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Effects of landiolol on hemodynamic response and seizure duration during electroconvulsive therapy

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Abstract
Purpose. This study was done to evaluate the effect of landiolol, an ultra-short-acting beta-blocker, on the hemodynamic response and the duration of seizure activity during electroconvulsive therapy (ECT).
Methods. We designed a prospective, randomized, double-blinded, placebo-controlled, crossover study. Fourteen psychiatric patients participated. Landiolol ($0.1\,mg\cdot kg^{-1}$ or $0.2\,mg\cdot kg^{-1}$) or saline (placebo) was administered IV 1 min before the induction of anesthesia. Unconsciousness was induced with propofol $1.0\,mg\cdot kg^{-1}$ IV, and muscle paralysis was produced with succinylcholine $0.6\,mg\cdot kg^{-1}$ IV. Subsequently, electrical stimulus was administered to elicit a seizure, and the duration of the motor seizure activity was noted.
Results. The heart rate (HR) and rate-pressure product (RPP) before ECT were significantly decreased in the $0.2\,mg\cdot kg^{-1}$ landiolol group compared with these parameters in the placebo and $0.1\,mg\cdot kg^{-1}$ landiolol groups. Both the $0.1\,mg\cdot kg^{-1}$ and $0.2\,mg\cdot kg^{-1}$ doses significantly attenuated the degree of tachycardia and RPP after ECT in comparison with the placebo group. Pretreatment with $0.2\,mg\cdot kg^{-1}$ landiolol resulted in a significantly shorter duration of motor seizure than that in the placebo group (21 ± 13 s vs 27 ± 12 s).
Conclusion. As the landiolol dose of $0.2\,mg\cdot kg^{-1}$ caused shorter seizure duration, and because the hemodynamic effects after ECT of the $0.1\,mg\cdot kg^{-1}$ and $0.2\,mg\cdot kg^{-1}$ doses were similar, it was concluded that a $0.1\,mg\cdot kg^{-1}$ landiolol bolus was the appropriate dose pretreatment before ECT.

Key words Landiolol · Electroconvulsive therapy · Hemodynamic response · Duration of seizure

Introduction

In recent years, electroconvulsive therapy (ECT) has assumed an increasingly important role in the treatment of severe and medication-resistant depression and mania, as well as in the treatment of schizophrenic patients [1].

However, ECT is frequently associated with acute hyperdynamic responses: transient tachycardia and hypertension. The magnitude of hemodynamic responses to ECT appears to be independent of the duration of the motor and electro encephalogram (EEG) seizure activity [2]. The hemodynamic response to ECT can produce myocardial ischemia and even infarction [3], as well as transient neurologic ischemic deficits, intracerebral hemorrhage, and cortical blindness [4,5]. Because of the possible cardiovascular morbidity associated with ECT, various drugs have been administered in an effort to minimize the acute hemodynamic changes [6]. Recommended pretreatment regimens to block the ECT-induced hyperdynamic response include trimethaphan [7], nitroprusside [8], alfentanil [9], clonidine [10], propranolol [11], labetalol [12], esmolol [13–15], nicardipine [16], and remifentanil [17].

Landiolol is a newly developed highly cardioselective beta-blocker. This agent is approximately nine times more potent in beta-blocking activity in vivo and eight times more cardioselective in vitro than esmolol [18]. The cardiodepressant effect of landiolol is less than that of esmolol [19,20]. Recently, a bolus injection of landiolol ($0.1\,mg\cdot kg^{-1}$, IV) was reported to be useful for attenuating the acute hemodynamic responses without reducing seizure duration during ECT [21]. However, comparison of the effects of different bolus doses and their effects during ECT have not been thoroughly investigated.

We hypothesized that landiolol would attenuate the transient hyperdynamic response to ECT in a dose-dependent fashion without interfering with the seizure

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activity. Therefore, we designed a prospective, randomized, double-blinded, placebo-controlled, crossover study to assess the effects of two different bolus doses of landiolol (versus saline) on the acute hemodynamic response and the duration of motor seizure activity in patients undergoing a series of ECT treatments.

Patients and methods

After gaining approval from the Research Ethics Board of the Showa University School of Medicine (Tokyo, Japan), we obtained informed consent from 14 patients undergoing ECT treatments for major depressive or psychiatric disorders. All treatments were performed in the operating room at the Showa University Northern Yokohama Hospital (Yokohama, Japan). Patients with clinically significant cardiovascular, respiratory, renal, or hepatic disease, or with hypotension, bradycardia, arrhythmia, second- or third-degree atrioventricular block, or hypertension, as well as those using beta-adrenergic blockers or other antihypertensive drugs were excluded from the study. All patients received ECT two times a week given during a 2-week period.

All patients received their usual chronic psychotherapeutic medications (such as antidepressants) in the morning before each ECT session, and no premedication was given. Each patient received one of two different doses of landiolol (0.1 mg·kg^{-1} or 0.2 mg·kg^{-1}) or a placebo (saline) before the induction of anesthesia, according to a randomized, double-blinded, crossover study design. Noninvasive systolic blood pressure (SBP) and mean arterial blood pressure (MAP), three-lead electrocardiogram (ECG), instantaneous heart rate (HR), and oxygen saturation values were recorded before landiolol or saline administration as baseline values. Then, all patients were preoxygenated.

A 10-ml syringe containing an equivalent volume of either saline or landiolol (0.1 mg·kg^{-1} or 0.2 mg·kg^{-1}) was prepared in advance by a researcher not involved in the data collection. Landiolol (or placebo) was administered at time zero by hand-held bolus, over 5 s, 1 min before the induction of anesthesia and exactly 3 min before ECT. Subsequently, unconsciousness was induced with propofol 1.0 mg·kg^{-1} IV. On loss of responsiveness to verbal commands, a blood pressure cuff was inflated on the left leg to isolate the circulation, so that the duration of motor seizure activity could be measured. Succinylcholine 0.6 mg·kg^{-1} IV was then administered for muscle relaxation. The patients were ventilated using a face mask with 100% oxygen. Three minutes after the administration of landiolol or saline, an electrical stimulus was delivered via bitemporal electrodes, using a Sakai CS-1 apparatus (Sakai Medical Instruments, Tokyo, Japan) at 110 V setting for 5 s. Motor seizure duration was evaluated, using a one-channel EEG and the tourniquet technique, as the time from the ECT stimulus to the cessation of tonic-clonic motor activity in the isolated leg. If the patient manifested a sustained increase in SBP (>190 mmHg, lasting >2 min) after the electrical stimulus, rescue bolus doses of nicardipine (1 mg) were administered. All variables were continuously recorded until 15 min after ECT.

Multiple comparisons were made by using one-way analysis of variance, followed by the Scheffe test. Comparisons for repeated measures were made by using linear mixed effect models, followed by least squares means. Statistical analysis was performed using SAS software, version 8.02 (SAS Institute, Cary, NC, USA). Probability values of less than 0.05 were required to reject the null hypothesis. We reported values as means ± SD in the Tables and as means ± SE in the Figures.

Results

Fourteen patients, with 84 treatments, were initially enrolled. Three patients with 18 treatments (placebo, $n = 6$, landiolol 0.1 mg·kg^{-1}; $n = 6$, landiolol 0.2 mg·kg^{-1}; $n = 6$) were excluded from the statistical analysis because they received nicardipine in all of their ECT events due to hypertension after ECT. Finally, 66 treatments in the 11 remaining patients (3 men and 8 women) were evaluated. All of the finally evaluated patients had a diagnosis of major depression. Their mean age (±SD) was 66 ± 7 years (range, 50–76 years), and mean body weight was 45 ± 6 kg (range, 35–54 kg). There were no significant differences in baseline SBP, MAP, or HR among the three groups. HR decreased significantly after 0.2 mg·kg^{-1} landiolol compared with that in the placebo group (Table 1). Pretreatment with landiolol 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1} was found to blunt significantly the increase in HR in comparison to that in the placebo group (Fig. 1). In the placebo group, all HR values after ECT were significantly higher than the baseline value. In the landiolol 0.1 mg·kg^{-1} group, HR values were significantly higher than the baseline value until 2 min after ECT. In the landiolol 0.2 mg·kg^{-1} group, however, HR values after ECT did not change significantly compared with the baseline value (Fig. 1). In all groups, SBP values were significantly higher than the baseline value until 4 min after ECT. The SBP values in the 0.2 mg·kg^{-1} landiolol group were significantly lower than those in the placebo group until 2 min after ECT, whereas there were no significant differences between the two landiolol groups (Fig. 2). Pretreatment with landiolol 0.1 mg·kg^{-1} or 0.2 mg·kg^{-1} was found to blunt significantly the increase in the rate-pressure product (RPP) in comparison to that in the placebo group (Fig. 3). In the placebo group, all RPP values

Table 1. Hemodynamic values at baseline and immediately before (pre-ECT) electroconvulsive therapy (ECT) in the three groups

	Placebo	Landiolol groups	
Variable	Normal saline ($n = 22$)	0.1 mg·kg^{-1} ($n = 22$)	0.2 mg·kg^{-1} ($n = 22$)
Baseline values			
SBP (mmHg)	122 ± 19	122 ± 22	123 ± 20
MAP (mmHg)	84 ± 9	89 ± 16	87 ± 13
HR (bpm)	69 ± 18	70 ± 18	72 ± 20
Pre-ECT values			
SBP (mmHg)	122 ± 23	121 ± 20	114 ± 20
MAP (mmHg)	86 ± 11	88 ± 14	83 ± 14
HR (bpm)	75 ± 17	68 ± 16	64 ± 15*

* $P < 0.05$ versus placebo group
Values are means ± SD and numbers of treatments (n)
SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate

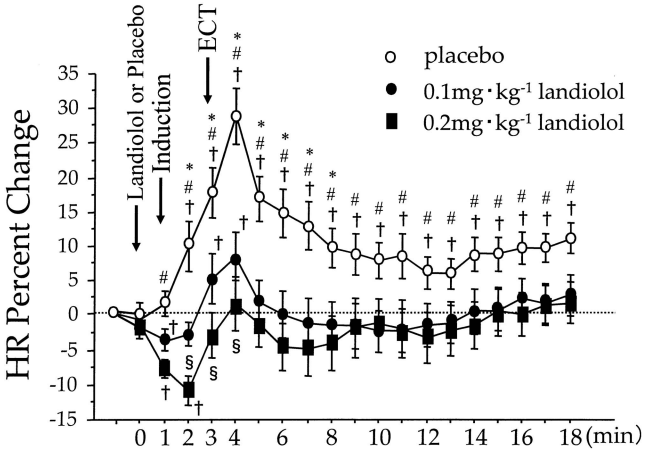

Fig. 1. Heart rate (*HR*) percent change every minute during electroconvulsive therapy (*ECT*). Values are means ± SE for the placebo, 0.1 mg·kg^{-1} landiolol, and 0.2 mg·kg^{-1} landiolol groups. * $P < 0.05$ versus 0.1 mg·kg^{-1} landiolol group. # $P < 0.05$ versus 0.2 mg·kg^{-1} landiolol group; § $P < 0.05$ between the two landiolol groups; † $P < 0.05$ versus baseline values. *Dotted line*, baseline

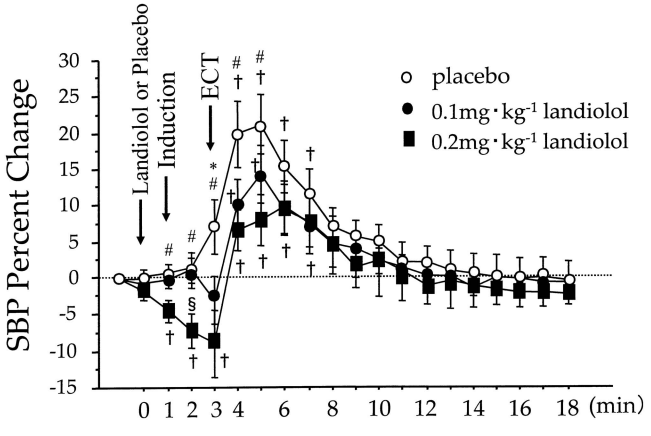

Fig. 2. Systolic blood pressure (*SBP*) change every minute during electroconvulsive therapy (ECT). Values are means ± SE. For *P* values, see Fig. 1. legend

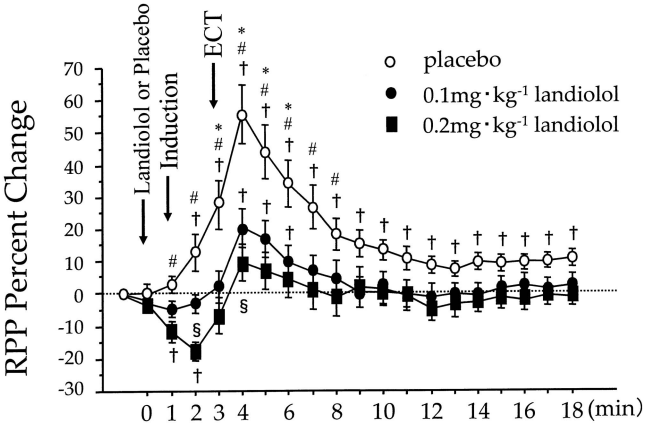

Fig. 3. Rate pressure product (*RPP*) percent change every minute during electroconvulsive therapy (ECT). Values are means ± SE. For *P* values, see Fig. 1. legend

after ECT were significantly higher than the baseline value. In the landiolol 0.1 mg·kg^{-1} group, RPP values were significantly higher than the baseline value until 3 min after ECT. In the landiolol 0.2 mg·kg^{-1} group, however, RPP values after ECT did not change significantly compared with the baseline value (Fig. 3). The duration of the motor seizure was significantly shorter with 0.2 mg·kg^{-1} landiolol compared with that in the placebo group (Table 2). There were no adverse events that could be attributed to landiolol.

Discussion

The results of this study indicate that landiolol, a novel beta-adrenergic blocker, given as an 0.1 or 0.2 mg·kg^{-1} IV bolus as pretreatment significantly attenuates the cardiovascular response to ECT. The results also showed a significant decrease in motor seizure duration with the landiolol 0.2 mg·kg^{-1} bolus, compared with the duration in the placebo group.

Table 2. Duration of motor seizure after electroconvulsive therapy

	Placebo	Landiolol groups	
Variable	Normal saline ($n = 22$)	0.1 mg·kg^{-1} ($n = 22$)	0.2 mg·kg^{-1} ($n = 22$)
Motor seizure (s)	27 ± 12	23 ± 9	21 ± 13*

* $P < 0.05$ versus placebo group
Values are means ± SD and numbers of treatments (n)

Landiolol is created by altering the chemical structure of esmolol, an other ultrashort acting beta-adrenergic blocker, to produce a greater degree of cardioselectivity and more potency [18]. Landiolol is approximately nine times more potent on a weight basis in beta-blocking activity in vivo than esmolol [18]. Landiolol has a short duration (half-life of 4 minutes) of activity, enabling rapid recovery after cessation of administration by hydrolysis of its ester link [18]. Bolus injection of landiolol has been reported to attenuate HR significantly, with less cardiodepressant effect than esmolol, in rabbits [19]. Furthermore, a bolus injection of landiolol (0.1 mg·kg^{-1}, IV) was reported to be useful for attenuating acute hemodynamic responses without reducing seizure duration during ECT [21]. The present study also showed that landiolol, at 0.1 mg·kg^{-1} and 0.2 mg·kg^{-1}, significantly attenuated the increase in HR and RPP after ECT. Therefore, the results of our study also indicate that the features of landiolol are suitable for its use in ECT.

Weinger et al. [13] reported that, immediately after ECT, SBP transiently increased by 30%–40%, and HR was increased by 20% or more, resulting in a two- to threefold increase in the RPP, an index of myocardial oxygen consumption. The placebo group in our study showed that SBP was transiently increased by 20%, and HR was increased by 29%, resulting in a 56% increase in the RPP. It has also been reported that significant increases in HR and SBP continue for 3–5 min after the application of the electrical stimulus [2]. Thus, it is important to attenuate the hyperdynamic response after ECT, particularly in patients with hypertension, and in those with cardiovascular or cerebrovascular diseases. In the present study, the degree of tachycardia and RPP increase after ECT in both landiolol groups was significantly less than that in the placebo group. The HR and RPP values in our placebo group were still significantly increased 15 min after ECT. However, 3 min after ECT, the HR and RPP values in both landiolol groups had not changed significantly compared with the baseline value. Therefore, landiolol was considered to be useful for the attenuation of the hyperdynamic response during the whole period of ECT. Because of the rapid onset of action of landiolol, the negative chronotropic effect of landiolol could have contributed to the immediate attenuation of tachycardia and RPP after ECT. The decreased HR and SBP values immediately after administration of the landiolol bolus were not considered to be clinically significant. Our data support the view that pretreatment with a landiolol bolus injection is appropriate for attenuating the tachycardia and increased RPP that occur in response to ECT, without causing bradycardia or hypotension. We believe that suppression of the RPP increase is associated with the attenuation of tachycardia.

The therapeutic effect of ECT depends on a cerebral seizure. It is recommended that seizure duration should be monitored during each treatment, both by observation of motor activity and by the monitoring of at least one channel of electroencephalogram (EEG) activity [22]. Thus, we measured seizure duration using a tourniquet technique and a one-channel EEG. But we substituted isolated limb myoclonic activity for the one-channel EEG as the dependent variable for seizure duration, because we considered that the data with one-channel EEG was not sufficient to show seizure duration. Seizure duration, as measured by EEG, correlates well with the duration of isolated limb myoclonic activity [13]. Electrical manifestations of a seizure are present for 5–8 s longer than the limb movement [13]. Esmolol appears to decrease seizure duration in a dose-related fashion. Esmolol 1.0 mg·kg^{-1} [13] or 1.4 mg·kg^{-1} [14] bolus did not decrease the duration of seizure, whereas esmolol 2.86 mg·kg^{-1} bolus [14] significantly shortened the duration. Even in studies using larger doses of esmolol, however, seizure duration was only moderately reduced and this did not jeopardize the therapeutic efficacy of ECT [14,15].

In our study, there was a significant difference in seizure duration between the placebo group and the 0.2 mg·kg^{-1} landiolol group, but no significant difference between the placebo group and the 0.1 mg·kg^{-1} landiolol group. Thus, landiolol bolus also appears to have a dose-related effect on seizure duration. Because many of the anesthetic drugs used for ECT have anticonvulsant properties, they would be expected to decrease the duration of ECT-induced seizure activity in a dose-dependent manner. The use of larger than necessary doses of general anesthetics would shorten the duration of ECT-induced seizure activity and could adversely affect the efficacy of the ECT treatment [6]. Oda et al. [23] reported that the increase in both heart rate and

bispectral index after tracheal intubation under 1 minimum alveolar concentration (MAC) sevoflurane anesthesia was suppressed by the concomitant administration of either esmolol or landiolol. Therefore, landiolol and esmolol appear to have general anesthetic properties. The reason why higher doses of landiolol and esmolol suppress seizure activity is thought to be that the similar chemical structures and general anesthetic properties of the two drugs would presumably affect seizure duration if a sufficient dose were given.

In summary, both landiolol $0.1\,mg{\cdot}kg^{-1}$ and $0.2\,mg{\cdot}kg^{-1}$ bolus doses were found to be effective in attenuating the hemodynamic response to ECT. As the $0.2\,mg{\cdot}kg^{-1}$ dose caused a shorter seizure duration, and the hemodynamic effects after ECT of the $0.1\,mg{\cdot}kg^{-1}$ and $0.2\,mg{\cdot}kg^{-1}$ doses were similar, it was concluded that pretreatment with a $0.1\,mg{\cdot}kg^{-1}$ landiolol bolus dose achieved similar HR reduction after ECT to that produced by $0.2\,mg{\cdot}kg^{-1}$, without shortening the duration of the motor seizure. A potential weakness of the study is the exclusion of individuals who were administered a rescue drug, which may have led to selection bias. Further study is necessary to investigate the degree of the contribution of landiolol to seizure duration during ECT.

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References

1. Thompson JW, Weiner RD, Myers CP (1994) Use of ECT in the United States in 1975, 1980 and 1986. Am J Psychiatry 151:1657–1661
2. Fu W, Stool LA, White PF, Husain MM (1997) Acute hemodynamic responses to electroconvulsive therapy are not related to the duration of seizure activity. J Clin Anesth 9:653–657
3. Friedman J, Gordon N (1992) Electroconvulsive therapy in Parkinson's disease: a report on five cases. Convuls Ther 3:204–210
4. Weisberg LA, Elliott D, Mielke D (1991) Intracerebral hemorrhage following electroconvulsive therapy. Neurology 41:1849
5. Rikher KV, Johnson R, Kamal M (1997) Cortical blindness after electroconvulsive therapy. J Am Board Fam Pract 10:141–143
6. Ding Z, White PF (2002) Anesthesia for electroconvulsive therapy. Anesth Analg 94:1351–1364
7. Tewfik GI, Wells BG (1975) The use of Alfonad for the alleviation of cardiovascular stress following electroconvulsive therapy. J Ment Sci 10:636–644
8. Ciraulo D, Lind L, Salzman C, Pilon R, Elkins R (1978) Sodium nitroprusside treatment of ECT-induced blood pressure elevations. Am J Psychiatry 135:1105–1106
9. Nguyen TT, Chibber AK, Lustik SJ, Kolano JW, Dillon PJ, Guttmacher LB (1997) Effect of methohexitone and propofol with or without alfentanyl on seizure duration and recovery in electroconvulsive therapy. Br J Anaesth 79:801–803
10. Fu W, Stool LA, White PF, Husain MM (1998) Is oral clonidine effective in modifying the acute hemodynamic response during electroconvulsive therapy? Anesth Analg 86:1127–1130
11. Husum B, Vester-Andersen T, Buchmann G, Bolwig TG (1983) Electroconvulsive therapy and intracranial aneurysm. Prevention of blood pressure elevation in a normotensive patient by hydralazine and propranolol. Anaesthesia 38:1205–1207
12. Castelli I, Steiner LA, Kaufman MA, Alfille PH, Schouten R, Welch CA, Drop LJ (1995) Comparative effects of esmolol and labetalol to attenuate hyperdynamic states after electroconvulsive therapy. Anesth Analg 80:557–561
13. Weinger MB, Partridge BL, Hauger R, Mirow A (1991) Prevention of the cardiovascular and neuroendocrine response to electroconvulsive therapy: I. Effectiveness of pretreatment regimens on hemodynamics. Anesth Analg 73:556–562
14. Kovac AL, Goto H, Pardo MP, Arakawa K (1991) Comparison of two esmolol bolus doses on the haemodynamic response and seizure duration during electroconvulsive therapy. Can J Anaesth 38:155–158
15. Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA (1990) Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg 71:384–388
16. Avramov MN, Stool LA, White PF, Jusain MM (1998) Effects of nicardipine and labetalol on the acute hemodynamic response to electroconvulsive therapy. J Clin Anesth 10:394–400
17. Recart A, Rawal S, White PF, Byerly S, Thornton L (2003) The effect of remifentanil on seizure duration and acute hemodynamic responses to electroconvulsive therapy. Anesth Analg 95:1047–1050
18. Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, Sakaki K, Hachiya K, Ichioka Y, Kawamura M (1992) Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. Chem Pharm Bull 40:1462–1469
19. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H (2001) In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. Can J Anaesth 48:985–989
20. Sugiyama A, Takahara A, Hashimoto K (1999) Electrophysiologic, cardiohemodynamic and beta-blocking actions of a new ultra-short-acting beta-blocker, ONO-1101, assessed by the in vivo canine model in comparison with esmolol. J Cardiovasc Pharmacol 34:70–77
21. Sakamoto A, Ogawa R, Suzuki H, Kimura M, Okubo Y, Fujiya T (2004) Landiolol attenuates acute hemodynamic responses but does not reduce seizure duration during maintenance electroconvulsive therapy. Psychiatry Clin Neurosci 58:630–635
22. Greenberg RM, Kellner CH (2005) Electroconvulsive therapy: a selected review. Am J Geriatr Psychiatry 13:268–281
23. Oda Y, Nishikawa K, Hase I, Asada A (2005) The short-acting beta 1-adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. Anesth Analg 100:733–737