

# Reconsideration of Augmentation Strategies in Electroconvulsive Therapy: Effects of the Concurrent Use of a Reduced Dose of Propofol with Divided Supplemental Remifentanyl and Moderate Hyperventilation on Electroconvulsive Therapy-Induced Seizure Production and Adverse Events

Kohki Nishikawa<sup>1\*</sup>, Michiaki Yamakage<sup>2</sup>

<sup>1</sup>Department of Anesthesia, Muroran City General Hospital, Muroran, Japan

<sup>2</sup>Department of Anesthesiology, Sapporo Medical University School of Medicine, Sapporo, Japan

Email: [\\*murohosp082@kujiran.jp](mailto:murohosp082@kujiran.jp)

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## Abstract

**Background:** Although several treatment strategies to enhance the efficacy of electroconvulsive therapy (ECT) have been discussed, there have been no reports on the combined use of these treatments. The purpose of this study was to evaluate the efficacy and safety of concurrent use of moderate hyperventilation and a reduced dose of propofol combined with divided remifentanyl in ECT practice. **Methods:** Sixty patients scheduled to receive a total of 300 ECT treatments were randomly assigned to have the three interventions: a standard dose (1 mg/kg) of propofol (group P/N); a standard dose of propofol and moderate hyperventilation with end-tidal pressure of carbon dioxide (ETCO<sub>2</sub>) of 30 - 35 mmHg (group P/H); and a reduced dose (0.5 mg/kg) of propofol with divided supplemental remifentanyl and moderate hyperventilation (group RP/H). Patients in group RP/H received remifentanyl 1 µg/kg followed by propofol 0.5 mg/kg for unconsciousness and thereafter remifentanyl 1 µg/kg immediately before the ECT stimulus. **Results:** Patients in

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\*Corresponding author.

group RP/H showed significantly longer durations of electroencephalographic (EEG) seizures in the early phase of ECT course ( $P < 0.01$  and  $0.05$ ) and lower electrical stimulus in the late phase of ECT course ( $P < 0.05$  in each) than those in groups P/N and P/H, respectively. **Conclusions:** The use of a reduced dose of propofol combined with divided supplemental remifentanyl under moderate hyperventilation during ECT can offer advantages over the use of a standard dose of propofol with or without moderate hyperventilation in terms of more seizure augmentation and/or lower electrical stimulus.

## Keywords

**Electroconvulsive Therapy, Moderate Hyperventilation, Reduced Dose of Propofol, Seizure Duration, Electrical Stimulus Intensity**

## 1. Introduction

Electroconvulsive therapy (ECT) has been used as a highly efficacious treatment of mood and psychotic disorders, and the duration of ECT-induced seizure activity has been extensively studied as a possible marker for clinical efficacy. Although the effect of generalized seizure duration on the clinical outcome remains unclear, no seizure or a brief seizure duration is considered to be less effective ECT [1]. Advanced age [2], increment of ECT treatments [3], and the use of hypnotic agents with anticonvulsant properties [4] [5], have been reported to increase seizure thresholds, and high initial seizure thresholds have been shown to result in shorter seizure duration. Augmentation strategies for enhancing seizure production may therefore be required for patients with high seizure thresholds and with shortened seizures or inability to elicit seizures.

For augmentation of therapeutic seizures in ECT [6], several procedures, including hyperventilation [7]-[9] and the use of remifentanyl [10]-[14] or ketamine [15] [16], have been reported to have varying degrees of success. The American Psychiatric Association [1] first recommends restimulation at higher intensities for patients with suboptimal seizure induction, and next suggests hyperventilation in the management of patients with inadequate seizure induction after restimulation. Severely high stimulus intensities and/or a markedly high level of hyperventilation for patients refractory to optimal seizure production in the maximal ECT settings may however contribute to the severe cognitive dysfunction and/or cerebral hypoxia and myocardial ischemia induced by cerebral and coronary vasoconstriction.

On the other hand, we expected that concomitant use of some augmentation treatments for strategies with less adverse effects for enhancing outcomes would be appropriate. To the best of our knowledge, however, there have been no reports on this combined technique.

The present study was therefore conducted to evaluate whether concomitant application of a reduced dose of propofol combined with divided remifentanyl supplementation and moderate hyperventilation for ECT procedures led to greater seizure augmentation and/or fewer side effects compared with a standard use of propofol with or without moderate hyperventilation.

## 2. Materials and Methods

After obtaining IRB approval at Muroran City General Hospital and written, informed consent from each patient, patients with a variety of psychiatric conditions were enrolled in a prospective, randomized, controlled trial. Exclusion criteria were age younger than 20 years or older than 80 years, myocardial infarction in the previous 6 months, coronary artery disease, atrial fibrillation or flutter, heart block, uncontrollable hypertension, chronic respiratory disease, cerebrovascular diseases, and drug allergy. ECT treatments were given to all patients 3 times per week with 2-day intervals. One sequential ECT treatment consisted of 5 to 10 ECT treatment sessions. None of the patients was premedicated. The patients were assigned to the following three groups ( $n = 20$  each) in a stratified, randomized order: 1) a group in which patients had propofol alone for anesthetic induction and received normoventilation [end-tidal carbon dioxide partial pressure (ETCO<sub>2</sub>) of 40 - 45 mmHg] before ECT (group P/N); 2) a group in which patients had propofol alone and received moderate hyperventilation (ETCO<sub>2</sub> of 30 - 35 mmHg) before ECT (group P/H); and 3) a group in which patients had a reduced dose of propofol with

divided infusion of remifentanyl and received moderate hyperventilation (ETCO<sub>2</sub> of 30 - 35 mmHg) before ECT (group RP/H).

Patients in groups P/N and P/H received propofol at 1 mg/kg over 20 sec, and patients in group RP/H had remifentanyl at 1 µg/kg over 60 sec, followed by propofol at 0.5 mg/kg over 10 sec to induce unconsciousness. On loss of consciousness, a blood pressure cuff was inflated on the right or left leg, and 1 mg/kg succinylcholine was administered intravenously. Patients in group RP/H were thereafter given remifentanyl at 1 µg/kg over 60 sec again immediately before the ECT stimulus. All medication with remifentanyl was prepared in a 10-mL syringe diluted with 0.9% normal saline. From after succinylcholine infusion to immediately before the ECT stimulus, patients in group P/N were manually ventilated using a facemask with 100% oxygen with normoventilation being performed, and patients in groups P/H and RP/H were ventilated with hyperventilation performed. After resolution of muscle fasciculation and manual ventilation over 120 sec, a suprathreshold electrical stimulus was delivered via bifrontotemporal electrodes with a Thymatron DGX device (Somatos, Palo Alto, CA, USA) by a psychiatrist. The magnitude of stimulus intensity provided by ECT was predetermined by age for each patient's first ECT ("half-age" stimulation strategy) [17]. The pulse width was 1.0 millisecond, and the frequency was 70 Hz. When an inadequate seizure appeared with the half-age stimulation setting, stimulus intensity was determined by the stepwise increase method [18] from the next treatment.

Systolic blood pressure (SBP), mean arterial blood pressure (MAP), heart rate (HR), and oxygen saturation were recorded before and after anesthesia and at 0, 1, 2, 3, 4, and 5 min after the ECT stimulus. Baseline MAP and HR were determined from the average of three consecutive readings. The rate-pressure product (RPP) was calculated from SBP and HR in each ECT session. The durations of motor and electroencephalographic (EEG) seizure activities were recorded using electromyographic (EMG) and EEG monitors attached to the ECT device as the times from the electrical stimulus to cessation of tonic-clonic motor activity in the isolated foot and to postictal EEG suppression, respectively. Times from the ECT stimulus to spontaneous breathing and to response to a simple verbal command (emergence time) were assessed. Adequate seizure duration was defined as an EEG seizure duration of more than 25 sec or motor seizure duration of more than 20 sec [18]. Hypotension and bradycardia during ECT were defined as a decrease of more than 30% from baseline MAP and HR of less than 45 beats per minute (bpm), respectively. Data were collected during the first 5 ECT sessions for all patients.

A power analysis was performed on the basis of the previously reported 39% - 48% prolongation in the duration of motor seizure activity with remifentanyl [14]-[19], and results of the analysis suggested that a sample size of 18 - 20 patients in each group would have a 90% power to detect a 39% - 48% difference in motor seizure duration with Type I error probability of 0.05. Data are presented as means ± SD and numbers (*n*). Patients' characteristics and recovery profiles were compared using single-factor analysis of variance (ANOVA) with *post hoc* tests. Statistical intergroup comparisons of electrical stimulus intensity, EEG, and motor seizure durations and hemodynamic data in the series of five sessions were performed using repeated-measures ANOVA followed by Student's *t*-test. The percentages of ECT sessions with EEG seizure duration >25 sec, motor seizure duration >20 sec, and peak RPP values > 20,000 were compared using the chi-square test for independence. A probability value less than 0.05 was considered significant.

### 3. Results

Sixty patients were recruited for the study, and a total of 300 ECT treatment sessions were evaluated. The patients suffered from major depression (12 patients) or schizophrenia (48 patients) refractory to drug therapy. Groups P/N, P/H, and RP/H were comparable with respect to age, weight, sex distribution, and percentage of patients with a history of hypertension (Table 1).

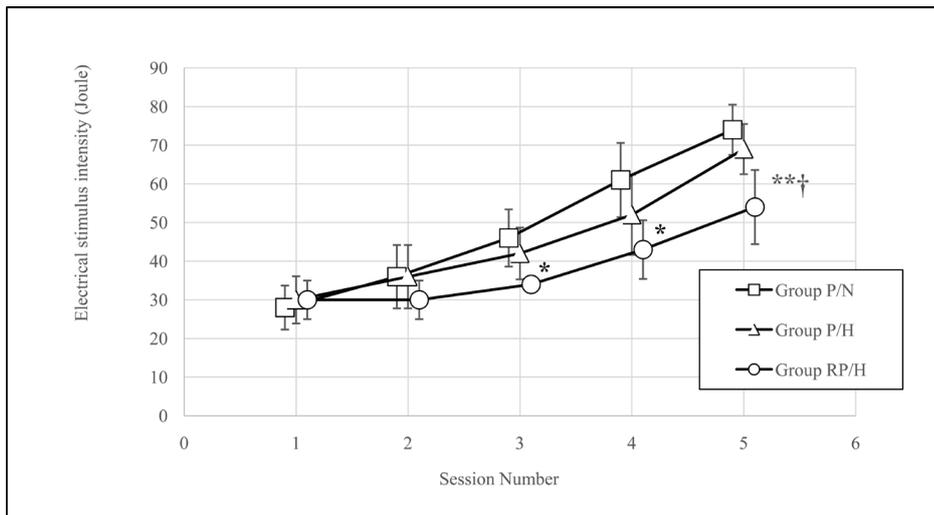
Electrical stimulus intensities by session number for the three groups are presented in Figure 1. Although the stimulus intensities required increased gradually with session number in all three groups, no significant difference in the stimulus doses in the first and second ECT sessions was found among the three groups. Stimulus intensities in the third ( $P < 0.05$ ), fourth ( $P < 0.05$ ), and fifth ( $P < 0.01$ ) ECT sessions were however significantly lower in group RP/H than in group P/N. In addition, patients in group RP/H had significantly lower intensities than those in group P/H in the fifth ECT session ( $P < 0.05$ ).

Mean EEG seizure duration was significantly longer in patients in group RP/H than in group P/N in the first and second ECT sessions ( $P < 0.01$ ). Patients in group RP/H also showed a significantly longer duration of EEG seizure activity than those in group P/H in the second session ( $P < 0.05$ ). A significantly longer prolongation of EEG seizures was also found in patients in group P/H than in those in group P/N ( $P < 0.05$ ) (Figure 2). The

**Table 1.** Demographic data of the three groups.

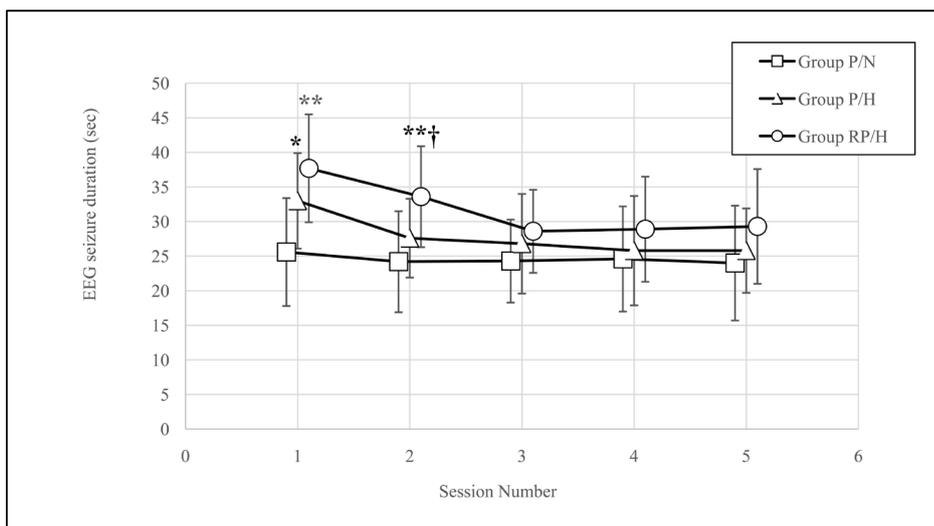
	P/N (n = 20)	P/H (n = 20)	RP/H (n = 20)
Sex (M/F)	12/8	11/9	13/7
Age (yr)	59.9 ± 8.6	62.6 ± 9.7	58.0 ± 11.2
Weight (kg)	56.8 ± 10.7	57.3 ± 8.2	52.8 ± 16.2
Disease (S/D)	14/6	13/7	15/5
HT/NT	9/11	10/10	11/9

S: Schizophrenia, D: depression, HT: Hypertension, NT: Normotension; Values are expressed as means ± SD or n.



\**P* < 0.05 in group RP/H compared with group P/N in the third and fourth ECT sessions. \*\**P* < 0.01 in group RP/H compared with group P/N in the fifth ECT session. †*P* < 0.05 in group RP/H compared with group P/H in the fifth ECT session. ECT: electroconvulsive therapy, Group P/N or P/H: normoventilated or hyperventilated group receiving a standard dose of propofol, Group RP/H: hyperventilated group receiving a reduced dose of propofol with remifentanyl.

**Figure 1.** Electrical stimulus intensities by session number in the three groups. Values are expressed as mean ± SD.



\*\**P* < 0.01 in group RP/H compared with group P/N in the first and second ECT sessions. \**P* < 0.05 in group P/H compared with group P/N in the first ECT session. †*P* < 0.05 in group RP/H compared with group P/H in the second ECT session. EEG: electroencephalogram, ECT: electroconvulsive therapy, Group P/N or P/H: normoventilated or hyperventilated group receiving a standard dose of propofol, Group RP/H: hyperventilated group receiving a reduced dose of propofol with remifentanyl.

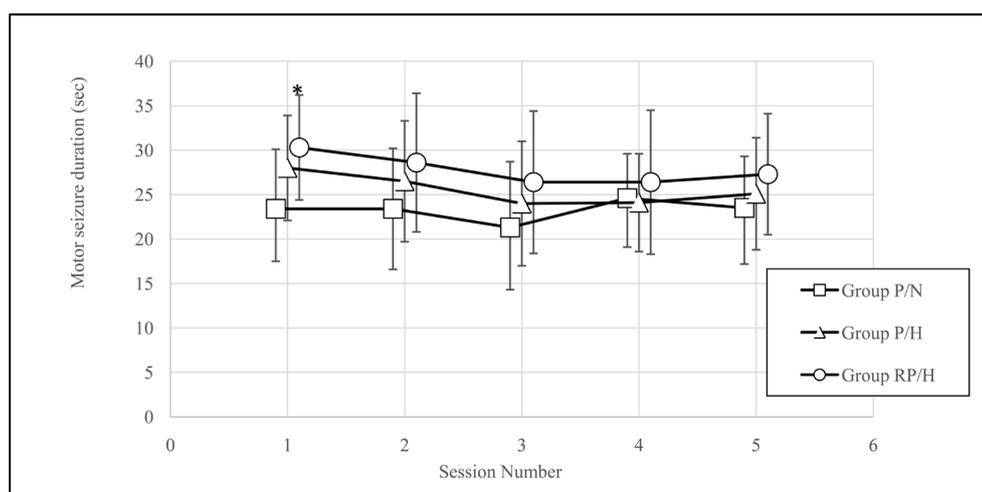
**Figure 2.** EEG seizure durations by session number in the three groups. Values are expressed as mean ± SD.

duration of motor seizures was significantly longer in patients in group RP/H than in those in group P/N only in the first ECT session ( $P < 0.05$ ) (Figure 3). The percentage of sessions with EEG seizure duration of longer than 25 sec was significantly larger in group RP/H (88%) than in group P/N (60%) in a total of 100 sessions in each group ( $P < 0.05$ ). Motor seizure durations of longer than 20 sec were seen in 86% of a total of 100 sessions in group RP/H and in 75% of those in group P/N, but the difference was not significant (Table 2). The time to spontaneous breathing and awakening time were both significantly increased in patients in group RP/H than in those in groups P/N and P/H ( $P < 0.01$ ) (Table 2). Only one patient in group P/N developed emergence agitation in this study.

Regarding hemodynamic responses after the ECT stimulus, the percentage increases from post-anesthetic values to peak post-ictal values of MAP ( $\Delta$  MAP) and ( $\Delta$  HR) tended to be larger in group RP/H than in groups P/N and P/H in each ECT session, but the differences were not significant (Table 3). Doses of rescue intravenous ephedrine and verapamil were also not significantly different among the three groups (Table 2). Maximal values of RPP in each ECT session (Table 4) and the percentages of ECT sessions with peak RPP of greater than 20,000 (Table 2) were both similar among the three groups. None of the patients in the three groups developed arrhythmias or showed ECG signs of myocardial ischemia.

#### 4. Discussion

The present study showed that the concomitant use of a reduced dose of propofol with divided remifentanyl supplementation at 2  $\mu$ g/kg and moderate hyperventilation with  $ETCO_2$  of 30 - 35 mmHg resulted in significant



\* $P < 0.05$  in group RP/H compared with group P/N in the first ECT session. ECT: electroconvulsive therapy, Group P/N or P/H: normoventilated or hyperventilated group receiving a standard dose of propofol, Group RP/H: hyperventilated group receiving a reduced dose of propofol with remifentanyl.

**Figure 3.** Motor seizure durations by session number in the three groups. Values are expressed as mean  $\pm$  SD.

**Table 2.** Comparative data of the three groups.

	P/N (n = 20)	P/H (n = 20)	RP/H (n = 20)
No. of ECT sessions with motor seizure duration > 20 sec (%)	75	83	86
No. of ECT sessions with EEG seizure duration > 25 sec (%)	60	73	88*
No. of ECT sessions with peak RPP value > 20,000 (%)	15	17	21
Time to spontaneous breathing (min)	3.1 $\pm$ 1.0	3.8 $\pm$ 1.6	6.5 $\pm$ 2.5***††
Emergence time (min)	5.1 $\pm$ 1.0	5.9 $\pm$ 1.6	7.7 $\pm$ 2.8***††
Verapamil (mg)	0.2 $\pm$ 0.6	0.3 $\pm$ 0.7	0.4 $\pm$ 0.9
Ephedrine (mg)	1.3 $\pm$ 2.7	1.1 $\pm$ 2.4	2.1 $\pm$ 3.0

ECT: electroconvulsive therapy, EEG: electroencephalogram, RPP: rate-pressure product; Values are expressed as means  $\pm$  SD or n. \* $P < 0.05$  compared with group P/N; \*\* $P < 0.01$  compared with group P/N; †† $P < 0.05$  compared with group P/H.

**Table 3.** Hemodynamic changes after the ECT stimulus in the three groups.

	Increase for MAP baseline (%)			Increase for HR baseline (%)		
	P/N (n = 20)	P/H (n = 20)	RP/H (n = 20)	P/N (n = 20)	P/H (n = 20)	RP/H (n = 20)
<b>ECT#1</b>	46.8 ± 24.3	45.3 ± 24.4	56.4 ± 21.0	42.1 ± 28.7	57.9 ± 12.1	61.6 ± 17.5
<b>ECT#2</b>	44.6 ± 23.1	47.0 ± 22.3	58.0 ± 23.7	45.7 ± 20.9	56.3 ± 14.8	62.5 ± 16.6
<b>ECT#3</b>	45.8 ± 17.8	46.6 ± 16.7	58.4 ± 19.2	48.8 ± 20.7	53.3 ± 14.0	56.3 ± 18.8
<b>ECT#4</b>	41.0 ± 23.0	45.3 ± 22.3	59.1 ± 21.4	45.8 ± 11.9	53.5 ± 12.6	57.3 ± 20.6
<b>ECT#5</b>	49.4 ± 20.7	50.8 ± 17.1	55.6 ± 20.5	50.2 ± 19.7	51.5 ± 12.4	52.6 ± 18.9

ECT: electroconvulsive therapy, MAP: mean arterial blood pressure, HR: heart rate; Values are expressed as means ± SD.

**Table 4.** Maximal value of RPP by session number in each group.

	P/N (n = 20)	P/H (n = 20)	RP/H (n = 20)
<b>ECT#1</b>	13,552 ± 4144	13,916 ± 6820	13,435 ± 4010
<b>ECT#2</b>	14,871 ± 3566	14,402 ± 6955	15,124 ± 6238
<b>ECT#3</b>	13,218 ± 5741	14,745 ± 6833	16,277 ± 4899
<b>ECT#4</b>	13,570 ± 4610	15,951 ± 5385	15,863 ± 5577
<b>ECT#5</b>	13,288 ± 4781	15,220 ± 5995	15,695 ± 4223

ECT: electroconvulsive therapy, RPP: rate-pressure product; Values are expressed as means ± SD.

prolongations of both EEG seizure durations in the first and second sessions and motor seizure duration in the first session and a larger number of ECT sessions with EEG seizure duration of more than 25 sec compared to the use of a standard dose of propofol alone, with a significant reduction in the electrical requirement during ECT. In addition, it produced no significant differences in hemodynamic changes after ECT compared with the use of standard dose of propofol with or without moderate hyperventilation.

A favorable clinical outcome of ECT has been reported to depend on the production of adequate therapeutic seizures. Although propofol has a major disadvantage in that it is an anticonvulsant and decreases seizure duration in a dose-dependent fashion, several studies decreasing the dosage of propofol by addition of remifentanyl [11]-[14] have demonstrated a significant prolongation of duration of seizure activities. Moreover, severe acute hyperdynamic responses to ECT caused by reducing the standard dose of propofol could have been attenuated to an acceptable outcome by the additional injection of remifentanyl immediately before ECT in our previous study [14]. In the present study, with the aim of more seizure augmentation and/or fewer side effects, the efficacy and safety of the concurrent use of moderate hyperventilation and a reduced dose of propofol combined with divided remifentanyl in ECT practice were evaluated.

Patients undergoing ECT commonly have gradual increases in electrical stimulus intensities to produce a seizure with an increasing number of ECT treatments, and higher stimulus intensities are likely to cause increased levels of cognitive impairment [20]. In the present study, however, the incidences of cognitive side effects were not significantly different among the three groups despite significant differences in stimulus doses.

Regarding the relationship between hyperventilation and seizure duration in ECT, Chater *et al.* [7] and Pande *et al.* [8] demonstrated a correlation between excessive hyperventilation-induced severe hypocapnia (ETCO<sub>2</sub>: 20 - 27 mmHg) prior to ECT and seizure duration in the early phase of ECT practice. However, since it is difficult to safely use these methods, Sawayama *et al.* [9] used moderate hypocapnia (ETCO<sub>2</sub>: 30 mmHg) by moderate hyperventilation and found that there was a significant prolongation of the duration of EEG seizures, but not of motor seizures. They suggested that lower levels of hyperventilation and/or stimulus intensity were the reason for failure in motor seizure prolongation. In the present study with the half-age stimulation setting, enhancing effects of moderate hyperventilation (ETCO<sub>2</sub>: 30 - 35 mmHg) on ECT-induced seizure activities were also observed only in EEG seizures, while the combination of moderate hyperventilation and the use of a reduced dose of propofol led to significant increases in both durations of EEG and motor seizures, without higher electrical stimulus intensities. The proposed explanation for this observation was that a decrease in seizure thresholds due to the reduction of propofol dosage by anesthetic-sparing effects of remifentanyl might have facilitated more augmentation of moderate hyperventilation-mediated enhancement of seizure activities. However, these effects

did not appear to be sustained, as was also observed in the present study, and therefore other augmentation techniques are necessary to maintain seizure quality.

As adverse effects associated with hyperventilation, Bergsholm *et al.* [21] found that hypocapnia induced by hyperventilation markedly augmented the ECT-induced increase in HR and RPP. In the present study, although the percentages of  $\Delta$  HR for the baseline and peak RPP values tended to be greater in groups P/H and RP/H than in group P/N in each session, there were no significant differences among the three groups. For these reasons, first, the use of lower levels of hypocapnia (ETCO<sub>2</sub> 30 - 35 mmHg) in groups P/H and RP/H compared with the severe levels (ETCO<sub>2</sub> of 14 mmHg) used in the above study might have blunted the increase in HR after the ECT stimulus. Second, no significant difference between groups P/N and P/H was detected in the increase in SBP after ECT, which was consistent with the report by Bergsholm *et al.* [21] that hyperventilation did not cause an increase in BP. Third, although a high electrical dosage has been reported to result in marked hemodynamic lability [22], the stimulus intensity required in group RP/H was close to or lower than in groups P/N and P/H in each session in this study. Considering these findings, patients in group RP/H might have had no significant increase in RPP compared with those in groups P/N and P/H because of similar rises in SBP and HR after ECT. In general, although augmented interventions associated with longer seizures have been reported to have longer emergence times [23] [24], a similar tendency was found in the present study. Delayed emergence from anesthesia also appeared to be greatly related to the use of remifentanyl rather than to moderate hyperventilation in the present study.

As for positioning of electrodes, unilateral ECT has been reported to cause less severe cognitive side effects, though an electrical dosage 500% above the seizure threshold is needed for efficacy equivalent to that of bilateral ECT, and such a high electrical dosage would be associated with marked hemodynamic lability [22]. In the current study, the aim of which was to determine an acceptable augmenting strategy for patients responding poorly to standard ECT treatment, bilateral ECT was thus used for electrode placement.

One limitation of the present study was the inability to record continuous blood pressure readings due to the required cycling time of the blood pressure cuff; thus, the highest value after ECT stimulus may have been overlooked.

## 5. Conclusion

Concurrent application of a reduced dose of propofol combined with divided supplemental remifentanyl and moderate hyperventilation for ECT procedures would offer advantages over the use of a standard dose of propofol with or without moderate hyperventilation in terms of a significant prolongation of seizure duration in the early phase and a significant reduction in the electrical requirement in the late phase during the ECT course.

## Competing Interest

The authors have no conflicts of interest to declare, financial or otherwise.

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