Effect of Prophylactic Bronchodilator Treatment on Lung Resistance after Tracheal Intubation

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Background: After induction of anesthesia, lung resistance increases. We hypothesized that prophylactic bronchodilator treatment before tracheal intubation would result in a lower lung resistance after placement of the endotracheal tube.

Methods: Forty-two adult patients were randomized to receive one of three inhaled medications 1 h before surgery. All patients first underwent pulmonary function tests. Patients then received either inhaled albuterol (360 µg) (n = 12), inhaled ipratropium bromide (72 µg) (n = 15) or a placebo inhalation (n = 15). Two, 5, and 15 min after tracheal intubation, lung resistance was measured using the method of von Neergard and Wirtz.

Results: Patients who received either bronchodilator had significantly lower lung resistance after intubation than those receiving placebo. At 2 min, lung resistances were 12.7 ± 1.4 cmH$_2$O·l^{-1}·s^{-1} (mean ± SEM) for the placebo group, 6.4 ± 3.1 cmH$_2$O·l^{-1}·s^{-1} for the ipratropium-treated group ($P < 0.05$ vs. placebo), and 7.2 ± 0.8 cmH$_2$O·l^{-1}·s^{-1} for the albuterol-treated group ($P < 0.05$ vs. placebo). The differences in lung resistance persisted through the final measurement at 15 min. Three of fifteen placebo-treated patients developed audible wheezing whereas no patients developed wheezing in either bronchodilator-treated group ($P < 0.05$ by Fisher's exact test). Although smokers and nonsmokers in the placebo group developed similar resistances after intubation, bronchodilator treatment resulted in lower resistance in nonsmokers than in smokers ($P < 0.05$).

Conclusions: Prophylactic treatment with either an inhaled β$_2$-adrenergic agonist or an inhaled cholinergic antagonist produced lower lung resistance after intubation when compared with an inhaled placebo medication. The effect was more pronounced in nonsmokers than in smokers. (Key words: Anesthetic techniques: tracheal intubation. Pharmacology, bronchodilators: albuterol; ipratropium. Lungs, airway: bronchoconstriction. Measurement techniques: pulmonary function tests.)

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AFTER induction of anesthesia and intubation of the trachea, lung resistance (R$_L$) appears to increase,[1–4] although precise comparisons are difficult because different methods of measurement are used in awake *versus* anesthetized patients. Because of the relationship between R$_L$ and lung volume, high R$_L$ after induction has largely been attributed to the decreased lung volume after induction and tracheal intubation.[5,6]

In awake, topically anesthetized volunteers without known reactive airway disease, intubation of the trachea resulted in a small increase in lower airway resistance despite no consistent change in lung volume.[7] The authors speculated that this was due to parasympathetically mediated reflex bronchoconstriction resulting from upper airway stimulation.

We hypothesized that R$_L$ after induction and intubation could be reduced by pretreatment with bronchodilating drugs. We also hypothesized that R$_L$ after intubation might be partially predictable based on preoperative history and pulmonary function testing, and that we could similarly predict those patients most likely to benefit from pretreatment with a bronchodilator.

To test these hypotheses, we randomly administered an inhaled bronchodilator or an inhaled placebo before anesthetic induction and tracheal intubation and measured R$_L$ after intubation. Both a β$_2$-adrenergic agonist, albuterol, and an anticholinergic bronchodilator, ipratropium bromide, were tested. The latter choice

seemed particularly pertinent given that the larynx and trachea receive extensive parasympathetic innervation.

Materials and Methods

After a protocol approved by the Human Subjects Committees of the University of Washington School of Medicine and the Seattle Veterans' Affairs Medical Center, informed consent was obtained from 42 patients about to undergo elective noncardiac surgery. Subjects were excluded if they had unstable cardiac disease or if they were being treated with either theophylline or corticosteroids for obstructive airways disease. Patients were randomized to receive either ipratropium, albuterol or a placebo by random envelope withdrawal, resulting in 15 patients randomized to each of the placebo and ipratropium groups and 12 randomized to the albuterol group.

Forced vital capacity, 1-s forced expiratory volume, and forced expiratory flow at mid–lung volume were determined preoperatively in all patients. One hour before surgery, patients were given four puffs of inhaled medication (72 μg ipratropium total or 360 μg albuterol total). The medications were delivered *via* a spacer device (Aerochamber, Monaghan Medical Corp., Plattsburgh, NY) to optimize drug delivery. The doses chosen have been documented to provide maximal bronchodilating effect in most subjects.[8,9]

Patients received no preanesthetic medication. Drugs for induction of anesthesia were mandated by the protocol to include only thiopental, succinylcholine, and either fentanyl, sufentanil, or alfentanil. The actual doses used were left to the decision of the patient's primary anesthesiologist. The patient's tracheas were intubated with an endotracheal tube that had a pressure sensing 3 Fr catheter extending two cm beyond the distal tip of the tube. The catheter tip was thus positioned at 22–24 cm from the teeth. An esophageal balloon was placed with the balloon positioned in the middle third of the esophagus. The balloon and the tracheal catheter were connected to a differential pressure transducer (MP-45-28, Validyne, Northridge, CA) to provide transpulmonary pressure. Flow through the endotracheal tube was measured using a heated pneumotachograph (Hans Rudolph Inc., Kansas City, MO) coupled with a second differential transducer (MP-45-14, Validyne).

After tracheal intubation, the patients' lungs were ventilated mechanically with oxygen at a tidal volume of 550 ml at a ventilatory rate of 15 breaths/min with flow rates of 30–40 l/min. The tidal volume was confirmed by integration of the pneumotachograph signal. Additional doses of the induction drugs were given by the primary anesthesiologist as deemed necessary to control pulse and blood pressure but no other anesthetic agents were given for the first 5 min after tracheal intubation. Resistance measurements were collected at 2 and 5 min after intubation. After 5 min, isoflurane was added to the inhaled mixture at a concentration left to the discretion of the primary anesthesiologist based on hemodynamic responses. In 37 of the 42 patients repeat measurements were made at 15 min. Five patients could not have the measurements repeated because surgical requirements interfered with the measurements.

Auscultation of the chest was performed in all patients by one of the authors (HKK) after the 2-min measurement to determine if wheezing was present.

R_L was calculated from the flow, pressure and volume curves using the technique of von Neergaard and Wirtz.[10–12] Measurements were made at volumes of 100, 200, 300, and 400 ml greater than end-expiratory volume and the results averaged.

Opioid doses were all converted to fentanyl equivalence using a potency ratio of 15 for sufentanil and 0.25 for alfentanil. Doses are thus expressed as the equivalent in μg of fentanyl.[13]

Data were analyzed using analysis of variance to determine differences among the three groups and least significant difference testing was used to compare individual groups. A level of $P < 0.05$ was chosen for rejection of the null hypothesis. All data are presented as mean ± SEM.

Results

Baseline characteristics of the three groups are presented in table 1. There were no differences among the groups in age, male/female distribution, weight, baseline pulmonary functions, pack-years of smoking, or proportion of patients that smoked. Induction doses of drugs were 5.3 ± 0.3 mg/kg of thiopental, 4.7 ± 0.6 μg/kg of fentanyl or the equivalent of sufentanil or alfentanil, and 1.8 ± 0.2 mg/kg of succinylcholine. The drug doses include all drugs given during the first 5 min of anesthesia. There were no differences among the three groups.

Mean end-tidal isoflurane concentration at the time of the 15 min measurement was 0.65 ± 0.06% with no differences among the groups.

Table 1. Baseline Characteristics

Variables/Groups	Placebo	Ipratropium	Albuterol
n	15	15	12
Males/females	13/2	12/3	9/3
Age (yr)	56 ± 4	62 ± 4	57 ± 4
Weight (kg)	82 ± 5	74 ± 4	79 ± 7
FVC (% predicted)	88 ± 5	86 ± 5	90 ± 7
FEV_1 (% predicted)	80 ± 5	78 ± 5	83 ± 7
FEV_1/FVC (%)	63 ± 3	59 ± 2	63 ± 3
FEF_{25-75} (% predicted)	69 ± 8	60 ± 6	67 ± 11
Smoking (packs/yr)	32 ± 8	28 ± 9	30 ± 10
Smokers (n)	10	9	10

Data are mean ± SEM.

Patients receiving a bronchodilator had significantly lower R_L at 2 and 5 min after intubation, with the difference persisting even after 10 min of isoflurane (fig. 1).

Preoperative pulmonary function tests did not differ among the three treatments. Despite the exclusion of patients taking theophylline or steroids for chronic lung disease, the group demonstrated preoperative spirometric values well below predicted (table 1). The forced expiratory flow at mid–lung volume and the 1-s forced expiratory volume/forced vital capacity ratio were indicative of some degree of obstructive lung disease with values in the smokers lower than in the nonsmokers (table 2).

Preoperative pulmonary function tests did not correlate with R_L after intubation in any treatment group, even when stratified by smoking history. This poor correlation is demonstrated in table 3 where correlation coefficients between forced expiratory flow at mid–
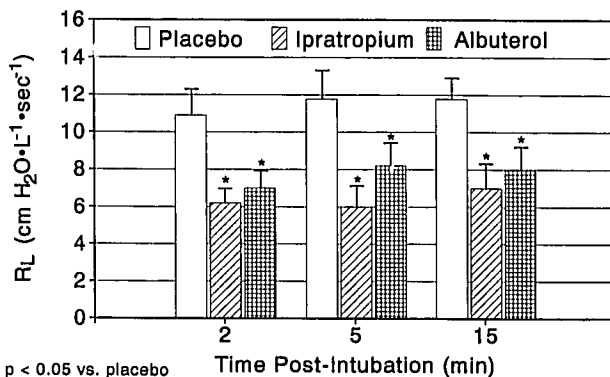
Fig. 1. Lung resistance (mean ± SEM) after intubation in albuterol- and ipratropium-treated groups compared with placebo. *$P < 0.05$ *versus* placebo by analysis of variance.

Table 2. Baseline Pulmonary Function Tests for Smokers *Versus* Nonsmokers

	FEV_1 (% Predicted)	FVC (% Predicted)	FEV_1/FVC (%)	FEF_{25-75} (% Predicted)
Nonsmokers	88 ± 4	90 ± 5	67 ± 2	85 ± 8
Smokers	77 ± 4	86 ± 4	59 ± 2*	57 ± 5*

Data are mean ± SEM.

* $P < 0.05$ *versus* nonsmokers.

lung volume and postintubation R_L are provided. Correlation with other pulmonary function indices was even poorer.

There was no difference in R_L between smokers and nonsmokers in the placebo group. However, nonsmokers treated with a bronchodilator had a lower R_L when compared with smokers (fig. 2), with a mean value of R_L that was 64% greater in the treated smokers than in the treated nonsmokers.

Audible wheezing occurred in 3 of 15 patients in the placebo group but in 0 of the 27 patients treated with bronchodilator ($P < 0.05$ by Fisher's exact test for the placebo group *versus* both treated groups combined).

The only side effect or patient complaint noted was one patient in the albuterol group who noted muscle tremor.

Discussion

The important findings of this study are that after anesthetic induction and tracheal intubation, both R_L and the incidence of wheezing can be decreased by pretreatment with either an inhaled anticholinergic drug or an inhaled β_2-adrenergic agonist. Postintubation R_L was lower for treated nonsmokers than for treated smokers. However, there was no difference between smokers and nonsmokers in the placebo group.

Resistance measurements are highly dependent on lung volume[5,6] making comparisons of pre- and post-induction measurements inexact. Because of this, we

Table 3. Pearson's Correlation Coefficients (r) for FEF_{25-75} with Lung Resistance

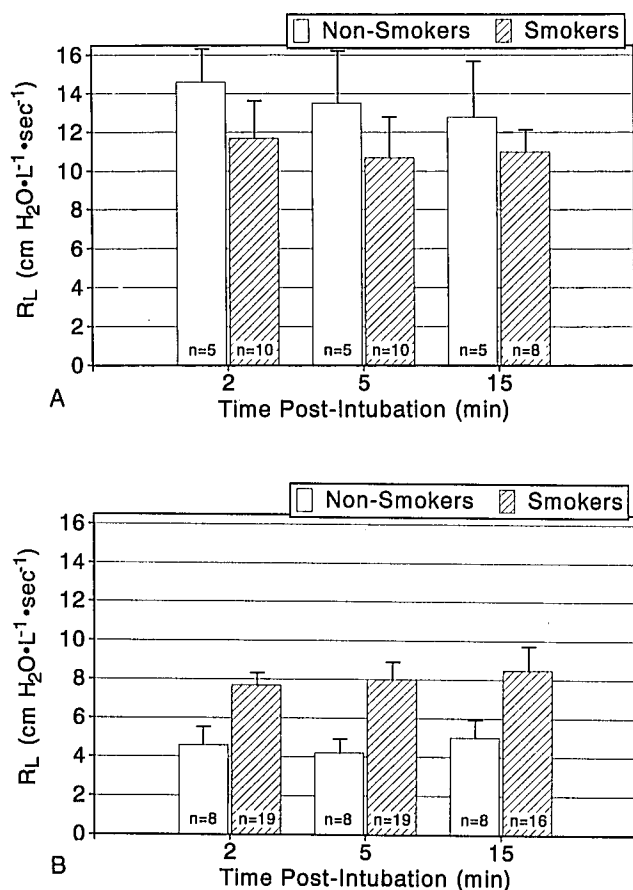|	2 Min	5 Min	15 Min
All patients	0.02	−0.05	−0.09
Placebo	0.19	0.00	0.07
Treated (either drug)	−0.30	−0.19	−0.24

Fig. 2. Lung resistance after intubation is compared between smokers and nonsmokers. There is no difference in placebo-treated patients (*A*) but markedly lower resistance in bronchodilator-treated patients (*B*). In these graphs, albuterol and ipratropium groups have been combined. $P < 0.05$ for smokers *versus* nonsmokers by analysis of variance for repeated measures for treated patients.

did not make preinduction measurements of R_L but used spirometry as a method to assess the degree of preexisting obstructive disease.

The results of the preoperative pulmonary function tests suggest that our patient group had a moderate degree of obstructive lung disease, especially among the smokers. The lack of a smoking history was a more useful predictor of low resistance after treatment than were the preoperative spirometric results.

Despite the difficulty in making comparisons pre- and postinduction, results from studies by other investigators support the notion that R_L increases after induction.[2,4,6] The reversibility of the increase has not previously been tested, however. If the increase were due

entirely to decreased lung volume, it is improbable that such a marked response to bronchodilators would have been found. We cannot be certain that bronchodilator treatment did not lead to a larger lung volume postinduction and thereby decrease R_L, although it seems unlikely because treatment of airway obstructive disease usually decreases lung volume.

Although we suspect that bronchodilator therapy prevented an increase in R_L after intubation, an alternative explanation is that the bronchodilators reduced baseline (preinduction) resistance rather than reducing the response. However, the magnitude of the difference between treated and nontreated patients exceeds the 15 percent threshold response considered to be normal after bronchodilator treatment of patients whose airways have not been stimulated.

The lesser response to bronchodilators in smokers was surprising in that smokers are often said to have reactive airways. However, this result may reflect a higher fixed resistance in smokers than in nonsmokers. The airway response to tracheal intubation may be a normal reflex response that may even be blunted in smokers by the presence of chronic irritation and inflammation. However, this remains speculation.

The lack of correlation of the response with preoperative pulmonary function tests was disappointing because we had hoped to define subgroups that might be more likely to benefit from treatment. The response data may not have correlated because abnormal findings in laboratory pulmonary function tests demonstrate obstructive lung disease but may be attributable to a variety of processes, including loss of elastic tissue from the supporting parenchyma, luminal narrowing from bronchial mucosal inflammation, reactive airways, or a combination of the above. This heterogeneity may limit their usefulness in defining a subgroup with increased reactivity.

We tested both an anticholinergic bronchodilator and a β_2-adrenergic agonist because the former is thought to have more effect on the larger, innervated central airways and the latter on smaller airways.[9,14,15] In addition, experimentally, β_2-adrenergic agonists may not block a potent cholinergic stimulus.[16] However, we found both drugs to be highly and equally efficacious.

We had originally hypothesized that patients with a history of cigarette smoking might have more reactive airways and thus might benefit more from treatment. In fact, we found just the opposite, with nonsmokers having a much greater apparent benefit. One possible explanation is that there is a higher fixed resistance in

smokers. Alternatively, airway inflammation can weaken the inhibitory M2 cholinergic autoreceptor and may thus create a more intense response in smokers.[17]

This study measured R_L, which includes tissue resistance in addition to airway resistance, because the latter cannot be readily measured in anesthetized patients. It is thus possible that some of the differences were due to tissue resistance.[18] In clinical practice, R_L is a more relevant measurement than airway resistance in terms of effect on airway pressures.

We used the von Neergaard and Wirtz technique to calculate R_L because it is the most frequently used and most reliable technique in anesthetized subjects.[10-12] Different techniques of measurement produce different absolute results but with good correlation.[11] These differences need to be considered when comparing results among studies.

Although our values of R_L are high compared with values of 1 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ cited for normal awake patients, they are comparable to values found in a prior study by Dohi and Gold of immediate postintubation R_L.[4] In that study, R_L was calculated using the isovolumetric method[9] and R_L averaged 5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ in patients without a history of obstructive lung disease and 9 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ in patients with a history of obstructive lung disease. To compare our results, we recalculated resistances from our original raw data using the isovolumetric method for the 5 min point and found a mean R_L of 7.5 ± 2.3 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ for the placebo group, 2.5 ± 0.5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ for the ipratropium group, and 3.1 ± 0.5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ for the albuterol group ($P < 0.05$ for albuterol and ipratropium vs. placebo).

The higher values found using the von Neergard and Wirtz method when compared with the isovolumetric method confirm the previous findings of Bergman and Waltemath[11] that the two methods provide results that are mathematically related but that higher absolute values result using the former method in anesthetized humans.

A potential confounding variable in our studies are the induction drugs used.[4,19,20] Virtually all induction drugs appear to have potential effects on R_L. We chose to create a protocol using the drugs we felt were most commonly used to facilitate tracheal intubation. In ad-

dition, the effects of these drugs on R_L have generally been found to be modest.

The effects of barbiturates on airway tone are controversial.[21-23] In the clinical range, thiopental results in some constriction but at slightly higher doses, bronchodilation results.[24]

The effect of fentanyl on bronchial smooth muscles is similarly controversial.[25,26,‖] Neto and Auler found that 30 $\mu g/kg$ of fentanyl given intravenously during anesthesia resulted in an increase in resistance and a decrease in compliance.[27] This dose is many-fold our average dose of 4.7 $\mu g/kg$. In addition, any direct effects of the narcotics may be offset by their ability to limit the stimulation produced by the endotracheal tube.

We were surprised that among the placebo patients studied after 15 min there was no change in R_L compared with the earlier measurements despite the use of isoflurane. Isoflurane does have bronchodilating properties in response to a histamine challenge[28] and some changes might have been expected. However, the concentration of isoflurane was not controlled but was adjusted as needed for hemodynamic control. This was generally a fairly low dose—a mean of 0.57 MAC—because it was before incision, and isoflurane appears to be a relatively weak bronchodilator at low concentrations.[28]

In summary, we found that pretreatment of patients with an inhaled bronchodilator before anesthetic induction and tracheal intubation routinely decreases R_L and reduces the likelihood of clinical wheezing. We did not test whether pretreatment affects the likelihood of respiratory complications either intra- or postoperatively but feel that such a study seems warranted given the marked effects seen in our patients.

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