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CLINICAL REPORT

Effects of landiolol on left ventricular function during electroconvulsive therapy: a transthoracic echocardiographic study

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Abstract The purpose of this study was to examine the effects of landiolol on left ventricular (LV) systolic function, using transthoracic echocardiography, during electroconvulsive therapy (ECT). Fourteen patients undergoing ECT were studied. Bilateral ECT was performed after administration of thiopentone (2 mg/kg), succinylcholine (1 mg/kg), and initiation of assisted mask ventilation with 100% oxygen. Patients received a bolus injection of landiolol (0.125 mg/kg) or saline immediately after anesthetic induction and prior to electrical shock. LV systolic function was examined by transthoracic echocardiography prior to anesthetic induction, throughout the ECT procedure, and for 10 min after the seizure. Electrical shock resulted in a significant decrease in fractional area change (FAC) when compared with the awake condition in the control group [FAC when awake: 48 ± 3%; 1 min after ECT: 38 ± 4%*; 2 min after ECT: 36 ± 4%*; 3 min after ECT: 40 ± 3%*; mean ± standard deviation, $*p < 0.05$ compared with awake]. Landiolol infusion stabilized systemic hemodynamics and LV systolic function. The study demonstrated that landiolol is a suitable agent to minimize hemodynamic changes and transthoracic echocardiographic variability after ECT.

Keywords Electroconvulsive therapy · Echocardiography · Beta-1 selective antagonist

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Introduction

Electroconvulsive therapy (ECT) was introduced into clinical practice after the realization that psychiatric symptoms are improved after a seizure in patients suffering from both schizophrenia and epilepsy. Recently, ECT has taken an increasingly important role in treating severe and medication-resistant depression and mania, as well as schizophrenia patients with affective disorder, suicidal drive, vegetative dysfunction, and catatonic symptoms [1, 2]. There is much data showing the superiority of ECT to antidepressant drugs for treating depression. Pagnin et al. [3] analyzed the efficacy of ECT in depression by means a meta-analytic review compared with placebo or antidepressant drugs and showed that ECT is superior to antidepressant drugs. They concluded that ECT is a valid therapeutic tool for treating depression, including severe and resistant forms.

ECT is associated with the risk of cardiac morbidities [1, 2, 4, 5], including myocardial infarction and cardiac rupture [4, 5]. In order to prevent ECT-induced changes in systemic hemodynamics, investigators have used various antihypertensive agents [1, 2], including alprenolol, nitroglycerin, nicardipine, esmolol, and labetalol [1]. We previously demonstrated that beta-blockers could effectively prevent an increase in heart rate when compared with other drugs [6, 7].

Landiolol is a newly developed, ultra-short-acting beta-1 blocker. This agent is approximately nine times more potent in beta-1 blocking activity and eight times more cardioselective than esmolol [8]. Nomoto et al. [9] demonstrated the efficacy of landiolol for stabilizing systemic hemodynamics during ECT. We previously characterized the time course of changes in left ventricular (LV) systolic function during ECT using an echocardiographic automated border-detection system [10, 11]. Until now, no data existed regarding the effects of landiolol on LV systolic function during ECT. The purpose of this study was to characterize the effects of landiolol on LV systolic function during ECT using the echocardiographic system.

Case report

Informed consent was obtained from patients or their families. All protocols were approved by the local institutional clinical study committee. Fourteen American Society of Anesthesiology (ASA) I or II patients who were scheduled to undergo ECT were studied. None of the patients had a history of cardiovascular disease. All patients underwent ECT at least six times (three times per week at 1- or 2-day intervals). To avoid induction of the parasympathetic reflex, all patients received atropine sulfate (0.01 mg/kg IM) 30 min prior to the ECT procedure. Measured parameters included blood pressure (BP), heart rate, oxygen saturation (SpO_2; measured by pulse oximetry on the left index finger), end-expiratory partial pressure of carbon dioxide (end-tidal CO_2) at the nostrils (Capnomac UltimaTM; Datex Co, Ltd., Helsinki, Finland), and electrocardiogram (ECG; lead II). Measurements were initiated prior to ECT and were terminated at the end of the procedure. Anesthesia was induced using thiopentone (2 mg/kg intravenously over 15 s) [6] followed by succinylcholine (1 mg/kg intravenously). Assisted mask ventilation was initiated with 100% oxygen. One minute after the injection of landiolol or saline, an electroshock stimulus was applied bilaterally for 5 s. End-tidal CO_2 was maintained at 30–35 mmHg, and the SpO_2 value was maintained above 98% by manual mask assistance throughout the therapy.

Fourteen patients diagnosed with major depression were randomly divided into two groups: control (placebo) group and landiolol infusion group, with group selection being determined by a random number table. All patients received their usual chronic psychotherapeutic medications (such as antidepressants) in the morning before each ECT session, and no premedication was given. Based on our previous reports of the lowest effective landiolol dose for hemodynamic stabilization [6], an intravenously administered dose of 0.125 mg/kg ($n = 7$) was selected in this study over doses of 0.25 and 0.50 mg/kg. As a control ($n = 7$), another group of patients received the same volume of saline. All persons present at the ECT session were blinded to the identity of the drug administered to each patient (drugs were given via a foil-covered cylinder and lines). Data were analyzed at a later time by an individual also blinded to the treatment regimens.

Transthoracic echocardiography (Hewlett Packard SONOS 5500^R, 3.5 MHz transducer, Andover, MA, USA) with an automated border detection system (Acoustic Quantification^R system) was employed to measure LV fractional area change (FAC), as previously described [10, 11]. Briefly, LV parasternal short-axis images were recorded at the midpapillary muscle level. LV area was calculated in each cardiac cycle and displayed as a waveform. Values of end-systolic and end-diastolic LV areas were then automatically averaged over five cardiac cycles, taking into account the expiration phase. Acoustic quantification was recorded on video tape to assess validity of the gain setting.

The following LV indices were measured for each patient: end-systolic area (ESA), end-diastolic area (EDA), and FAC [FAC = (EDA − ESA)/EDA × 100]. According to our previous report [10], we used the quotient of systolic BP and (EDA–ESA) as an index of LV afterload. Regional wall motion abnormality (RWMA) was defined as a worsening in wall motion of any segment by two or more grades for at least 1 min, as independently determined by two experienced echocardiographers. An ischemic episode was defined as at least 1 min of new-onset ST segment depression from baseline of 1 mm or greater for at least 1 min or new ST elevation of 2.0 mm or greater from baseline in a non-Q-wave lead.

Statistical analysis

All data are expressed as means ± standard deviation (SD). Changes in mean values were compared with baseline values using one-way repeated measure of analysis of variance (ANOVA). Schiff's method was used for multiple comparisons. Data between the two groups was analyzed by the unpaired t test. Statistical significance was set at $p < 0.05$. All calculations were performed on a Macintosh computer with SPSS (SPSS, Inc., Chicago, IL, USA) and Stat View 5.0 software (Abacus Concepts, Inc., Berkeley, CA. USA). Adequate cardiac images were obtained from all patients by transthoracic echocardiography. There were no differences in demographic data between the two groups (Table 1). There were no significant differences in heart rate and mean arterial BP (MAP), EDA, ESA, FAC, or systolic BP/EDA–ESA when comparing the two groups in the awake condition (Table 2). Following the electrical shock, increases in heart rate and MAP were observed in the

control group but not in the landiolol group. This increase lasted 5 min after the shock. No change in EDA after the shock was observed in either group. In contrast, increases in ESA after the shock was observed in the control group but not the landiolol group, with the increase lasting 3 min. A decrease in FAC after the shock was observed in the control group, but not the landiolol group. Increases in systolic BP/EDA–ESA after the shock were observed in the control group but not in the landiolol group.

No RWMA or ST segment changes were observed in any of the patients during baseline conditions or after ECT.

Discussion

This study demonstrated that landiolol could prevent increases in HR, MAP, and systolic BP/EDA–ESA and could also prevent a decrease in FAC after the electrical shock. Recent guidelines have recommended the use of the ultrashort-acting beta-blocker, esmolol, and the alpha-/beta-blocker, labetalol, as antihypertensive medication in patients undergoing ECT who have coexisting cardiovascular diseases [1, 2]. Although many reports [1, 2, 12, 13] have demonstrated the efficacy of esmolol and landiolol in preventing abrupt hemodynamic changes after electrical shock, few studies using esmolol have performed echocardiographic assessment of LV systolic function during ECT [12, 14]. Although O'Connor et al. [12] showed the efficacy of esmolol (1 mg/kg) for preventing hemodynamic changes associated with ECT, they found no beneficial effect of esmolol pretreatment on the incidence of RWMA. In this study, we focused on assessing RWMA during ECT, in particular, the effects of landiolol on LV systolic performance as assessed by echocardiography, and found that landiolol could effectively prevent decreases in LV systolic performance and hemodynamic instability during ECT. LV preload, grossly estimated from EDA, appeared unaltered during the study. Hence, decreased LV systolic performance observed in the control group may be mostly attributable to the increase in both ESA and the index of LV afterload.

Table 1 Demographic data of the two groups

	Control	Landiolol	*p* Value
Age (year)	65 ± 12	68 ± 10	0.55
Weight (kg)	49 ± 6	50 ± 6	0.77
Height (cm)	157 ± 4	158 ± 5	0.84

Values are expressed as mean ± standard deviation

Table 2 Time course of changes in hemodynamic variables in the two groups during electroconvulsive therapy (ECT)

Measurement time	1	2	3	4	5	6	7
Heart rate (beats/min)							
Control	77 ± 11	74 ± 9	100 ± 12*,#	96 ± 10*,#	93 ± 7*,#	76 ± 3	76 ± 8
Landiolol	75 ± 9	76 ± 7	78 ± 2	74 ± 4	76 ± 3	73 ± 5	73 ± 4
MAP (mmHg)							
Control	83 ± 6	78 ± 6	129 ± 10*,#	122 ± 10*,#	112 ± 8*,#	98 ± 4*,#	85 ± 6
Landiolol	84 ± 4	78 ± 6	111 ± 3*	109 ± 3*	93 ± 4	86 ± 3	86 ± 4
End-diastolic area (cm^2)							
Control	9.7 ± 0.9	10.0 ± 0.6	10.1 ± 0.8	9.7 ± 0.7	9.7 ± 0.4	9.7 ± 0.6	9.9 ± 0.3
Landiolol	9.8 ± 1.1	9.9 ± 1.0	10.0 ± 0.7	9.9 ± 0.6	9.8 ± 0.7	9.9 ± 0.7	9.7 ± 0.5
End-systolic area (cm^2)							
Control	4.9 ± 0.2	4.8 ± 0.2	6.1 ± 0.1*,#	6.1 ± 0.2*,#	5.7 ± 0.2*,#	5.1 ± 0.2	4.9 ± 0.2
Landiolol	5.0 ± 0.2	4.8 ± 0.3	5.2 ± 0.3	5.0 ± 0.2	5.0 ± 0.2	4.8 ± 0.2	4.9 ± 0.2
Fractional area change (%)							
Control	48 ± 3	51 ± 4	38 ± 4*,#	36 ± 4*,#	40 ± 3*,#	47 ± 3	50 ± 1
Landiolol	47 ± 7	50 ± 6	47 ± 4	48 ± 3	48 ± 4	50 ± 4	48 ± 3
Systolic BP/EDA-ESA ($mmHg/cm^2$)							
Control	22 ± 3	19 ± 2	38 ± 6*,#	41 ± 8*,#	33 ± 4*,#	26 ± 3	21 ± 2
Landiolol	23 ± 7	20 ± 4	27 ± 3	26 ± 3	24 ± 3	21 ± 3	22 ± 3

Values are expressed as mean ± standard deviation

MAP mean arterial pressure, *EDA* end-diastolic area, *ESA* end-systolic area, *BP* blood pressure

1: awake, 2: 1 min after thiopental administration, 3: 1 min after electrical shock, 4: 2 min after electrical shock, 5: 3 min after electrical shock, 6: 5 min after electrical shock, 7: 10 min after electrical shock

* $p < 0.05$ compared with period 1, # $p < 0.05$ compared with landiolol group

To attenuate hemodynamic instability, beta-blockers such as esmolol, labetalol, or landiolol are often used during ECT. However, there is a clinically problematic concern as to whether such agents affects seizure duration. Van den Broek et al. [15] reported that although a bolus dose of 80 mg of esmolol i.v. reduced the increases in hemodynamic variables during convulsions compared with placebo, seizure duration measured by EEG was reduced from 9.9 to 5.83 s. Sakamoto et al. [13] reported that administration of 0.1 mg/kg of landiolol immediately before anesthesia blunted the increase in heart rate and BP without affecting seizure duration or causing adverse hemodynamic effects such as bradycardia or hypotension. We previously compared the effects of esmolol and landiolol on hemodynamic variables during ECT. Heart rate was stabilized by 1.0 mg/kg esmolol i.v. and 0.5 mg/kg landiolol, whereas increase in mean BP was improved by esmolol but not by landiolol [16]. Nomoto et al. [9] showed that 0.1 and 0.2 mg/kg bolus doses of landiolol were found to be effective in attenuating the hemodynamic responses to ECT. In addition, they concluded that because the 0.2 mg/kg dose of landiolol causes a shorter seizure duration, and the hemodynamic effects of the 0.1- and 0.2-mg/kg dose of landiolol after ECT were similar, pretreatment with a 0.1 mg/kg landiolol bolus dose was suitable for attenuation of hemodynamic alterations during ECT. Seizure duration is one of the variables used to assess the adequacy of convulsions, and reduction in seizure duration may interfere with therapeutic efficacy. Whereas it has become clear that neurophysiological characteristics other than seizure duration, such as amplitude, symmetry, coherence, and postictal suppression, are important for seizure quality, the effects of esmolol, labetalol, or landiolol influences on these characteristics are not yet known. Further research is required to elucidate the effects of these three drugs on these neurophysiological characteristics.

Echocardiographic examination is a noninvasive method of assessing LV function and can be used to detect ischemic changes in the form of RWMA [17]. Our study demonstrated that LV systolic function transiently decreased after electrical shock in the control group. As an abrupt change in hemodynamics might precipitate myocardial ischemia in susceptible patients, it is important to avoid such events in patients with ischemic coronary disease. Our data suggest that landiolol is a suitable agent for stabilizing LV systolic performance and systemic hemodynamics.

This study has several limitations. First, although we attempted to characterize any RWMA induced by ECT, not all segments of the LV were examined. Thus, we were was unable to definitely determine whether new RWMA occurred after ECT. Second, the automated border detection system did not take the papillary muscles into account, potentially resulting in low values of EDA and ESA and underestimation of the LV area.

In summary, the study demonstrated that landiolol is a suitable agent to minimize systemic hemodynamic changes and transthoracic echocardiographic variability after ECT.

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