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Effects of Remifentanil and Alfentanil on Cardiovascular Responses to Laryngoscopy and Double-lumen Endobronchial Intubation

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Background: This study examined the cardiovascular responses to double-lumen endobronchial intubation during rapid sequence induction of anesthesia, and compared the effect of remifentanil and alfentanil in a randomized, double-blind, placebo-controlled study in three groups of 20 elderly patients each.

Methods: Anesthesia was induced with intravenous thiopental (4－6 mg/kg) immediately followed by either remifentanil 2 μg/kg, alfentanil 30μg/kg, or saline (placebo) given over 30 sec. Succinylcholine 1.5 mg/kg was given for neuromuscular block. The laryngoscopy and intubation were performed 60 sec later.

Results: The intubation significantly increased systolic arterial pressure (SAP) and heart rate (HR) in all groups. The maximum pressure changes in the remifentanil and alfentanil groups (36 ± 26 and 33 ± 30 mmHg, respectively) were significantly lower than the 83 ± 35 mmHg in the control group. The maximum HR in the remifentanil (77 ± 13 bpm) and alfentanil (80 ± 13 bpm) groups was lower when compared to controls (93 ± 11 bpm). The norepinephrine and epinephrine concentrations increased after intubation in the control group but remained unaltered in both the alfentanil and remifentanil groups. There were no significant differences between the remifentanil and alfentanil groups in HR, SAP or catecholamines at any time. Five patients in the remifentanil group and three in the alfentanil group received ephedrine for hypotension.

Conclusions: Endobronchial intubation elicited a significant pressor response, and that both remifentanil and alfentanil similarly attenuated the pressor response. However, the incidence of hypotension confirms that both drugs should be used with caution in elderly patients. **(Korean J Anesthesiol 2007; 52: S 14～20)**

Key Words: alfentanil, catecholamines, endobronchial intubation, hypertension, remifentanil, tachycardia.

INTRODUCTION

Laryngoscopy and tracheal intubation usually result in increased blood pressure and heart rate (HR) caused, in part, by a reflex sympathetic discharge.[1-3] Little information is available as to whether endobronchial intubation with a double-lumen tube (DLT) induces similar responses as those with single-lumen tube during general anesthesia, although one study reported a similar response between two techniques.[4] The main portion of the DLT is placed in the lower trachea approximately 1 to 2 cm above the carina, with the bronchial extension inserted far enough into one of the main bronchi. Because of the length and thickness of the tube and the associated carinal stimulation on placement, some differences in the responses could exist between endobronchial and endotracheal intubation. The assumption is supported by the findings that the cardiovascular responses to airway stimulation differ in their magnitude at different sites within the airways in human,[5] and that duration[6] and forces applied during laryngoscopy[7] are related to circulatory responses.

Most of patients who require endobronchial intubation are old aged patients, who are prone to develop myocardial ischemia during such abrupt hemodynamic changes because of their high prevalence of atherosclerotic coronary artery disease.[8] Many drugs have been shown to be effective in modifying hemodynamic response to endotracheal intubation.[9-12] Remifentanil

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is relatively new, ultrashort-acting, potent μ-opioid agonist with a pharmacological profile ideal for the treatment of brief noxious stimuli.[13] Although many studies have compared remifentanil with alfentanil,[11,12] none has attempted to compare them in patients for whom endobronchial intubation is performed. The present study was therefore aimed to determine the cardiovascular responses to endobronchial double-lumen intubation, and to compare the effect of remifentanil and alfentanil in modifying these responses in old aged patients.

MATERIALS AND METHODS

After obtaining approval from the Ethics Committee and written informed consent, we studied 60 patients aged 60 years and older undergoing elective thoracic surgery and requiring lung isolation using a left DLT. Patients were excluded if any of the followings applied: anticipated difficulty with intubation, and patients who took medications that would influence autonomic or cardiovascular response to laryngoscopy and intubation and those with preoperative arterial blood pressures of > 150/90 mmHg.

All patients were premedicated with midazolam 0.1 mg/kg orally 60 min before the induction of anesthesia. Before arrival in the operating room, patients had an IV catheter placed to allow administration of IV fluids and medications. Additionally, a 20-gauge catheter was inserted into a radial artery connected to a pressure transducer (Deltran, Utah Medical Products, Utah, USA) to measure blood pressure and to take blood samples. Heart rate was determined from electrocardiogram (ECG) traces. For each patient, a rest period of at least 30 min was provided between the time of cannulation and the start of the study.

After breathing 100% oxygen, anesthesia was induced with IV thiopental 4−6 mg/kg given over 30 s immediately followed by IV injection over 30 s of either remifentanil 2μg/kg (n = 20), alfentanil 30μg/kg (n = 20), or placebo (n = 20) in double-blind and by random allocation. Cricoid pressure was applied as consciousness was being lost. Succinylcholine 1.5 mg/kg was given over 5 s soon after administration of the study drug, and laryngoscopy and left bronchial intubation were then performed 60 s later using a disposable polyvinyl chloride DLT (Bronchocath, Mallinckrodt) by a skilled anesthesiologist. All patients were ventilated manually with 1.2% isoflurane (inspired) in 100% oxygen throughout the study period to maintain end-tidal CO_2 between 35 and 40 mmHg by adjusting the tidal volume (8−10 ml/kg) and respiratory frequency (8−12 breaths/min). Each treatment was prepared up to 10 ml with 0.9% saline by a third party, so that the investigators were unaware of their identity. Repeated doses of vecuronium were administered to provide complete muscle relaxation during the surgical procedure. The size of the left-sided DLT for each patient was chosen based on the measurement of the left bronchial diameter on chest radiograph or computed tomographic scan, as described by Hannallah et al.[14,15] Proper placement of the DLT was confirmed by using fiberoptic bronchoscopy in every patient after the conclusion of the study because bronchoscopy itself may stimulate the airway resulting in different response. A humidifier (Thermovent 600, Portex, UK) was used. The duration of laryngoscopy (defined as the time from the beginning of laryngoscopy and to inflation of the bronchial cuff) and any difficulties in laryngoscopy or endobroncheal intubation were noted. Data from patients in whom intubation required more than 60 s were excluded.

Arterial pressure (mmHg) and HR (bpm) were record immediately before injection of the induction agent (baseline), just before laryngoscopy and intubation, and at 1-min intervals for 5 min after endobronchial intubation. Hypertension was defined as a systolic arterial blood pressure (SAP) more than 130% of the baseline value or > 160 mmHg, whereas hypotension was defined as SAP < 70% of the baseline value or < 90 mmHg. Tachycardia and bradycardia were defined as a HR more rapid than 110 bpm and less than 50 bpm, respectively. A dysrhythmia was defined as any ventricular or supraventricular premature beat or any sustained rhythm other than sinus. Ephedrine (4 mg increments) was administered for hypotension (SAP < 90 mmHg, or a decrease of > 30% from baseline values for more than 60 s) and atropine, in 0.5 mg increments, for bradycardia (HR less than 50 bpm for more than 60 s). For hypertension (SAP > 200 mmHg, or an increase of > 30% above baseline for > 60 s) or tachycardia (HR > 130 bpm for > 60 s), the inspired isoflurane concentration was increased in increments of 0.5%.

Arterial blood samples were drawn before the induction (baseline), just before laryngoscopy and intubation, and 1, 2, and 5 min after the intubation. The samples were collected into prechilled tubes containing EDTA-Na and immediately centrifuged at 3,000 rpm for 15 min at 4°C. The plasma was stored at −70°C until assayed for catecholamine concentrations. Plasma concentrations of norepinephrine and epinephrine were measured in duplicates using the technique of high-pressure liquid chroma-

Table 1. Demographic Data

	Control (n = 20)	Remifentanil (n = 20)	Alfentanil (n = 20)
Sex (M/F)	16/4	16/4	18/2
Age (yr)	67 ± 5	65 ± 5	66 ± 4
Weight (kg)	62 ± 10	67 ± 12	64 ± 9
Height (cm)	163 ± 7	165 ± 9	165 ± 8
Hemoglobin (g/dl)	13.0 ± 1.8	13.7 ± 1.3	13.0 ± 1.0
Intubation time (s)	27 ± 9	2 5 ± 11	28 ± 9

Values are means ± SD. n: number of patients. There were no statistically significant differences among the groups.

tography.[16] The assay sensitivity was 10.0 pg/ml, and within-run precision coefficients of variation were 13.5% and 14.2% for norepinephrine and epinephrine, respectively.

The power calculation for including 20 patients was based on being able to show a difference of 30 mm Hg in SAP after intubation between the remifentanil and alfentanil groups in preliminary study (17 patients per group for 80% power with $P < 0.05$). All results are expressed as mean ± SD. Statistical analyses of the data were performed by two-way analysis of variance with repeated measures. A Scheffè test was used for multiple pair-wise comparisons when a significant difference was indicated with analysis of variance. Complication rates among the groups were analyzed using χ^2 test where appropriate. A P value < 0.05 was considered statistically significant.

RESULTS

One patient in the remifentanil group and 2 in the control group were excluded because of an unanticipated difficult endobronchial intubation with duration of intubation more than 60 s. One patient treated with alfentanil developed chest wall rigidity, which made ventilation of the lungs difficult during the induction of anesthesia. This case was also excluded from data analysis. There were no significant differences among the groups with respect to sex ratio, age, weight, height, and the time required for performing laryngoscopy and endobronchial intubation (Table 1).

Baseline SAP did not significantly differ among the groups. Induction of anesthesia with thiopental combined with either remifentanil, alfentanil or saline caused a significant reduction of SAP in all groups; however, the reduction in both remifentanil and alfentanil groups was greater than control group ($P < 0.05$). The endobronchial intubation then significantly increased SAP in all groups. Both remifentanil and alfentanil attenuated the pressor response and sped the restoration of blood pressure toward control level. The maximum increase of SAP from pre-intubation values in the remifentanil and alfentanil groups (36 ± 26 and 33 ± 30 mmHg, respectively) was significantly lower than that in the control group (83 ± 35 mmHg). In patients given remifentanil or alfentanil, no overall change in SAP occurred when compared with pre-induction baseline value (Fig. 1).

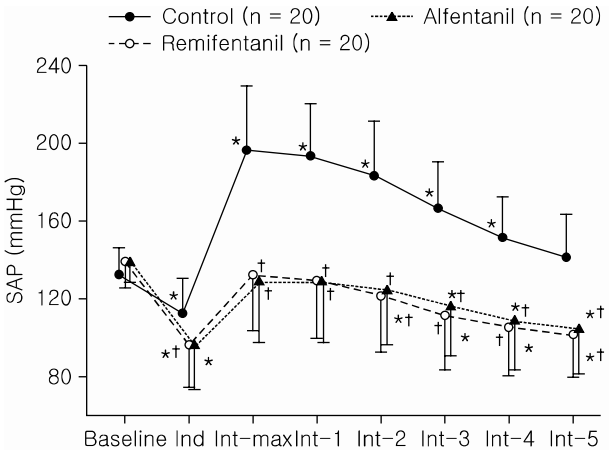

Fig. 1. Systolic arterial pressure (SAP) before and after endobronchial intubation in patients given either remifentanil 2μg/kg, alfentanil 30μg/kg, or saline (control). Values are means ± SD. n: number of patients, Ind: immediately before laryngoscopy and intubation, Int-max: maximum response within 1 min after intubation, Int-1, 2, 3, 4, and 5: responses at 1, 2, 3, 4 and 5 min after intubation. *: $P < 0.05$ versus baseline, † $P < 0.05$ versus control group. Remifentanil and alfentanil similarly abolished the pressor responses to endobronchial intubation.

Baseline HR did not significantly differ among the groups. HR increased after anesthetic induction in the control group but remained unchanged in both remifentanil and alfentanil groups. In response to endobronchial intubation, HR increased similarly (6−11 bpm) in all groups; however, the peak values were lower in the remifentanil and alfentanil groups (77 ± 13 and 80 ± 13 bpm, respectively) than in the control (93 ± 11 bpm) ($P < 0.05$) (Fig. 2).

Individual values of SAP exceeded 130% of the preinduction baseline value or 160 mmHg in 25 (42%) of the 60 patients studied. The incidence of hypertension was significantly lower, and that of hypotension was significantly higher in both remifentanil and alfentanil groups than in the control ($P < 0.05$). Eight patients in the control group and none in either

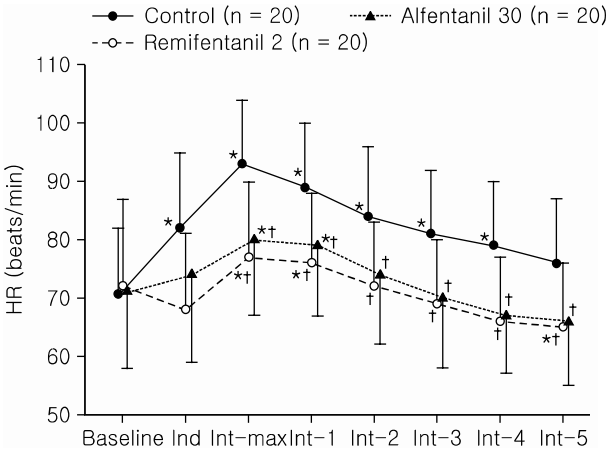

Fig. 2. Heart rate (HR) before and after endobronchial intubation in patients given either either remifentanil 2μg/kg, alfentanil 30μg/kg, or saline (control). Values are means ± SD. n: number of patients, Ind: immediately before laryngoscopy and intubation, Int-max: maximum response within 1 min after intubation, Int-1, 2, 3, 4, and 5: responses at 1, 2, 3, 4 and 5 min after intubation. *: $P < 0.05$ versus baseline, † $P < 0.05$ versus control group. Remifentanil and alfentanil similarly attenuated the tachycardiac responses to endobronchial intubation.

Table 2. Incidence of Adverse Effects

	Control (n = 20)	Remifentanil (n = 20)	Alfentanil (n = 20)
Hypertension	18 (8)	4*	3*
Hypotension	2	7 (5)*	8 (3)*
Tachycardia (HR > 110 bpm)	2	0	1
Bradycardia (HR < 50 bpm)	0	1	1
Dysrhythmia	2	0	2

*: $P < 0.05$ versus control group. n: number of patients, HR: heart rate. Numbers in parenthesis are patients who required escape medication.

remifentanil or alfentanil group required an increase in the inspired concentration of isoflurane to treat hypertension. In contrast, five patients in the remifentanil group and three patients in the alfentanil group required ephedrine 8 mg to treat hypotension (SAP < 90 mm Hg more than 60 s). There were no significant differences in the incidence of tachycardia and bradycardia among groups, and no patient required treatment for bradycardia. Premature ventricular contractions appeared immediately after the endobronchial intubation in two patients each in the control and alfentanil groups. The arrhythmias disappeared spontaneously without treatment (Table 2).

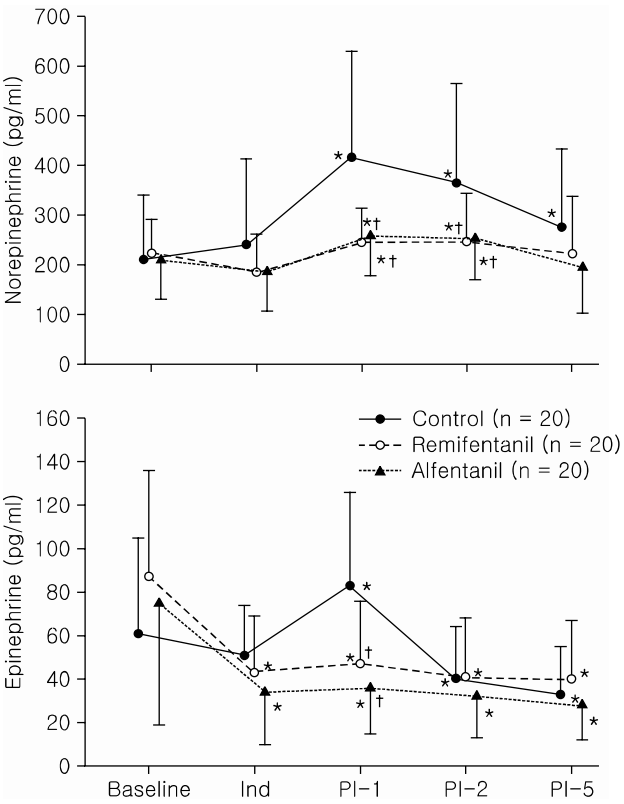

Fig. 3. Plasma concentrations of norepinephrine and epinephrine in patients given either remifentanil 2μg/kg, alfentanil 30μg/kg, or saline (control). Values are means ± SD. Norepinephrine and epinephrine measured in pg/ml plasma. n: number of patients, Ind: immediately before laryngoscopy and intubation, PI-1, PI-2 and PI-5: 1, 2 and 5 min after the onset of intubation, respectively. *: $P < 0.05$ versus baseline; † $P < 0.05$ versus control group. Both remifentanil and alfentanil attenuated norepinephrine and abolished epinephrine responses to endobronchial intubation.

Fig. 3. shows the plasma catecholamine concentrations before and after endobronchial double-lumen intubation. Basal concentrations of norepinephrine and epinephrine were not different among the groups. Induction with thiopental with or without opioids did not affect the plasma concentrations of norepinephrine, but thiopental with remifentanil or alfentanil significantly decreased epinephrine concentrations. The endobronchial intubation then caused an increase in norepinephrine concentrations measured at 1 and 2 min following intubation in all groups, the degree of which was lower in both remifentanil and alfentanil groups than in the control group. Plasma epinephrine concentrations were also increased significantly after intubation in the control group, which was then abolished by

both remifentanil and alfentanil.

DISCUSSION

Our results demonstrated that endobronchial intubation with DLT elicited a significant pressor response: the magnitude of which may be greater when compared with standard endotracheal intubation.[1-3] In our controls, mean maximum increase in SAP above awake baseline values was 64 ± 29 mmHg, whereas in studies where thiopental has been used for induction of anesthesia, the pressor and tachycardiac responses to endotracheal intubation have been of the magnitude of 22−40 mmHg, or an increase of 30% compared with baseline preinduction values and of 15−20 bpm, respectively.[1-3] However, both remifentanil 2μg/kg and alfentanil 30μg/kg given as a bolus before endobronchial intubation similarly and effectively attenuated the cardiovascular and catecholamine responses, but with high incidence of hypotension.

In contrast to our results, Thompson et al.[4] who studied 20 adult patients scheduled to undergo elective surgery requiring the routine use of a DLT, found that the increases in HR and SAP after endobronchial intubation were of similar magnitude and duration to the well-described responses to laryngoscopy and tracheal intubation, i.e. mean increases of 15−20 bpm and 30−40 mmHg, respectively, for approximately 5−6 min. In that study, patients were ventilated with 1% isoflurane and 50% nitrous oxide in oxygen for about 4 min before intubation. Inhaled anesthetics including nitrous oxide have been shown to attenuate the activity of the sympathetic nervous system, which is responsible for pressor response.[17,18] Therefore, the discrepancy between two studies may be accounted for by differences in anesthetic technique. Furthermore, both studies used escape medication for hypertension (SAP > 200 mmHg more than 60 s) occurred during intubation in 3 (30%) of 10 control patients in their study and 8 (40%) of 20 control patients in our study, so the untreated pressor responses may have been greater than those reported in these articles. Another possibility may related to the small number of cases (10 patients each group) to reach statistical significance in their study. It is likely that a study with a larger number of cases would have yielded a statistically significant result.

It has been well known that the endotracheal intubation increases SAP in proportion to plasma norepinephrine levels.[3] Similarly, norepinephrine concentrations increased significantly following endobronchial intubation in association with pressor response in the control group, but these increases were attenuated by both remifentanil and alfentanil. Pretreatment with analgesic doses of opioid medication is of limited effectiveness in altering the norepinephrine responses associated with laryngoscopy and intubation. However, when higher doses of opioid analgesics are administered (e.g., fentanyl 8μg/kg or alfentanil 15μg/kg), norepinephrine responses are more effectively attenuated. In fact, high dose fentanyl (> 50μg/kg) is claimed to produce "stress free anesthesia and both the pressor and the catecholamine responses to laryngoscopy are abolished.[19] Pretreatment with high-dose of opioid, but not small dose, may attenuate or completely block the norepinephrine response following laryngoscopy and intubation. The concentrations of epinephrine also increased significantly in the control group, but this increase was abolished by either remifentanil or alfentanil. In previous studies, in which patients were not premedicated with an opioid analgesic, epinephrine was also found to increase in response to tracheal intubation.[2,10] If patients were premedicated with a small dose of opioid, no significant changes in epinephrine concentrations were demonstrated in response to intubation.[20] Pretreatment with an opioid, even in small doses, may prevent the increase of epinephrine, but not that of norepinephrine, following laryngoscopy and intubation.

Single bolus dose of 2μg/kg of remifentanil was effective in modifying the cardiovascular response to endotracheal intubation in a previous study,[21] so this dose was chosen for our study. Pharmcokinetic modelling indicates a 20-fold greater potency for remifentanil than for alfentanil.[22] A bolus dose of remifentanil 2μg/kg approximates to alfentanil 30μg/kg based on relative potency of 1 : 15. The similarity in results between two study groups suggests that the doses of remifentanil and alfentanil chosen were comparable. Remifentanil has a rapid onset of action similar to alfentanil with a time to peak plasma concentration effect of 60 s.[23] Moreover, it has a context-sensitive half-life of approximately 3 min compared to alfentanil's 58.5 min after a 4-h infusion.[24] This rapid elimination property appear to provide an advantage over alfentanil in alleviating brief, intense noxious stimuli such as those produced by endobronchial intubation for any operation of short duration, or when a prolonged opioid effect is undesirable (e.g., Cesarean section). We omitted continuous infusion of remifentanil because the clearance and volume of distribution of remifentanil are reduced and the pharmocodynamic effects are greater in the elderly.[25]

Previous studies have shown that in elderly patients a bolus

dose of remifentanil 0.5μg/kg followed by an infusion of 0.1 μg/kg/min or a bolus dose of alfentanil 10μg/kg is effective in attenuating the hemodynamic responses to intubation.[12] Cardiovascular and catecholamine responses during tracheal intubation are less marked when propofol is used for induction of anesthesia compared with thiopental.[26] In particular, the elderly are known to be sensitive to the hypotensive effects of propofol.[27] They used propofol as an induction agent whereas we used thiopental. In addition, they used rocuronium as a muscle relaxant for intubation while we used succinylcholine, which has a sympathomimetic activity. The different hemodynamic responses between the two studies may be related to different anesthetic techniques and/or different intubation techniques (endotracheal versus endobronchial). Therefore, optimal dose of remifentanil or alfentanil to prevent cardiovascular response to intubation seems be titrated according to induction agent, muscle relaxant, age or intubation techniques used during induction of anesthesia.

Most of patients who require DLT double-lumen endobronchial intubation are elderly patients. Cardiovascular instability may contribute to perioperative myocardial ischemia and cardiac morbidity in these patients.[6,28,29] Pressor responses observed in the control patients were more pronounced than those reported in numerous earlier studies with patients for whom endotracheal intubation was performed.[1-3] Often, endobronchial intubation is achieved not easily in one attempt with some difficulties. Moreover, fiberoptic bronchoscopy to confirm proper placement of the DLT may stimulate airway resulting in prolonged pressor response. When endobronchial intubation with DLT is indicated especially in old aged patients, effective measures including opioids should be implemented to minimize the stress responses. Nonetheless, since elderly patients are more sensitive to cardiovascular depression with opioids[30] and not a few patients indeed required vasopressor to treat hypotension in the present study, precautions should be taken to avoid adverse events associated with their use during anesthetic induction.

In summary, the present study demonstrated that a significant pressor and tachycardiac effects combined with an elevation of plasma catecholamine concentration occurred in response to an endobronchial intubation with the use of thiopental and succinylcholine, and that remifentanil and alfentanil in the doses examined were similarly effective in reducing the cardiovascular response to laryngoscopy and endobronchial intubation, but with a high incidence of hypotension in the old aged patients. Further investigation is necessary to determine which dose of remifentanil would provide stable hemodynamics during endobronchial intubation in old aged patients.

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