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Effects of Rapacuronium on Respiratory Function during General Anesthesia

A Comparison with cis-*Atracurium*

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Background: **With its introduction for widespread clinical use, there has been an increase in reports of bronchospasm related to the administration of rapacuronium. As it is commonly used for rapid sequence intubation, it has been suggested that these effects may be related to an inadequate depth of anesthesia. The current study examines the airway effects of rapacuronium in tracheally intubated, anesthetized adults.**

Methods: **Endotracheal intubation was accomplished without the use of neuromuscular blocking agents. Dynamic compliance, tidal volume, peak inspiratory flow rate, peak expiratory flow rate, and peak inflating pressure were measured after administration of either rapacuronium (1.5 mg/kg) or *cis*-atracurium (0.2 mg/kg) to 20 adult patients (10 received rapacuronium and 10 received *cis*-atracurium) anesthetized with propofol–remifentanil.**

Results: **Statistically significant increases in peak inflating pressure (22 ± 6 to 28 ± 9 cm H_2O, $P = 0.0012$) and decreases in dynamic compliance (108 ± 43 to 77 ± 41 ml/cm H_2O, $P = 0.0001$), peak inspiratory flow rate (0.43 ± 0.11 to 0.39 ± 0.09 l/s, $P = 0.0062$), peak expiratory flow rate (0.67 ± 0.10 to 0.59 ± 0.09 l/s, $P = 0.0015$), and tidal volume (744 ± 152 to 647 ± 135 ml, $P = 0.0293$) occurred after administration of rapacuronium. No changes were seen after administration of *cis*-atracurium.**

Conclusion: **These data demonstrate that rapacuronium, but not *cis*-atracurium, has significant airway effects in intubated, mechanically ventilated adults.**

RAPACURONIUM is a steroidal, nondepolarizing neuromuscular blocking agent (NMBA), marketed as an alternative to succinylcholine. Initial clinical trials have suggested that rapacuronium can provide an onset time and clinical effect similar to succinylcholine, allowing for endotracheal intubation within 60 s.[1,2] These properties make it an effective alternative to succinylcholine for rapid sequence intubation while avoiding the adverse-effect profile associated with succinylcholine.[3] Initial clinical trials demonstrated a low adverse-effect profile with rapacuronium. The manufacturer's package insert for rapacuronium (Organon Inc., West Orange, NJ) reports an incidence of bronchospasm of 3.2% in 1,965 patients who received rapacuronium compared with 2.1% in 572 patients who received succinylcholine. However, subsequent studies demonstrated a higher incidence of respiratory side effects with rapacuronium when compared with succinylcholine.[4] Furthermore, recent case reports provide anecdotal information of severe respiratory compromise associated with rapacuronium administration.[5,6] Such problems have led to the suggestion that rapacuronium may have some direct or indirect effect on respiratory function. The current study compared the airway effects of rapacuronium and *cis*-atracurium after administration to tracheally intubated, mechanically ventilated, anesthetized adults.

Methods

The study was approved by the institutional review board of the University of Missouri. Written informed consent was obtained from each patient. The population included patients aged 18 yr or older who were undergoing elective, nonthoracic, surgical procedures. Patients with a history of asthma or any type of chronic lung disease were not eligible. A history of tobacco use was obtained but did not disqualify patients from the study. The patients were fasted for 8 h, and an intravenous infusion of lactated Ringer's solution was started. Premedication was provided by intravenous midazolam (1–2 mg). The patient was transported to the operating room, and routine monitors were placed. Anesthesia was induced with a combination of propofol (2–3 mg/kg) and remifentanil (2–4 μg/kg), and the patient's trachea was intubated without the use of NMBAs with a 7.5–8.0-mm cuffed endotracheal tube. Maintenance anesthesia was provided by a continuous infusion of propofol and remifentanil adjusted to maintain a Bispectral Index of 50–60. Mechanical ventilation was provided using an Ohmeda 7810 Anesthesia Ventilator (Ohmeda Inc., Madison, WI) with a tidal volume (V_t) of 8–10 ml/kg, an inspiratory-to-expiratory ratio of 1:2, a rate adjusted to maintain the end-tidal carbon dioxide from 35 to 40 mmHg, and a fraction of inspired oxygen of 0.5 using a mixture of air and oxygen. No changes were made in the ventilator settings during the study protocol. After endotracheal intubation, an esophageal balloon was placed and connected to the Bicore CP 100 monitor (Allied Healthcare Products Inc., Riverside, CA). The esophageal balloon was placed distally to a premeasured point so that it was beyond the lower third of the esophagus. It was then withdrawn to a point where end-expiratory pressure was most negative. Transpulmo-

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nary pressure was measured *via* the Bicore CP 100 Monitor using a differential pressure transducer connected to the esophageal balloon and to the airway between the endotracheal tube and the anesthesia circuit. The Bicore CP 100 Monitor also measures inspiratory and expiratory flow rates using a variable area obstruction pneumotachograph. Once the balloon was placed and the machine calibrated according to the manufacturer's recommendations, baseline data were recorded every 2 min during a 10-min period, yielding five data points for each variable. The readings provided are an average of the variables during the preceding 2 min. The variables measured included dynamic compliance (C_{dyn}), peak inspiratory flow rate (PIFR), peak expiratory flow rate (PEFR), peak inflating pressure (PIP), and V_t. After the baseline variables were measured, the patients received either *cis*-atracurium (0.2 mg/kg) or rapacuronium (1.5 mg/kg) administered over 10 s. The randomization included an equal distribution of the initial 20 data sheets to either rapacuronium or *cis*-atracurium and their blinded selection from the file. The same pulmonary variables were measured at 2-min intervals for a total of 10 min after administration of the NMBA. All pulmonary data collected, both before and after the administration of the NMBA, were measured during a stable plane of anesthesia, without any noxious stimuli, before the start of the surgical procedure. The five readings for each pulmonary variable before the administration of the NMBA were averaged and taken as the baseline. The five recordings after the administration of the NMBA were also averaged.

Statistical Analysis

The baseline and post-NMBA readings from each patient were analyzed using a paired, two-tailed, *t* test. The baseline pulmonary variables (C_{dyn}, PIFR, PEFR, V_t, and PIP) and the demographic data for patients who received rapacuronium and those that received *cis*-atracurium were compared using an unpaired, two-tailed, *t* test. The number of patients who received rapacuronium or *cis*-atracurium and had a 25% or greater decrease in C_{dyn} or a 25% or greater increase in PIP was compared using a chi-square analysis with a contingency table and Yates correction. All data are expressed as the mean ± SD, with $P < 0.05$ considered significant.

Results

Twenty patients were enrolled in the study. Rapacuronium was administered to 10 patients and *cis*-atracurium was administered to 10 patients. There were no differences in the demographics between the two groups (table 1). In the patients who received rapacuronium, no statistically significant difference was noted in the five respiratory variables between the five smokers and the five nonsmokers; therefore, all of the rapacuronium data are considered together. Statistically significant decreases in C_{dyn}, PIFR, PEFR, and V_t and increases in PIP occurred after administration of rapacuronium (table 2, figs. 1 and 2), whereas no changes were observed after administration of *cis*-atracurium (table 3). The mean of the five C_{dyn} values after the administration of the NMBA decreased by 25% or more from baseline in 5 of 10 patients who received rapacuronium compared with 0 of 10 patients who received *cis*-atracurium ($P = 0.04$). The mean of the five PIP values after the administration of the NMBA increased by 25% or more from baseline in 5 of 10 patients who received rapacuronium compared with 0 of 10 patients who received *cis*-atracurium ($P = 0.04$). Two patients who received rapacuronium had increases of PIP to greater than 40 cm H_2O. During the study protocol, no treatment was administered for the respiratory changes occurring after administration of rapacuronium. The respiratory variables returned to baseline values 20–30 min after administration of rapacuronium. There was no change in oxygen saturation or blood pressure. No patient developed urticaria or rash.

Table 1. Demographic Variables of the Two Groups

	Rapacuronium	*cis*-Atracurium
Age (yr)	50.5 ± 18.5	43.9 ± 14.2
Weight (kg)	87.0 ± 18.7	87.8 ± 22.4
Gender (M/F)	4/6	6/4
Tobacco use	5	7

Discussion

The current study demonstrates that rapacuronium has significant effects on respiratory function in anesthetized, adult patients. We noted changes in V_t, compliance (C_{dyn}, PIP), and indicators of airway resistance (PIFR, PEFR) after administration of rapacuronium. No such changes were observed after administration of *cis*-atracurium. In addition to reaching statistical significance, several of the patients experienced what may be considered clinically significant changes, with 5 of 10 patients who received rapacuronium having a 25% decrease from baseline in C_{dyn} or a 25% increase from baseline in PIP. By administering the NMBA after endo-

Table 2. Respiratory Variables before and after Rapacuronium

	Before Rapacuronium	After Rapacuronium	*P* Value
PIFR (l/s)	0.43 ± 0.11	0.39 ± 0.09	0.0062
PEFR (l/s)	0.67 ± 0.10	0.59 ± 0.09	0.0015
PIP (cm H_2O)	22 ± 6	28 ± 9	0.0012
Vt	744 ± 152	647 ± 135	0.0293
C_{dyn} (ml/cm H_2O)	108 ± 43	77 ± 41	0.0001

PIFR = peak inspiratory flow rate; PEFR = peak expiratory flow rate; PIP = peak inflating pressure; Vt = tidal volume; C_{dyn} = dynamic compliance.

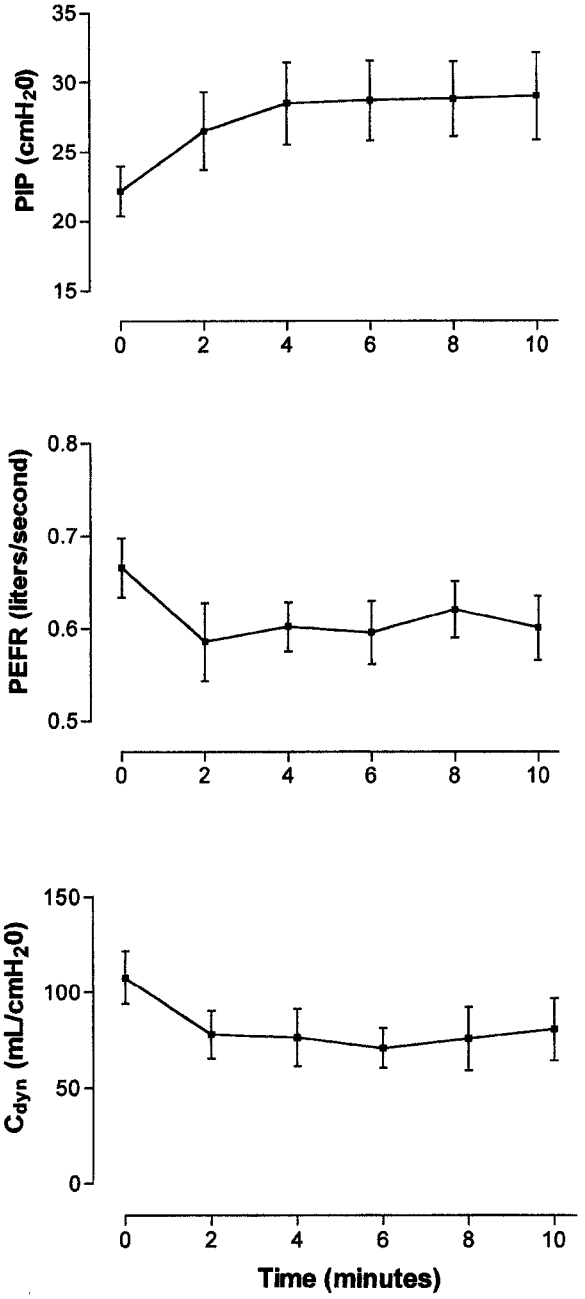

Fig. 1. Time course (in minutes on the x-axis) of changes in peak inflating pressure (PIP; *top*), peak expiratory flow rate (PEFR; *middle*), and dynamic compliance (C_{dyn}; *bottom*) after administration of rapacuronium. The baseline measurements are labelled as time 0. Statistically significant changes in PIP, PEFR, and C_{dyn} occurred after administration of rapacuronium (see also table 2).

tracheal intubation and without any noxious stimuli, we were able to eliminate the possibility that placement of the endotracheal tube was the sole factor responsible for the bronchospasm. It has been speculated that bronchospasm occurring after use of rapacuronium for rapid sequence intubation may result from reflex bronchoconstriction initiated by irritant receptors in response to endotracheal intubation during an inadequate depth of anesthesia. Several different variables may be measured to assess respiratory function during anesthesia. In clinical practice, V_t and PIP are assessed most commonly. For the purpose of clinical research, other variables may be monitored, including C_{dyn}, resistance, PIFR, and PEFR. C_{dyn} has been suggested as a more sensitive measure of distal airway changes and inspiratory function, while resistance may be more reflective of proximal or large airway changes. Because resistance requires the estimation of transpulmonary pressure as well as flow rates, any factor that either increases transpulmonary pressure or decreases the flow rate will increase resistance. Therefore, resistance may be a less sensitive indi-

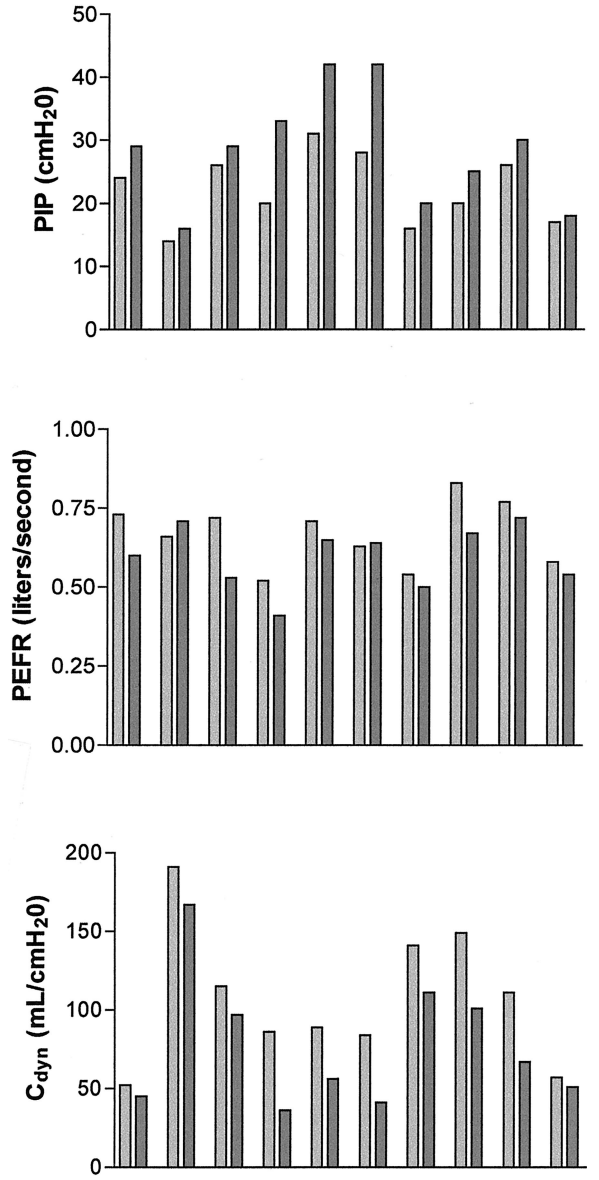

Fig. 2. Changes in peak inflating pressure (PIP; *top*), peak expiratory flow rate (PEFR; *middle*) and dynamic compliance (C_{dyn}; *bottom*) after administration of rapacuronium to the 10 study patients. For each patient, the preadministration value is represented in light gray and the postadministration value in dark gray.

Table 3. Respiratory Variables before and after *cis*-Atracurium

	Before *cis*-Atracurium	After *cis*-Atracurium	*P* Value
PIFR (l/s)	0.50 ± 0.14	0.52 ± 0.17	NS
PEFR (l/s)	0.69 ± 0.10	0.69 ± 0.10	NS
PIP (cm H_2O)	24 ± 5	25 ± 6	NS
Vt	836 ± 180	839 ± 194	NS
C_{dyn} (ml/cm H_2O)	94 ± 43	93 ± 48	NS

PIFR = peak inspiratory flow rate; PEFR = peak expiratory flow rate; PIP = peak inflating pressure; Vt = tidal volume; C_{dyn} = dynamic compliance.

cator than PEFR as a marker of expiratory function. Other factors may affect PIFR and PEFR. PIFR can be affected by the specific type of ventilator used as the ventilators may step-down the inspiratory flow rate if there is increased pressure required for delivery of the V_t. In addition, the PEFR will decrease as the delivered V_t decreases. For these reasons, it is possible that the most valid measurements reported in the current study are C_{dyn} and V_t.

We chose to use a combination of propofol and remifentanil for maintenance anesthesia. Although it is possible that deep inhalational anesthesia with its bronchodilator properties could prevent the changes we noted after administration of rapacuronium,[7,8] it is unlikely that a deep level of inhalational anesthesia could be achieved during rapid sequence intubation, thereby limiting its practical application. On the other hand, intravenous anesthetic agents are commonly used for induction during rapid sequence intubation; therefore, we chose to use these agents (propofol, remifentanil) as the anesthetic for this study. In addition, recent clinical trials and laboratory investigations have demonstrated that propofol has beneficial effects on the airway, acting to inhibit bronchospasm, and may therefore be an effective agent for the induction of anesthesia in patients with asthma.[9–11]

As we have eliminated the intubation event as the etiologic factor in the bronchospasm in the current study, what are the possible explanations for our findings? Levy *et al.*[12] investigated changes in plasma histamine concentrations after rapacuronium doses of 1, 2, and 3 mg/kg in 47 adult patients. One patient who received 1 mg/kg, one who received 2 mg/kg, and three who received 3 mg/kg had increases in the plasma histamine concentration greater than 1 ng/ml. Seven of the 47 patients developed bronchospasm, but none had elevated histamine concentrations. Of the five patients who had histamine concentrations greater than 1 ng/ml, no cardiorespiratory sequelae, including bronchospasm, were noted.

There are several subtypes of muscarinic receptors in the airway. The M_1 receptors, located on the smooth muscle, when stimulated by acetylcholine, initiate muscle contraction. M_2 receptors, located on the distal terminal of nerve endings at the neuromuscular junction, when stimulated by acetylcholine, act as a negative feedback mechanism and inhibit the further release of acetylcholine, thereby decreasing ongoing smooth muscle contraction. M_3 receptors, located on the postsynaptic side of the neuromuscular junction, when stimulated by acetylcholine, result in muscle contraction. Zappi *et al.*[13] evaluated the effects of the NMBAs pipecuronium and rocuronium on human bronchial smooth muscle in an *in vitro* preparation. They suggested that, because of varying effects on nicotinic and muscarinic acetylcholine receptors, the airway effects of NMBAs would vary. They demonstrated that pipecuronium, but not rocuronium, inhibited pilocarpine-stimulated prejunctional M_2 receptors. In an animal model, Okanlami *et al.*[14] also demonstrated variable effects of several NMBAs (pancuronium, mivacurium, doxacurium, and pipecuronium) on the M_2 and M_3 muscarinic receptors. However, they noted that, although they found that pipecuronium was an M_2 receptor antagonist and could potentiate reflex-induced bronchoconstriction, these effects occurred only at concentrations greater than those achieved in clinical practice. Although studies are needed to address the effects of rapacuronium on the various subtypes of muscarinic receptors in the airway, it is possible that rapacuronium may block prejunctional M_2 receptors and thereby interfere with the negative feedback mechanisms that regulate acetylcholine release at the neuromuscular junction of the airway.

In conclusion, we demonstrated that rapacuronium, but not *cis*-atracurium, has significant respiratory effects in intubated, mechanically ventilated adults. Because of the small study sample, we could draw no conclusion concerning the effects of a history of tobacco use on the airway changes occurring with rapacuronium. Further work is needed to identify the mechanisms responsible for these effects. As the administration of rapacuronium was separated from endotracheal intubation, mechanisms other than inadequate depth of anesthesia must be responsible. As we used a propofol–remifentanil anesthetic, future studies are needed to address the respiratory changes with other types of general anesthesia as well as delineation of potential methods to prevent the respiratory changes such as the administration of lidocaine, anticholinergic agents, or β-adrenergic agonists. With the clinical reports of respiratory compromise after administration of rapacuronium, the manufacturers have voluntarily withdrawn this agent from the market.

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