Reduction in post-intubation respiratory resistance by isoflurane and albuterol

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Purpose: This study examined the bronchodilating effects of 0.6 MAC and 1.1 MAC isoflurane (ISF) on respiratory system resistance (R_{rs}) following tracheal intubation and determined whether albuterol supplements that effect.

Methods: Sixty-seven adult patients were anaesthetized with 2 μg·kg^{-1} fentanyl and 5 mg·kg^{-1} thiopentone and their tracheas intubated following administration of 1 mg·kg^{-1} succinylcholine. Respiratory system resistance was measured following intubation and the patients then randomized to receive either 1.1 MAC ISF in oxygen or 0.6 MAC ISF in 50% nitrous oxide and oxygen. Ten minutes later, R_{rs} was again measured. Patients were then further randomized to receive albuterol or a placebo using incremental doses of 2, 5, and 10 puffs (albuterol puff = 90 μg) delivered via a metered dose inhaler at ten minute intervals.

Results: Isoflurane at 1.1 MAC decreased post-intubation R_{rs} by 23 $\pm$ 5% (mean $\pm$ sem) whereas the decrease was only 7 $\pm$ 5% for 0.6 MAC ISF ($P < 0.01$). Two puffs of albuterol resulted in a further decrease of 12 $\pm$ 3% (mean $\pm$ sem) in R_{rs} compared with a 2 $\pm$ 4% decrease in the placebo groups ($P < 0.05$). Additional puffs of albuterol resulted in no further changes in R_{rs}.

Conclusion: We conclude that following tracheal intubation the reduction in R_{rs} produced by ISF is highly concentration dependent. Albuterol results in a small further reduction in R_{rs}.

Objectif : Étudier l'effet bronchodilatateur de l'isoflurane (ISF) à 0,6 MAC et à 1,1 MAC sur la résistance du système respiratoire (R_{TS}) après l'intubation trachéale et déterminer si l'albutérol amplifie cet effet.

Méthodes : Soixante-sept adultes anesthésiés au fentanyl 2 μg·kg^{-1} et au thiopentone 5 mg·kg^{-1} ont été intubés après l'administration de succinylcholine 1 mg·kg^{-1}. La résistance du système respiratoire a été mesurée après l'intubation et les patients ont été répartis aléatoirement pour recevoir soit ISF 1,1 MAC ou ISF 0,6 MAC dans le protoxyde d'azote 50% en oxygène. Dix minutes plus tard, la R_{TS} a été mesurée de nouveau. Les patients ont été de nouveau répartis aléatoirement pour recevoir de l'albutérol ou un placebo en dose fractionnées de 2, 5 et 10 bouffées (une bouffée d'albutérol = 90 μg) délivrées par un inhalateur gradué à dix minutes d'intervalles.

Résultats : L'isoflurane à 1,1 MAC diminue la R_{TS} de 23 $\pm$ 5% (moyenne $\pm$ sem) alors que la diminution n'était que de 7 $\pm$ 5% avec l'isoflurane à 0,6 MAC ($P < 0,01$). Deux bouffées d'albutérol ont provoqué une nouvelle baisse de 12 $\pm$ 3% (moyenne $\pm$ sem) de la R_{TS} comparativement à 2 $\pm$ 4% dans le groupe placebo ($P < 0,05$). Les bouffées additionnelles d'albutérol n'ont pas modifié davantage la R_{TS}.

Conclusion : Après une intubation trachéale, la réduction de la R_{TS} produite par l'isoflurane dépend fortement de sa concentration. L'albutérol provoque une petite réduction additionnelle.

SEVERE bronchospastic episodes during anaesthetic care occur most often following intubation of the trachea and occur even in patients without previous history of airway hyperreactivity.[1] Respiratory resistance also increases after intubation even in normal volunteers[2] and both β_2-adrenergic agonists and cholinergic antagonists have been demonstrated to ameliorate this response.[3,4]

Although intubation of the trachea provides a potent stimulus to bronchoconstriction, it is generally followed in the operating room by the delivery of inhalational anaesthetics, which are potent bronchodilators.[5] Whenever the increase in respiratory resistance is high enough to be clinically evident, clinicians often consider additional treatment with an inhaled β_2-adrenergic agonist. In dogs, the addition of the β_2-adrenergic agonist albuterol during halothane anaesthesia shifts the dose response curve to the right (less responsive) for histamine-induced bronchoconstriction,[6] but no data exist in humans. Furthermore, it is difficult to know whether a dose-response curve to histamine mimics the expected responses to therapeutic agents following intubation-induced bronchomotor activity.

The purpose of the current study was to assess the concentration dependence of the bronchodilating effect of isoflurane following tracheal intubation and to assess whether albuterol provides further bronchodilation in the presence of isoflurane anaesthesia.

Methods

Written informed consent was obtained from 67 patients to participate in the study protocol approved by the Human Subjects Committees of the University of Washington School of Medicine and the Puget Sound Veterans Affairs Health Care System. Subjects were excluded if they were being treated with a β_2-adrenergic agonist inhaler, corticosteroids, or theophylline. Peak expiratory flow (PEF) was measured prior to induction of anaesthesia. Anaesthesia was induced in all patients with 5 mg·kg^{-1} thiopentone, 1 mg·kg^{-1} succinylcholine, and 2 µg·kg^{-1} fentanyl iv and the trachea then intubated with a cuffed endotracheal tube (ETT) with an inner diameter of 7.0–8.0 mm. Following intubation of the trachea, patients were paralysed with 0.1 mg·kg^{-1} vecuronium iv and the lungs were ventilated at a tidal volume of 10 ml·kg^{-1} at a rate of eight bpm and an I:E ratio of 1:3. Inspiratory flow was set at 30 L·min^{-1}.

Two minutes after intubation and prior to delivery of any inhalation anaesthetic, respiratory resistance (R_{rs}) was measured and heart rate and blood pressure

recorded. Patients were then randomized into two groups to receive either 0.6 MAC end-tidal isoflurane with N_2O 50% or to receive 1.1 MAC end-tidal isoflurane in oxygen. Rapid over-pressure up to isoflurane 5% was used to achieve these concentrations as quickly as possible, generally within the first two minutes. The end-tidal concentration was then held stable. Ten minutes later, a second set of measurements was made and each group further randomized to receive either albuterol or a placebo via a metered dose inhaler (MDI) using a spacer (Aerochamber, Monaghan Medical, Plattsburgh, New York) connected between the Y-piece of the circuit and the endotracheal tube. Patients received two puffs from the MDI and measurements were repeated 10 min later. Following that measurement, five additional puffs were given and the measurements repeated 10 min later. Lastly, another 10 puffs were given (cumulative dose of 17 puffs) and a final measurement made 10 min later. This resulted in four groups – 1.1 MAC isoflurane with and without albuterol and 0.6 MAC isoflurane with and without albuterol.

Measurements of R_{rs} were made using the isovolume method[7] after correction for the resistance of the endotracheal tube as previously described.[8] Prior to each patient the spirometer was calibrated for volume using a one litre syringe (Hans Rudolph Inc., Kansas City, MO). Using a pneumotachograph and personal computer, the ventilatory flow and pressure curves were sampled at 10 msec intervals and the volume curve was determined by integration of the flow curve. The pressure drop across the endotracheal tube was excluded by first constructing a pressure-flow curve for both the 7.5 and 8.0 mm endotracheal tubes. For each measurement, the pressure drop across the tube for the flow noted was subtracted from the pressure measurements used during calculation, resulting in a value for R_{rs} exclusive of the endotracheal tube. The isovolume method of resistance measurement is a technique applicable to mechanically ventilated patients and is based on measuring airway pressure and flow at identical volumes during inspiration and exhalation. Inspiratory pressure (Pi) is a function of respiratory compliance (C), inspiratory flow (Fi) and resistance (R). Expiratory pressure (Pe) is a function of respiratory compliance (C), expiratory flow (Fe) and resistance (R). Using V to represent lung volume above FRC, the equations are:

Pi = C/V + RFi and
Pe = C/V – RFe
Subtracting these two equations yields:
Pi – Pe = R(Fi + Fe) or R = (Pi - Pe)/(Fi + Fe)

This determination of R_{rs} is influenced by both inspiratory and expiratory resistance. Measurements of end-tidal isoflurane were made using a Datex Capnomac (Datex, Tewksbury, MA). The predicted value for peak expiratory flow (PEF predicted) was used to normalize PEF.

Data are expressed as mean ± SEM. Group comparisons for age, weight, height, pack-years of smoking, peak expiratory flow as a percent of predicted flow, and R_{rs} immediately after intubation were performed with analysis of variance. Group comparisons for sex and ASA status were performed with the Chi-square statistic. Correlations between continuous variables were determined with regression analysis.

Group differences in R_{rs} were detected with repeated measures analysis of variance with the between-subject factors of high/low isoflurane concentration and the presence/absence of albuterol. More explicit examination of the individual effects of isoflurane and albuterol was also performed. The effect of isoflurane was determined by calculating the percent change in R_{rs} between the post-intubation and post- isoflurane values of R_{rs} for each subject:

(post-isoflurane R_{rs})–(post-intubation R_{rs})/(post-intubation R_{rs}). An unpaired t test examined for differences between the percent change in R_{rs} for the two isoflurane concentrations.

The effect of albuterol was determined by calculating the percent change in R_{rs} between the post- isoflurane and the post-two puffs of inhaler values of R_{rs} for each subject:

(post-two puffs R_{rs})–(post-isoflurane R_{rs})/(post-isoflurane R_{rs}). Since the two albuterol and the two placebo groups were exposed to different isoflurane concentrations, the percent change in Rrs was analysed by factorial analysis using both isoflurane concentration and the presence/absence of albuterol as factors.

Results

There was no difference among the groups in height, weight, age, ASA class, or smoking history (Table I). Peak expiratory flow as a percentage of predicted did not differ among the groups (Table I) and was negatively correlated with the number of pack-years the patient had smoked ($P < 0.01$, r=–0.45). Only 18 of 67 patients had a percent of predicted peak expiratory flow to 1.0. Immediately after intubation R_{rs} averaged 10.3 ± 0.5 cm $H_2O \cdot L^{-1} \cdot sec$ and did not differ among the groups (Table II). The haemodynamic responses to the four regimens did not differ among the groups (Table III).

For all four groups there was a decrease in R_{rs} after ten minutes of isoflurane ($P < 0.05$ for each group)

TABLE I Baseline Characteristics by Group

	(n=17) 1.1 MAC ISF,	(n=15) 1.1 MAC ISF,	(n=21) 0.6 MAC ISF,	(n=14) 0.6 MAC ISF,
	albuterol	placebo	albuterol	placebo
Males/Females	16/1	15/0	20/1	14/0
Age(years)	53±4	59±3	57±3	57±3
Weight (kg)	83±5	84±5	79±4	91±5
Height (cm)	175.3±1.1	175.3±0.7	175±0.7	180.3±0.7
ASA	2±0.1	2±0.1	2±0.1	1.9±0.1
Smoking (pack years)	36±8	42±8	40±8	48±11
Peak Expiratory Flow (% of predicted)	92±4	92±6	84±3	89±4

Data are mean ± sem.

TABLE II Raw data for R_{rs}

Group	Rrs (cm H2O · L-J · sec)				
	Post - ETT	Post. ISF	2 Puffs	7 puffs	17 puffs
1.1 MAC ISF, albuterol	11.3±1.1	8.5±0.5	7.3±0.5*	7.2±0.7*	7.4±0.6*
1.1 MAC ISF, placebo	10.5±1.6	6.8±1.1	6.6±0.9	6.4±0.7	6.5±0.7
0.6 MAC ISF, albuterol	9.0±0.7	8.3±0.7	7.3±0.6*	7.5±0.7*	7.5±0.6*
0.6 MAC ISF, placebo	11.3±1.0	10.0±1.0	9.4±1.0	8.8±1.0*	8.3±0.9*

Data are mean + sem. *$p < 0.05$ vs post-ISF Rrs in same group.
(Post - ETT = R_{rs} following tracheal intubation)

TABLE III Hemodynamic Measurements

Group	Mean blood pressure (mmHg)					Heart rate (beats·min.)				
	Post - ETT	Post. ISF	2 Puffs	7 puffs	17 puffs	Post. ETT	Post. ISF	2 Puffs	7 puffs	17 puffs
1.1 MAC ISF, albuterol	112±8	78±4	74±3	74±2	78±4	86±4	77±4	74±4	75±4	76±4
1.1 MAC ISF, placebo	117±6	81±6	78±4	77±3	84±5	86±4	77±4	75±4	73±4	75±5
0.6 MAC ISF, albuterol	116±5	86±5	77±3	78±3	82±4	83±3	72±4	63±2	63±3	64±3
0.6 MAC ISF, placebo	117±5	89±6	79±4	83±4	84±5	95±4	75±4	67±3	65±3	65±4

Data are mean + sem. ISF = isoflurane. 2 puffs, 7 puffs, and 17 puffs represent cumulative doses of albuterol or placebo.
(Post - ETT = Post endotracheal intubation)

(Table II). When the percent change in R_{rs} was determined between the post-intubation and post-isoflurane conditions, those subjects who received 1.1 MAC isoflurane demonstrated a greater percent decrease in R_{rs} than the patients receiving 0.6 MAC isoflurane/N_2O 50% (23 ± 5% decrease vs 7 ± 5% decrease, $P = 0.01$) (Figure 1).

Repeated measures analysis of variance for the collective data for R_{rs} confirmed the significant difference in response between the two isoflurane concentrations ($P = 0.005$) but failed to demonstrate a significant effect of albuterol ($P = 0.58$). However, when the percent change in R_{rs} was determined between the conditions of 10 min of isoflurane and two puffs of albuterol, those subjects who received two puffs of albuterol demonstrated a greater decrease in R_{rs} than those who received placebo (12 ± 3% vs 2 ± 4%, $P = 0.03$) (Figure 2). In the same analysis the isoflurane concentration did not influence the albuterol effect ($P = 0.64$ for the effect of isoflurane concentration). The subsequent doses of albuterol or placebo did not change Rrs except for the placebo group at 0.6 MAC isoflurane ($P = 0.01$ by repeated measures analysis of variance of the 2, 7 and 17 puffs data).

Discussion

Following tracheal intubation, R_{rs} increases markedly. Much of this increase is due to the decrease in lung volume that occurs with induction of anaesthesia.[9] Respiratory resistance also increases due to bronchoconstriction, presumably because of vagally mediated increases in bronchial muscle tone resulting from direct mechanical stimulation. Prophylactic administration of a ß$_2$-adrenergic agonist will limit this response.[3,4,10]

Inhaled anaesthetics are effective in limiting bronchoconstriction induced by a wide variety of stimuli in animals and animal models.[11] Mechanisms of bron-

chodilation by inhaled agents include direct airway smooth muscle relaxation,[5] blockade of vagal airway reflexes and augmentation of ß-adrenergic tone.[12] Because of the multiple mechanisms of action and the differing efficacy of bronchodilating agents in response to different stimuli, it is difficult to predict whether the effects of bronchodilators such as methylxanthines or ß$_2$-adrenergic agonists will be additive with the bronchodilating effects of an inhaled anaesthetic. In a study of dose-response curves for histamine-induced bronchoconstriction in dogs, the addition of theophylline or atropine to halothane did not improve upon the response with halothane alone, but the addition of albuterol to halothane did reduce the bronchoconstriction response to histamine in comparison with halothane alone.[6]

The bronchodilating effects of isoflurane are well accepted clinically and have been studied in animals[13] but there are few human studies[14] and little data concerning concentration dependence. In a previous human study, we found that 1.1 MAC isoflurane did not add to the bronchodilating effect of the ß$_2$-adrenergic agonist fenoterol when fenoterol was given prior to intubation.[9] However, we wondered whether the converse was true, that adding a ß$_2$-adrenergic agonist would not supplement the effect of 1.1 MAC isoflurane. We also felt it important to study whether the effect might differ if albuterol treatment were added at a lower concentration of inhaled anaesthetic, since dog studies suggest that, at low concentrations, isoflurane is a relatively ineffective bronchodilator.[15]

We found that the dose response curve for isoflurane-induced bronchodilation was steep between 0.6 and 1.1 MAC, with a nearly four-fold greater reduction in R_{rs} at the higher dose. These human data for isoflurane dose-response are similar to previously reported dog data for histamine-induced bronchoconstriction.[15]
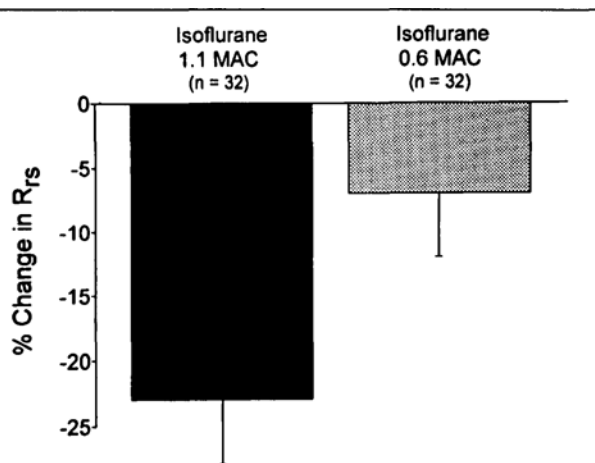
FIGURE 1   Decrease in respiratory system resistance (R_{rs}) by 1.1 vs. 0.6 MAC end-tidal concentration of isoflurane ($p = 0.01$ between 1.1 and 0.6 MAC). Results are expressed as a percentage change from R_{rs} after intubation.
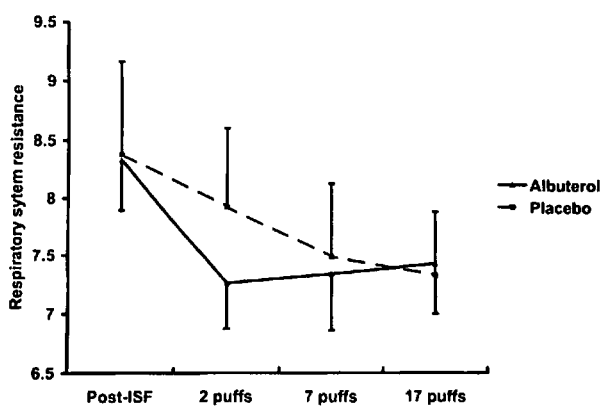

FIGURE 2   Respiratory system resistance (cm $H_2O \cdot L^{-1} \cdot sec^{-1}$) for albuterol (solid line) and placebo (dashed line) treated patients after 10 minutes of isoflurane (1.1 and 0.6 MAC end-tidal concentration combined) and following each dose of albuterol. The decline after two puffs of albuterol was significantly different from the decline after two puffs of placebo ($p = 0.03$) but further doses of albuterol produced no additional decreases in R_{rs}. By ten minutes later (after the 7 puffs) there was no difference between placebo and albuterol treated patients.

The initial benefit of albuterol in the presence of isoflurane was statistically significant compared with placebo. However, the 10% reduction beyond that of placebo is of questionable clinical importance. Furthermore, the same reduction in Rrs was achieved with ten more minutes of isoflurane plus placebo.

The inability of albuterol administration in excess of two puffs to achieve further reductions in R_{rs} suggests that either the dose response curve for albuterol is rela-

tively flat or that maximal bronchodilation was achieved at the lowest dose of albuterol in combination with isoflurane. In awake asthmatics, there is minimal additional benefit after two puffs of albuterol.[16,17] Furthermore, a comparable decline in Rrs occurred in the placebo group after 30 min of isoflurane, suggesting that isoflurane alone is capable of achieving comparable bronchodilation, albeit requiring a bit more time.

We previously studied whether isoflurane produced bronchodilation following tracheal intubation in patients pre-treated with the $\beta_2$adrenergic agonist fenoterol.[9] We found that pre-treatment produced bronchodilation that was not further supplemented by isoflurane, suggesting that fenoterol produced maximal dilation. The difference between the observation that a $\beta_2$agonist is not supplemented by isoflurane and the current finding that a $\beta_2$agonist does slightly supplement the effect of isoflurane may just be a reflection of sub-maximal bronchial relaxation from ten minutes of the inhaled anaesthetic alone.

Respiratory resistance declined slightly over time in the placebo group at low isoflurane concentration but not at the higher isoflurane concentration. The time dependence did not occur in the placebo group that received the higher dose of isoflurane, in whom considerable bronchodilation was achieved in the first ten minutes. The magnitude of this effect was small and there are several possibilities for why it occurred. A desensitization to the irritant effect of the tube may develop over time. Alternatively, end-tidal concentrations may not be the relevant concentration and at lower end-tidal concentrations, it may take longer to reach adequate concentrations of anaesthetic in the relevant tissue, be it smooth muscle or neural tissue. The continued decline also raises the possibility that the anaesthetic concentration in the target tissue was not yet at a steady-state, despite stability of the end-tidal concentration. End tidal concentration may not reflect the concentration in tracheo-bronchial muscular and neural tissue.

Assessing dose-response data for inhaled medication can be difficult because of wide variability in particle numbers and size that reach the lungs. The spacer device used has previously been found to be highly effective in producing drug delivery similar to that expected in the non-intubated patient.[18]

We studied endotracheal tube-induced bronchoconstriction in a population that excluded patients requiring daily bronchodilators. Hence, we excluded the patients who might be expected to show the greatest response. However, we felt it unethical to withhold a medication required by these patients, and chose instead to study patients not normally receiving

medication. Even apparently normal individuals develop a considerable reversible increase in R_{rs} following intubation[2,4] and patients with hyper-reactivity probably represent the extreme of this response. Although only three out of 67 of our patients gave a history of obstructive pulmonary disease, only 18 of the 67 had peak expiratory flow rates predicted, and 20 of 67 had flow rates <80% of predicted. Thus, our population probably represents a group with greater-than-average underlying airway obstruction, but does exclude patients at high risk for severe bronchoconstriction. Furthermore, a considerable proportion of patients with severe post-intubation bronchospasm have no previous history of airway hyperreactivity.[1]

Tracheal intubation produces a tracheal stimulus and is a model for studying bronchodilation, just as a pharmacological challenge with histamine or methacholine can be used to create a reproducible challenge. Because of the severity of adverse outcomes associated with bronchoconstriction,[1] we have not tested this stimulus in patients with severe hyper-reactivity and implications for that population must be inferred rather than tested directly. Based on the current study, we conclude that 1) isoflurane has a steep dose-response curve for bronchodilation in the 0.6–1.1 MAC range and 2) two puffs of albuterol may minimally supplement the bronchodilating effects of isoflurane under the conditions studied, but does not reduce Rrs to a level below that achieved by using isoflurane alone for a longer period of time.

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