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Target-controlled Infusion of Remifentanil during Propofol Induction in Hypertensive Patients: Effects of Three Different Remifentanil Concentrations on Hemodynamic Changes

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Background: This study compared the hemodynamic effects of target-controlled infusion (TCI) of remifentanil (4, 5, or 6 ng/ml) during propofol induction in normotensive and hypertensive patients. It was also examined whether increasing the remifentanil concentrations might reduce propofol consumption at the loss of consciousness (LOC).

Methods: Seventy five ASA 1 or 2 normotensive (N) and 75 ASA 2 hypertensive (H) patients were randomly allocated according to the remifentanil target effect-site concentration of 4, 5, 6 ng/ml (groups N4, N5, N6, H4, H5, H6 respectively). After the start of remifentanil TCI, when the target effect-site concentration of remifentanil had been reached, the TCI of propofol (4 μg/ml) was started. The effect-site concentration of propofol at LOC was recorded. When the target effect-site concentration of propofol was reached, 0.6 mg/kg of rocuronium was administered. Tracheal intubation was carried out after 2 minutes. The noninvasive blood pressure, heart rate (HR), bispectral index (BIS) and infused dose of remifentanil and propofol were recorded.

Results: Groups H5, H6 and N6 resulted in significant decrease in blood pressure after intubation. In groups N4 and H4, clinically significant increases in HR (above 25% of the baseline) were observed at 1 minute after intubation. The effect-site concentration of propofol at LOC was significantly lower in groups N6 and H6 compared to groups N4 and H4.

Conclusions: In hypertensive patients, a dosing requirement of lower effect-site concentration of 4 ng/ml remifentanil might be adequate during propofol induction. Increasing the remifentanil concentrations from 4 to 6 ng/ml may reduce the propofol requirements for hypnosis. **(Korean J Anesthesiol 2007; 53: S 12～8)**

Key Words: hypertension, propofol, remifentanil, target-controlled infusion (TCI), tracheal intubation.

INTRODUCTION

Patients with treated or untreated hypertension are more at risk of exaggerated cardiovascular responses to a laryngoscopy and tracheal intubation,[1] which may be associated with potentially detrimental hemodynamic changes and myocardial ischemia.[2] Many drugs including remifentanil have been used to help attenuate these responses.[3] Remifentanil is a new synthetic opioid that has a rapid onset of action and a short elimination half life (3－10 min), thereby making it an ideal adjunct for controlling the hemodynamic responses to brief but intense noxious stimuli.[4]

Several studies have examined the optimal bolus doses and continuous infusion rates of remifentanil during anesthesia induction with thiopental sodium or propofol.[5-9] Other studies have also reported that remifentanil inhibits the noxious stimuli during laryngoscopy and tracheal intubation in a dose dependent manner, which is reflected in the BIS variability.[10,11] Although there are several studies that have used the target-controlled infusion (TCI) of remifentanil during propofol induction,[10,11] reports of its optimal use in hypertensive patients have not yet been released. Moreover, there is a lack of an established dosing regimen for the TCI of remifentanil in hypertensive patients.

This study aimed to reveal which of the three different target effect-site concentrations of remifentanil (4, 5 and 6 ng/ml) with a TCI of 4 μg/ml propofol would be most superior in managing the hemodynamic responses to a laryngoscopy and tracheal intubation in normotensive and hypertensive

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patients. We also examined whether increasing the target effect-site concentration of remifentanil might accelerate the loss of consciousness, which might reduce the propofol requirement.

MATERIALS AND METHODS

After obtaining the approval of the institutional review board and written informed consent, seventy five ASA physical status 1 or 2 normotensive and seventy five ASA physical status 2 hypertensive patients, who were aged between 20 and 65 years and presenting for general, orthopedic, urologic and gynecologic surgical procedures, were enrolled in this study. Patients with a known impaired renal or hepatic function, psychiatric disorder, a history of chronic drug or alcohol abuse and those who were obese (body mass index, BMI $>$ 30 kg/m^2) or those with Mallampti score of 3 or 4 were excluded. Candidates with unexpected difficulties in intubation with more than 2 laryngoscopic attempts were excluded. There were no significant differences regarding height, gender ratio and baseline HR and BIS values between the normotensive and hypertensive groups. The patient's age, weight, BMI and the baseline MBP were significantly higher in the hypertensive groups than in the normotensive groups. Among the hypertensive patients, 13, 8 and 8 patients in group H4, H5, and H6, respectively, were currently taking antihypertensive medication (calcium channel blocker), and all these patients had taken their medication until the day of the surgery (Table 1).

The prehypertension category of the blood pressure classification, proposed by Chobanian et al.[12] in the JNC 7 report (The Seventh Report of the Joint National Committee), were not placed into the group classification of hypertension in this study. Patients were eligible to be in the normotensive group (N) if they had no history of hypertension and their admission systolic and diastolic blood pressure was $<$ 140 mmHg and $<$ 90 mmHg, respectively, on three occasions. Patients were eligible to be in the hypertensive group (H) if they had a history of hypertension or their admission systolic and diastolic blood pressure was $\geq$ 140 mmHg and $\geq$ 90 mmHg, respectively, on three occasions. The current use and the type of antihypertensive medication were noted in hypertensive patients. The normotensive and hypertensive patients were allocated randomly to one of the three groups in which each group received a target effect-site concentration of 4, 5, 6 ng/ml remifentanil (groups N4, N5, N6, H4, H5, H6). All patients had fasted for 8－12 hours before surgery and had been administered 100 ml/hr of crystalloid solution intravenously during the NPO. No sedative premedication was administered before surgery. Upon arrival at operating room, all patients were prehydrated with 5 ml/kg of a crystalloid solution before induction. The patients were pre-oxygenated with 100% oxygen for 3 minutes. After an intravenous injection of 0.2 mg glycopyrrolate to prevent bradycardiac episodes, each concentration of remifentanil was administered using a target-controlled infusion (TCI, Base Primea Orchestra®, Fresenius Vial, France) with the pharmacokinetic parameter set of Minto (K_{eo} of (0.595 － 0.007 × [age － 40])/min). When the target effect-site concen-

Table 1. Demographic and Baseline Hemodynamic Data for the Normotensive and Hypertensive Groups

	Normotensive groups			Hypertensive groups		
	N4 (n = 25)	N5 (n = 25)	N6 (n = 25)	H4 (n = 25)	H5 (n = 25)	H6 (n = 25)
Sex (M/F)	10/15	7/18	9/16	14/11	17/8	11/14
Age (yr)	41.0 ± 10.9	38.6 ± 10.3	44.7 ± 10.1	56.9 ± 5.3*	50.6 ± 6.2*	51.7 ± 8.1*
BMI (kg/m^2)	23.2 ± 3.0	23.0 ± 3.2	22.1 ± 3.4	24.9 ± 3.4*	25.2 ± 2.5*	24.5 ± 2.6*
Weight (kg)	62.8 ± 10.7	60.5 ± 9.8	59.2 ± 9.1	66.5 ± 11.7*	69.1 ± 8.5*	63.4 ± 8.8*
Height (cm)	164.1 ± 9.0	162.2 ± 6.5	161.5 ± 6.6	163.3 ± 8.5	165.4 ± 8.1	160.7 ± 6.9
MBP (mmHg)	85.4 ± 10.8	90.4 ± 7.9	90.1 ± 10.0	106.2 ± 7.9*	110.3 ± 15.0*	107.2 ± 11.1*
HR (beat/min)	73.3 ± 14.3	73.3 ± 13.7	73.7 ± 12.8	69.5 ± 9.7	73.0 ± 16.0	74.2 ± 13.3
BIS	97.1 ± 1.2	97.0 ± 2.1	96.4 ± 2.1	96.2 ± 3.2	96.5 ± 2.7	96.8 ± 1.3
Antihypertensive medication (CCB)	－	－	－	13	8	8

Values are reported as mean ± SD or number of patients. N4, N5, N6, H4, H5, H6: remifentanil target effect-site concentration of 4, 5 or 6 ng/ml in the normotensive and hypertensive patients respectively, BMI: body mass index, MBP: mean blood pressure, HR: heart rate, BIS: bispectral index, CCB: calcium channel blocker. *: $P < 0.05$ compared with the normotensive groups N4, N5 and N6, respectively.

tration of remifentanil had been reached, anesthesia was induced by a TCI of 4 ug/ml propofol using the pharmacokinetic parameter set of Marsh (K_{eo} of 1.21/min). The effect-site concentration of propofol at loss of consciousness (LOC) was recorded. The LOC was verified with the loss of response to verbal command and the loss of eyelash reflexes. Upon reaching the propofol target concentration of 4 ug/ml, 0.6 mg/kg of rocuronium was administered and tracheal intubation was performed after 2 minutes of mask ventilation.

The noninvasive blood pressure, heart rate (HR) and the bispectral index (BIS; A-2000^{TM}, Aspect Medical Systems, Newton, USA) were recorded before administration of any drug as a baseline, upon reaching the target effect-site concentration of remifentanil (TCe-remi), at LOC, upon reaching target effect-site concentration of propofol (TCe-ppf), before and 1, 2 and 5 minutes (+ 1 min, + 2 min, + 5 min) after tracheal intubation. The infused dose of remifentanil and propofol at TCe-remi, at LOC, at TCe-ppf, before and 1, 2 and 5 minutes after tracheal intubation were also recorded. The changes in the MBP and HR from the baseline at each measuring point were also calculated as a percentage and changes > 25% were considered clinically significant.

The decrease of the MBP below 50 mmHg after intubation and not increasing onwards were subjected to the administration of ephedrine 5-10mg intravenously. In case of the decrease of the HR below 50 beats/min, atropine 0.5 mg were to be administered intravenously.

Statistical analysis was performed by using SPSS v.12.0 (SPSS Science Inc., Chicago, IL, USA). The demographic data and the infused dose of remifentanil and propofol were analyzed by using fisher's exact test, unpaired t-test, one-way ANOVA with Tukey HSD multiple comparisons test where appropriate. The MBP, HR and BIS at each measuring point and the changes in the MBP, HR and BIS from the baseline to the measuring point were analyzed by one-way ANOVA and repeated measures of ANOVA with Tukey HSD multiple comparisons test where appropriate. A logistic regression analysis was used to identify factors such as age, BMI, remifentanil dose and the presence of hypertension which may be associated with the changes in MBP before and 1, 2 and 5 minutes after intubation. A P value < 0.05 was considered statistically significant. Sample size was calculated to detect a difference of 25% in MBP after intubation, for a type 1 error of 0.05 and a power of 0.8 and was based on data from a pilot study of 15 in each group.

RESULTS

The MBP, HR and BIS in both normotensive and hypertensive groups showed no significant changes during the TCI of remifentanil alone before the start of the propofol infusion.

The MBP in all normotensive groups decreased significantly at LOC, TCe-ppf and before intubation compared with the baseline (P < 0.05). In groups N4 and N5, the MBP instantly returned to the baseline values at 1 minute after intubation but decreased again at 2 and 5 minutes after intubation. However, the decreases in the MBP in group N6 were statistically significant at all measuring points after intubation. An analysis

Table 2. Changes in the Mean Blood Pressure and Heart Rate in the Normotensive Groups

	Baseline	TCe-remi	LOC	TCe-ppf	Before intubation	+ 1 min	+ 2 min	+ 5 min
MBP								
N4	85.4 ± 10.8	85.7 ± 11.0	75.0 ± 9.7*	70.8 ± 10.0*	67.0 ± 9.7*	89.6 ± 24.4	76.2 ± 16.7*	66.3 ± 11.0*
N5	90.4 ± 7.9	88.3 ± 8.4	77.4 ± 11.9*	73.4 ± 10.9*	69.6 ± 12.4*	82.0 ± 19.8	74.7 ± 12.5*	69.0 ± 11.4*
N6	90.1 ± 10.0	90.0 ± 11.5	73.4 ± 11.2*	70.3 ± 11.1*	66.2 ± 13.9*‡	74.6 ± 19.2*†	70.0 ± 15.5*	67.8 ± 13.2*
HR								
N4	73.3 ± 14.3	75.4 ± 16.6	77.6 ± 15.2	72.2 ± 14.5	73.8 ± 13.9	94.3 ± 17.6*§	84.3 ± 14.5*	74.6 ± 13.4
N5	71.0 ± 11.5	73.6 ± 12.5	75.0 ± 12.1	72.4 ± 11.7	73.9 ± 12.9	88.3 ± 16.7*	82.0 ± 14.0*	73.6 ± 12.0
N6	73.7 ± 12.8	75.7 ± 15.5	74.0 ± 14.4	67.6 ± 13.3*	69.3 ± 13.0*	80.8 ± 12.4*†	74.1 ± 11.6†	69.6 ± 12.1*

Values are reported as mean ± SD. TCe-remi: Target effect-site concentration of remifentanil, LOC: loss of consciousness, TCe-ppf: Target effect-site concentration of propofol, + 1 min: 1 minute after intubation, + 2 min: 2 minutes after intubation, + 5 min: 5 minutes after intubation, MBP: Mean blood pressure, HR: Heart rate, N4, N5, N6: remifentanil target effect-site concentration of 4, 5 or 6 ng/ml in normotensive patients. *: P < 0.05 compared with the baseline, †: P < 0.05 compared with group N4, ‡: values are under 75% of the baseline, §: values are above 25% of the baseline.

between the normotensive groups at 1 minute after intubation revealed the MBP value to be significantly lower in group N6 than in group N4. The MBP changes in groups N4 and N5 were within 25% of the baseline. However, the MBP values in group N6 before intubation showed decreases of more than 25% of the baseline (Table 2).

The MBP in all hypertensive groups was significantly lower than the baseline at LOC, TCe-ppf and before intubation ($P < 0.05$). In group H4, the MBP instantly returned to the baseline level at 1 minute after intubation but decreased again 2 and 5 minutes after intubation. However, the MBP in groups H5 and H6 was significantly lower at all measuring points after intubation than the baseline. An analysis of the hypertensive groups showed that the MBP at LOC, TCe-ppf, before and after intubation were significantly lower in group H6 than in group H4. It should be noted that the changes in the MBP in group H4 were within 25% of the baseline. The decreases in the MBP in group H6 at TCe-ppf, before and 2 and 5 minutes after intubation exceeded 25% of the baseline (Table 3).

Throughout the study, only one patient in group N6 required administration of ephedrine because the MBP dropped below 50 mmHg after intubation.

A logistic regression analysis showed that the remifentanil concentration differences have a statistically significant association with the decreases in the MBP before and 2 and 5 minutes after intubation. Other factors such as age and BMI did not show significant association with the decreases in the MBP before and at each measuring point after intubation.

The HR changes in groups N4 and N5 showed statistically significant increase at 1 and 2 minutes after intubation. In

Table 3. Changes of Mean Blood Pressure and Heart Rate in the Hypertensive Groups

	Baseline	TCe-remi	LOC	TCe-ppf	Before intubation	+ 1 min	+ 2 min	+ 5 min
MBP								
H4	106.2 ± 7.9	105.8 ± 9.4	95.0 ± 15.0*	91.3 ± 16.2*	83.9 ± 12.2*	105.0 ± 21.6	93.9 ± 13.5*	81.7 ± 11.6*
H5	110.3 ± 15.0	107.7 ± 11.7	92.1 ± 15.9*	89.8 ± 15.5*	77.0 ± 14.5*†	96.7 ± 26.2*	90.2 ± 17.6*	77.0 ± 10.6*†
H6	107.2 ± 11.1	103.8 ± 12.5	82.1 ± 13.4*†	77.8 ± 14.1*††	69.8 ± 11.7*††	81.8 ± 17.8*†	77.8 ± 16.0*††	69.6 ± 13.8*††
HR								
H4	69.5 ± 9.7	71.4 ± 15.2	72.8 ± 10.6	69.3 ± 11.9	71.2 ± 14.4	89.5 ± 17.6*§	80.0 ± 14.5*	72.2 ± 11.5
H5	73.0 ± 16.0	74.1 ± 17.4	72.6 ± 14.3	68.9 ± 12.5	68.6 ± 12.8	85.3 ± 16.4*	80.2 ± 13.2*	71.9 ± 12.8
H6	74.2 ± 13.3	77.4 ± 20.8	76.3 ± 12.8	73.0 ± 12.0	73.0 ± 13.1	85.7 ± 17.8*	78.6 ± 13.4*	73.7 ± 14.6

Values are reported as mean ± SD. TCe-remi: Target effect-site concentration of remifentanil, LOC: loss of consciousness, TCe-ppf: Target effect-site concentration of propofol, + 1 min: 1 minute after intubation, + 2 min: 2 minutes after intubation, + 5 min: 5 minutes after intubation, MBP: Mean blood pressure, HR: Heart rate, H4, H5, H6: remifentanil target effect-site concentration of 4, 5 or 6 ng/ml in hypertensive patients. *: $P < 0.05$ compared with the baseline, †: $P < 0.05$ compared with group H4, ‡: values are under 75% of the baseline, §: values are above 25% of the baseline.

Table 4. Bispectral Index Values in Normotensive and Hypertensive Groups

BIS	Baseline	TCe-remi	LOC	TCe-ppf	Before intubation	+ 1 min	+ 2 min	+ 5 min
N4	97.1 ± 1.2	95.1 ± 4.5	87.3 ± 13.4	70.4 ± 15.1	63.9 ± 7.8	61.0 ± 11.7	56.0 ± 9.0	50.8 ± 7.1
N5	97.0 ± 2.1	93.7 ± 5.5	88.5 ± 7.6	66.3 ± 15.4	61.0 ± 11.0	59.0 ± 12.9	55.5 ± 10.4	51.3 ± 11.8
N6	96.4 ± 2.1	91.4 ± 7.6	86.8 ± 11.6	66.6 ± 11.7	59.2 ± 9.4	59.2 ± 10.2	52.7 ± 10.4	48.1 ± 9.6
H4	96.2 ± 3.2	93.9 ± 4.2	83.4 ± 12.4	69.6 ± 17.6	57.2 ± 11.1	59.2 ± 12.8	53.5 ± 9.2	47.9 ± 11.4
H5	96.5 ± 2.7	91.7 ± 7.3	86.5 ± 10.3	69.6 ± 14.7	57.8 ± 12.0	55.9 ± 14.2	51.8 ± 11.5	44.5 ± 8.7
H6	96.8 ± 1.3	92.5 ± 7.7	83.5 ± 16.7	65.2 ± 14.9	53.8 ± 10.6	54.6 ± 8.4	48.8 ± 6.8	41.9 ± 7.3

Values are reported as mean ± SD. BIS = Bispectral Index, TCe-remi: Target effect-site concentration of remifentanil, LOC: Loss of consciousness, TCe-ppf: Target effect-site concentration of propofol, +1 min: 1 minute after intubation, + 2 min: 2 minutes after intubation, + 5 min: 5 minutes after intubation, N4, N5, N6, H4, H5, H6: remifentanil target effect-site concentration of 4, 5 or 6 ng/ml in normotensive and hypertensive patients respectively.

Table 5. The Effect-site Concentration and the Propofol Consumption by Weight at Loss of Consciousness

	N4	N5	N6	H4	H5	H6
Effect-site concentration of propofol (μg/ml)	3.22 ± 0.58	2.90 ± 0.53	2.77 ± 0.39*†	3.29 ± 0.60	3.16 ± 0.58	2.76 ± 0.63*†
Propofol consumption by weight (mg/kg)	1.43 ± 0.10	1.41 ± 0.08	1.40 ± 0.06	1.43 ± 0.13	1.43 ± 0.09	1.42 ± 0.10

Values are reported as mean ± SD. N4, N5, N6, H4, H5, H6: remifentanil target effect-site concentration of 4, 5 or 6 ng/ml in normotensive and hypertensive patients respectively. *: $P < 0.05$ compared with N4, †: $P < 0.05$ compared with H4.

group H6, the HR changes were statistically significant at TCe-ppf, before and after intubation. In hypertensive groups, HR increased significantly at 1 and 2 minutes after intubation. However, in terms of clinical significance, the increases in the HR only at 1 minute after intubation in groups N4 and H4 were more than 25%. The between-group differences in the HR showed statistically significant differences in group N6 at 1 and 2 minutes after intubation compared to group H4. Bradycardia was not observed (Table 2, 3).

There were no significant differences in the MBP and HR changes between hypertensive patients with antihypertensive medication and those with no antihypertensive medication.

The BIS values were similar among all groups at each measuring point. However, the mean BIS values in group N4 before and 1 minute after intubation and in group N5 before intubation were > 60. However the BIS values after intubation ranged from 40 to 60 in all groups (Table 4).

The amount of propofol consumption calculated according to weight at LOC was similar in all groups. However, LOC occurred at a significantly lower effect-site concentration of propofol in the remifentanil concentration groups of 6 ng/ml (groups N6, H6) compared to the remifentanil concentration groups of 4 ng/ml (groups N4, H4) (Table 5).

DISCUSSION

This study showed that the effect-site concentration of remifentanil 5 and 6 ng/ml for a laryngoscopy and tracheal intubation with a TCI of 4 μg/ml propofol produced more profound changes in blood pressure in the hypertensive groups than in the normotensive groups. The changes in the MBP of the normotensive patients were within 25% of the baseline at effect-site concentrations of 4 and 5 ng/ml remifentanil, and only showed decreases of more than 25% at an effect-site concentration of 6 ng/ml remifentanil. However, in the hypertensive patients, effect-site concentrations of remifentanil 5 and 6 ng/ml caused profound decreases in the MBP before intubation and even after intubation. The changes in the MBP in groups N4, N5 and H4 at all measuring points were within 25% of the baseline. However, the MBP in groups N6 and H5 before intubation and 5 minutes after intubation decreased by more than 25% of the baseline. Moreover, the MBP in group H6 decreased by more than 25% of the baseline at TCe-ppf, before intubation, and 2 and 5 minutes after intubation.

In a similar study of a TCI induction of 4 ug/ml propofol, Guignard et al.[10] compared the different effect-site concentrations (0, 2, 4, 8, 16 ng/ml) of remifentanil in normotensive patients. They reported that an effect-site concentration of 4 ng/ml remifentanil did not produce any change in the MBP before intubation nor any significant increase in the MBP at 1 minute after intubation compared with the preinduction values. On the other hand, the effect-site concentration of 8 and 16 ng/ml remifentanil resulted in significant decreases in the MBP at preintubation and 2 and 5 minutes after intubation. They concluded that remifentanil either attenuated or abolished the changes in the MBP after tracheal intubation in a dose-dependent manner. The decrease in the MBP in a dose-dependent manner was also found in this study, however, we also observed that less incremental doses from 4 ng/ml of remifentanil to 5 or 6 ng/ml also resulted in a dose-dependent effect on the MBP. Moreover the effect was more profound in the hypertensive patients.

This may confirm the view that hypertensive patients not only demonstrate exaggerated cardiovascular responses to the induction of anesthesia, but also are susceptible to episodes of hypotension.[1,9] Since hypertension is associated with an increased systemic vascular resistance, systemic vasodilation caused by anesthesia might have profound effects on arterial pressure in hypertensive patients.[13] The use of propofol in combination with remifentanil may also have increased susceptibility to

hypotension in these patients because synergism of the two drugs may have depressed cardiac contractility or cardiac output.[9,14] However, increased tendency to hypotension in the hypertensive groups may be attributed to factors other than the presence of hypertension or the increment of the remifentanil concentration because the hypertensive groups were older and more obese than the normotensive groups. In a study by Minto et al.,[15] age and lean body mass were significant covariates of the pharmacokinetic and pharmacodynamic model of remifentanil, and in this study the effects of age and BMI on the pharmacokinetic and pharmacodynamic parameters were provided by TCI with Base Primea Orchestra®. We also figured that a logistic regression analysis would show whether age and BMI had statistically significant correlation with the decrease in the MBP, and as for the result, neither of them showed significant association with the decrease in the MBP.

In other studies using remifentanil, bradycardia was reported with an increase in the remifentanil doses,[5,7] and another study confirmed that the bradycardiac episodes are reduced with the use of glycopyrrolate and prehydration.[8] In this study, because we have administered intravenous glycopyrrolate before induction, of which onset of action is 1－10 minutes and duration of anticholinergic effect is 7 hours, there was no episode of bradycardia. Glycopyrrolate, which is a synthetic quaternary ammonium anticholinergic, is known to have vagolytic effect on heart rate[16] and this effect may interfere with the interpretation of the unique effects of remifentanil on hemodynamic changes. However, as it was mentioned above, glycopyrrolate was prophylactically administered to prevent bradycardia because remifentanil decreases the cardiac index, which is associated with bradycardia. The increase of stroke volume in compensation to bradycardia does not occur during remifentanil infusion, therefore, heart rate plays a critical role in maintaining cardiac output.[17,18]

There were significant increases in the HR immediately after intubation in all the groups, and increases of more than 25% of the HR occurred only in groups N4 and H4. One of the possible explanation for this might be an inadequate blockade of sympathetic nervous system reflexes to larygnoscopy and tracheal intubation. But in terms of the MBP, changes in these groups immediately after intubation did not show significant increase and one does not assume this as an increased sympathetic reflexes. According to King et al.,[19] the blood pressure response appeared to be more easily completely blocked by deeper levels of anesthesia than the increase in the HR. Another explanation might be an inadequate level of anesthesia in these groups.

However the depth of anesthesia at the time of tracheal intubation was considered adequate in these groups, as it was depicted in the MBP and BIS, and a TCI of 4 ug/ml propofol as an induction agent is known to be adequate for producing loss of consciousness in 90% of patients.[10,20] According to Kil et al.,[21] infusion of target-effect site concentration of 3.5 μg/ml displayed the BIS value of 41.1 in Korean population. Although the BIS between 40 and 60 are recommended depth of anesthesia, the BIS of slightly over 60 (groups N4 and N5) does not imply clinically inadequate depth of anesthesia. Moreover, there was no evidence of intubation-induced arousal responses in these groups because the increases in the BIS after intubation were not significantly different to that before intubation. The BIS at LOC were $>$ 80 in all groups which do not seem to reflect the clinical observation of the loss of eyelash reflexes. Considering the time lag of 5－10 seconds in the BIS values and less than 20 seconds of interval between LOC and TCe-ppf, the BIS $<$ 70 at TCe-ppf may be acceptable in clinical significance.

The lack of significant differences in the BIS among the groups at each measuring point in this study may suggest that increasing the remifentanil concentration from 4 to 6 ng/ml does not affect the hypnotic component of anesthesia. However, another study using higher concentrations of remifentanil suggested that it might have some hypnotic properties.[22] In another study, it was also suggested that remifentanil prevents the increase in the BIS index associated with a laryngoscopy and tracheal intubation in a dose dependent manner.[10,11] The effect-site concentration of remifentanil used in this study might not have been high enough to induce an added hypnotic component in both groups.

This study showed that the amount of propofol comsumed by weight for LOC was similar in all groups, but there were significant decreases in the effect-site concentration of propofol at LOC in remifentanil concentration group of 6 ng/ml compared to remifentanil concentration group of 4 ng/ml. Milne et al.[23] suggested a dose-dependent decrease in propofol requirements with increasing remifentanil concentration. Their conclusion was that the effect of reducing the required amount of propofol at LOC was most prominent with a relatively high remifentanil concentration such as 8 ng/ml. However, this study might propose the beneficial effect of sparing propofol by increasing the remifentanil concentration even in a less

incremental dose of 6 ng/ml.

In conclusion, hypertensive patients may require a lower effect-site concentration of remifentanil than normotensive patients, and an effect-site concentration as low as 4 ng/ml remifentanil during propofol induction with TCI of 4 μg/ml might effectively attenuate the cardiovascular responses to a laryngoscopy and tracheal intubation. Increasing the remifentanil concentration in the moderate ranges from 4 to 6 ng/ml reduced the propofol requirements for hypnosis. Further investigation on optimal reduced target effect-site concentration of propofol with the use of a higher effect-site concentration of remifentanil, such as 6 ng/ml, in hypertensive population is warranted.

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