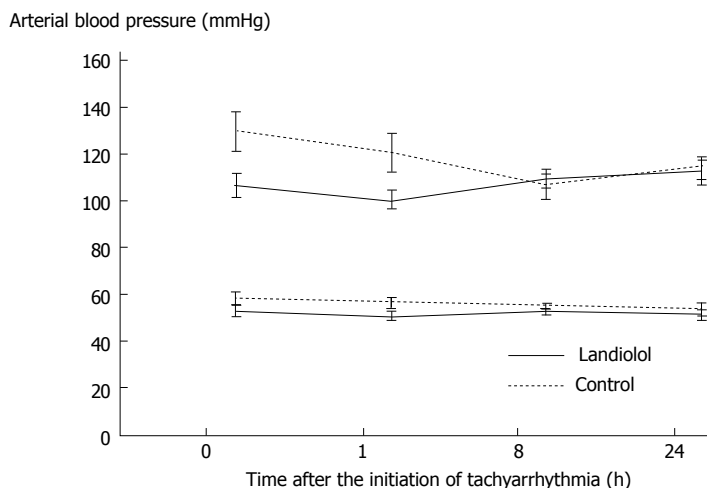
Baseline diastolic pulmonary arterial pressures were similar between groups and did not change (Figure 3). In the landiolol group, baseline CI was lower and did not decrease compared to the control group (Figure 3).

Finally, the duration of landiolol administration was 80.7 ± 78.5 h and the significant bradycardia have



Landiolo (µg/kg per minute)	6.27 ± 5.80	6.12 ± 4.72	5.47 ± 4.10	4.17 ± 4.28
Conversion to sinus rhythm				
Landiolo		25.6% <sup>b</sup>	55.3% <sup>a</sup>	69.7% <sup>b</sup>
Control		0%	18.2%	36.4%

**Figure 1 Heart rate and sinus rhythm conversion rate.** Rapid and substantial reduction of heart rate (HR) was observed in the landiolol group. Reduction in HR was observed in the landiolol group than the control. In addition, the conversion from supraventricular arrhythmia to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point. Results are expressed as mean ± SE. <sup>a</sup>P < 0.01, <sup>b</sup>P < 0.05 vs time 0 h.



Landiolo (µg/kg per minute)	6.27 ± 5.80	6.12 ± 4.72	5.47 ± 4.10	4.17 ± 4.28
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**Figure 2 Arterial pressure.** Landiolol did not change atrial blood pressure. Results are expressed as mean ± SE.

never been observed in any treated patients.

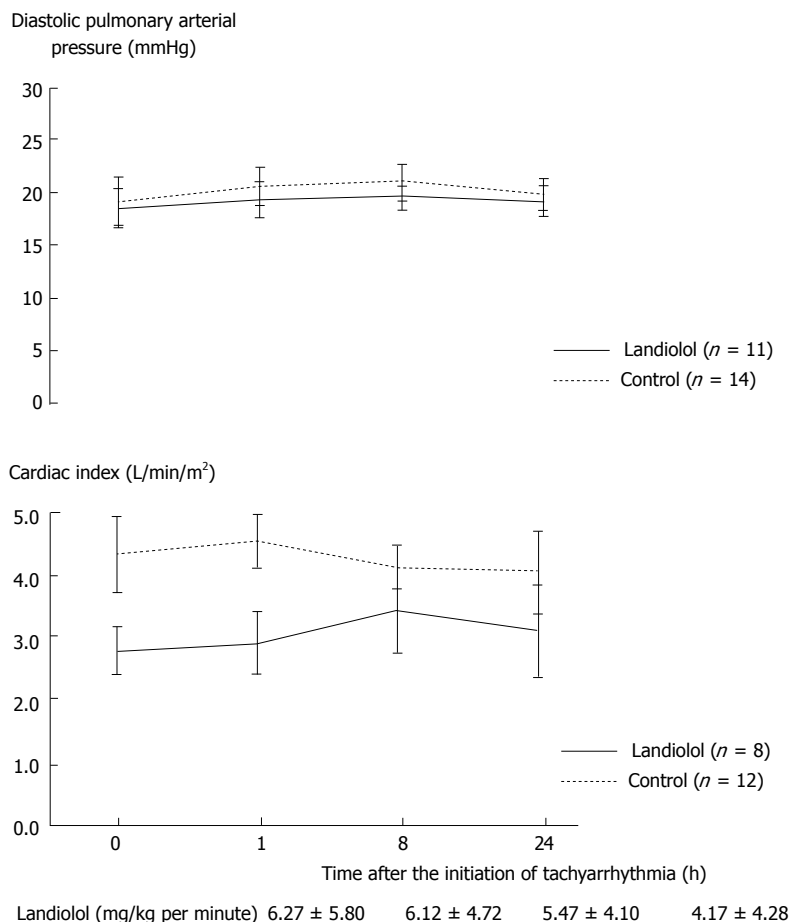
## DISCUSSION

This is the first report to investigate the clinical use of landiolol for treating supraventricular tachyarrhythmia in patients with severe sepsis. Its major findings are as follows: (1) low-dose landiolol rapidly and substantially reduced HR in septic patients with supraventricular tachyarrhythmia; (2) low-dose landiolol did not reduce arterial pressure and cardiac output; and (3) low-dose landiolol immediately and significantly converted supraventricular tachyarrhythmias to sinus rhythm in septic patients.

Severe infection or sepsis generally activates sympathetic nervous system. Plasma norepinephrine

and epinephrine plasma levels have been reported to be approximately 6 times and 60 times higher in conscious rats with endotoxemia than in control rats, respectively<sup>[5]</sup>. In 1 human study, the serum levels of both norepinephrine and epinephrine were significantly higher in postoperative patients with sepsis than in those without sepsis<sup>[4]</sup>. Moreover, by direct measurement of sympathetic nerve activity, renal sympathetic nerve activity was also increased approximately 3.5 fold by the systemic administration of lipopolysaccharide in rats<sup>[6,21]</sup>.

There is a close association between autonomic nervous system activity and supraventricular tachyarrhythmia. Sepsis-induced activation of the sympathetic nervous system is partially associated with supraventricular tachyarrhythmia in patients with severe sepsis<sup>[10]</sup>. Sympathetic activation of the heart facilitates



**Figure 3 Pulmonary arterial catheter parameters.** Landiolol did not affect diastolic pulmonary arterial pressure or cardiac index. Results are expressed as mean ± SE.

arrhythmogenesis by increasing calcium entry and the spontaneous release of calcium from the sarcoplasmic reticulum<sup>[22,23]</sup>. Therefore,  $\beta$  blockers are the reasonable drug for controlling HR in the presence of supraventricular tachyarrhythmia in septic patients. The landiolol infusion at the dose of 5-10  $\mu$ g/kg per minute much lower than described dose in the package insert, significantly decreased HR in 82% of postoperative patients with PAF<sup>[19]</sup>. Consistent with these previous studies, low-dose landiolol rapidly and substantially reduced HR in our septic patients with supraventricular tachyarrhythmia. Therefore, the low dose ( $6.3 \pm 3.3$  g/kg per minute) of landiolol administered was enough to inhibit excessive activation of sympathetic nerve activity and to significantly reduce HR in septic patients with tachyarrhythmia.

Landiolol reduced HR significantly without reducing arterial pressure and stabilized hemodynamics in postsurgical patients<sup>[11,17-20]</sup>. Consistent with these studies, landiolol neither reduces arterial pressure nor deteriorates hemodynamics in our septic patients. Recent prospective, multicenter, single-blind, randomized, parallel-group study showed that low-dose landiolol rapidly decreased HR of atrial fibrillation/flutter without an increase in the incidence of adverse events in patients with LV dysfunction<sup>[24]</sup>. Landiolol may have more negative chronotropic effect than negative inotropic effect, especially at a low dose. Landiolol has a higher  $\beta_1$ -selectivity ( $\beta_1/\beta_2 = 255$ ) and 8 times more

cardioselective than esmolol, which is also short-acting  $\beta_1$ -selective  $\beta$  adrenergic receptor blocker<sup>[11-14]</sup>. Landiolol exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol in rabbits<sup>[15,16]</sup>. Consistent with these reports, in our study, landiolol did not decrease CI despite HR reduction. Another reason is that HR reduction by landiolol causes better hemodynamics. The landiolol-induced HR reduction in patients with tachyarrhythmia allows sufficient left ventricular filling time, which subsequently allows more stroke volume. Moreover, the conversion to sinus rhythm, in part, results in sufficient atrial kick, which also creates more stroke volume. Therefore, landiolol did not decrease arterial pressure and stabilized hemodynamics.

The most impressive findings in our study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. A few case studies have reported landiolol-induced conversion to sinus rhythm in patients with atrial fibrillation or flutter<sup>[25,26]</sup>. Recently, landiolol has been reported to be more effective and safer than diltiazem for conversion to normal sinus rhythm in patients with postoperative atrial fibrillation after open heart surgery<sup>[20]</sup>. Landiolol-induced reduction of HR improves hemodynamics and converts supraventricular tachyarrhythmias to



sinus rhythm. However, landiolol may function as an antiarrhythmic agent and directly affects the restoration to sinus rhythm. The use of  $\beta$  blockers has recently been reported to have an anti-oxidative and anti-inflammatory effect. However, no study has reported the antiarrhythmic effect of landiolol in supraventricular tachyarrhythmia. As the excessive sympathetic nervous activation caused by sepsis may be associated with maintaining supraventricular arrhythmia, landiolol that has more direct suppressive effect of sympathetic activity than other drugs may cause the conversion to sinus rhythm.

Our study has several potential limitations. First, as this is the historical cohort study, the drug selection for managing tachyarrhythmia was mainly dependent on intensivists or primary doctors examining the patient then. These selection biases might have affected the results observed. However landiolol was administered in more hemodynamically unstable patients, such as lower systolic blood pressure and lower CI, than control group. Therefore we believe that these selection biases may not overestimate the benefit of landiolol that we observed in results. Second, baseline arterial pressure was relatively high, and diastolic pulmonary arterial pressure was not very low. Because sufficient volume resuscitation was first conducted in our study, few patients with intravascular hypovolemia were observed. Third, the number of patients performed a pulmonary arterial catheter analysis was relatively a few in present study. Therefore, the power of the statistical analysis may be weak. However, we did not need to perform a pulmonary arterial catheter analysis because the patients' hemodynamics did not worsen. Therefore, we are convinced that landiolol did not cause hemodynamic deterioration. Finally, we did not evaluate prognosis such as ICU stay length or mortality. Although ICU stay length was similar between the 2 groups, mortality was higher in the control group than in the landiolol group. We did not perform multivariate analysis of mortality; therefore, this requires further investigation.

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing tachyarrhythmias in patients with sepsis.

## ACKNOWLEDGMENTS

We thank patients and staff at Kanazawa University Hospital who participated in this project.

## COMMENTS

### Background

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The management of tachyarrhythmia is important as tachyarrhythmias have been identified as a major source of morbidity in critically ill patients. However it is often difficult because of unstable hemodynamics in septic patients.

### Research frontiers

Landiolol, an ultra-short-acting  $\beta_1$  selective adrenoceptor antagonist, exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other  $\beta$  blockers. The current research hotspots is whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in septic patients.

### Innovations and breakthroughs

Landiolol significantly reduced heart rate without any deterioration of hemodynamics. The most impressive finding in the study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias.

### Applications

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

### Terminology

Landiolol, a newly developed commercially available agent, is an ultra-short-acting  $\beta$ -adrenoceptor antagonist (a half-life of 4 min), has high  $\beta_1$  selectivity ( $\beta_1/\beta_2 = 255$ ) and exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol.

### Peer-review

The paper is interesting and well written.

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