

Both Local Anesthetics and Salbutamol Pretreatment Affect Reflex Bronchoconstriction in Volunteers with Asthma undergoing Awake Fiberoptic Intubation

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Background: Awake tracheal intubation may evoke reflex bronchoconstriction in asthmatics. Whether this effect is altered by the choice of the local anesthetic used or by pretreatment with a β_2 -adrenoceptor agonist is unknown. Therefore, we assessed the effect of awake fiberoptic intubation after lidocaine or dyclonine inhalation with or without pretreatment with salbutamol on lung function in asthmatic volunteers.

Methods: Bronchial hyperreactivity was verified by an inhalational histamine challenge. On four different days in a randomized, double blind fashion the volunteers ($n = 10$) inhaled either dyclonine or lidocaine with or without salbutamol pretreatment. FEV₁ was measured at baseline, following salbutamol or saline inhalation, after lidocaine or dyclonine inhalation, while intubated, and after extubation. Lidocaine and dyclonine plasma concentrations were also measured. Statistics: Two-way ANOVA, *post hoc* tests with Bonferroni correction, results are presented as mean \pm SD.

Results: Neither lidocaine nor dyclonine inhalation changed FEV₁ significantly from baseline compared with placebo inhalation (4.43 ± 0.67 l vs. 4.29 ± 0.72 l, and 4.53 ± 0.63 l vs. 4.24 ± 0.80 l, respectively). Salbutamol slightly but significantly increased FEV₁ (4.45 ± 0.76 l vs. 4.71 ± 0.61 l, $P = 0.0034$, and 4.48 ± 0.62 l vs. 4.71 ± 0.61 l, $P = 0.0121$, respectively). Following awake intubation FEV₁ significantly decreased under lidocaine topical anesthesia (4.29 ± 0.72 l to 2.86 ± 0.87 l) but decreased even more under dyclonine anesthesia (4.24 ± 0.80 l to 2.20 ± 0.67 l; $P < 0.0001$). While salbutamol pretreatment significantly attenuated the response to intubation, it did not eliminate the difference between the effects of lidocaine and dyclonine. Only minutes after extubation FEV₁ was similar compared with baseline.

Conclusion: In asthmatics, awake fiberoptic intubation evokes a more than 50% decrease in FEV₁ following dyclonine inhalation. Using lidocaine for topical anesthesia the decrease in FEV₁ is significantly mitigated (35%) and can be even further attenuated by salbutamol pretreatment. Therefore, combined treatment with lidocaine and salbutamol can be recommended for awake intubation while the use of dyclonine, despite its excellent and longer lasting topical anesthesia, may be contraindicated in patients with bronchial hyperreactivity.

TRACHEAL intubation increases airway resistance in patients with bronchial hyperreactivity.¹⁻⁴ Although this reflex bronchoconstriction can often be sufficiently mitigated or treated with a β_2 -adrenoceptor agonist, it can as

well be life threatening.⁵ However, to what extent reflex bronchoconstriction in asthmatics occurs following awake tracheal intubation under topical anesthesia is unknown.

For topical anesthesia to facilitate awake tracheal intubation the two local anesthetics lidocaine, an amide, and dyclonine, a ketone, have been used.^{6,7} Lidocaine and dyclonine differently affect the response to a histamine challenge. While lidocaine attenuated the response, dyclonine did not.^{8,9} How these findings relate to direct mechanical irritation by intubation, and what impact any differences between the two types of local anesthetics may have, can only be speculated.

Therefore, ten volunteers with mild asthma were fiberoptically intubated awake, under lidocaine or dyclonine topical anesthesia with or without salbutamol pretreatment. This occurred on four different days before intubation, with the endotracheal tube in place, and after extubation lung function measurements were performed to assess the amount of reflex bronchoconstriction.

Specifically, we tested the hypotheses that (1) awake tracheal intubation under topical anesthesia leads to a decrease in FEV₁, (2) there is no difference in the response to awake tracheal intubation when either lidocaine or dyclonine are used for topical anesthesia, and (3) pretreatment with salbutamol attenuates the response to awake tracheal intubation and eliminates possible minor differences in the response following topical anesthesia with either lidocaine or dyclonine.

Methods

Subjects

After study approval by the local ethics committee and informed written consent, 10 subjects (2 women, 8 men) were enrolled in this randomized, double blind, placebo-controlled study. The subjects had mild asthma as diagnosed by their history of recurrent dyspnoe attacks always relieved by the use of β_2 -adrenoceptor agonists and a positive response to an inhalational histamine challenge. All volunteers were free of symptoms on the study days. None of them had received a β -adrenergic medication within the 12 hours prior to the measurements and none of the subjects had used theophylline preparations or systemic corticosteroids within the past 3 months. One of the subjects was a smoker. Lung function at the screening visit and anthropometric data are presented in table 1.

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Table 1. Baseline Lung Function of 10 Mild Asthmatic Volunteers

Volunteer	Rtot [mbar · l ⁻¹ · s ⁻¹]	FEV ₁ [l]	FEV ₁ pred [l]	VC [l]	VCpred [l]	FRC [l]	FRCpred [l]	PC 20 [μg/ml]
1	0.282	3.61	4.51	5.35	5.67	4.51	3.46	6.3
2	0.180	5.57	4.38	7.04	5.60	4.77	3.61	14.2
3	0.244	4.58	3.97	5.69	5.06	3.62	3.44	10.3
4	0.340	4.72	4.11	5.96	5.13	3.22	3.29	8.7
5	0.254	4.92	4.98	5.86	6.34	3.99	3.72	14.9
6	0.250	4.21	4.54	5.10	5.74	3.76	3.53	16.8
7	0.390	3.76	3.77	5.03	4.37	2.87	2.99	14.8
8	0.230	4.73	3.83	5.73	4.84	3.44	3.34	15.1
9	0.260	3.74	3.60	4.68	4.20	3.17	2.97	15.6
10	0.310	4.83	5.34	5.65	6.79	3.68	3.79	14.4
Mean	0.274	4.47	4.30	5.60	5.37	3.70	3.41	13.1
SD	0.060	0.63	0.56	0.66	0.82	0.59	0.28	3.4

Rtot = airway resistance (body plethysmography); FEV₁ = forced expiratory volume in 1 s; VC = vital capacity; FRC = functional residual capacity; pred = predicted value; PC20 = Concentration of histamine required inhaled for a 20% decrease in FEV₁.

Measurements

Lung function measurements were performed in a body plethysmograph (Masterlab Jaeger, Würzburg, FRG) with an integrated spirometer (Jaeger, Würzburg, FRG) in each subject at the same time of day (± 1 h). On the initial screening visit, baseline vital capacity (VC) and forced expiratory volume in 1 s (FEV₁) were assessed. This was followed by an inhalational challenge with histamine to confirm bronchial hyperreactivity. Bronchial hyperreactivity was defined by a decrease of FEV₁ of at least 20% from baseline following inhalation of histamine in a concentration of more than 2.0 and less than 18 mg/ml.

Blood was drawn from an antecubital vein to measure lidocaine or dyclonine plasma concentrations by high-pressure liquid chromatography (HPLC, Waters 2690, with PDA spectrophotometric detection at 200 nm; lower level of detection 0.01 μg/ml coefficient of variation less than 0.5%).

Histamine Aerosol Challenge

Aerosol inhalation was performed with a nebulizer driven by compressed air at 30 psi (DeVilbiss No. 646, DeVilbiss, Somerset, PA) using a mouthpiece and a nose clip. The subjects were instructed to inspire from functional residual capacity (FRC) to inspiratory capacity at an inspiratory flow rate of less than 0.6 l/s. At end inspiration the subjects were advised to hold their breath for 5 s. Nebulization was triggered by inspiration and maintained for 0.8 s (Spira elektro 2 flow meter; Respiratory Care Center, Hämeenlinna, Finland). This maneuver was repeated five times.

The subjects were challenged with aerosolized saline, followed by increasing doses of histamine diphosphate (Sigma-Aldrich GmbH, Deisenhofen, FRG) diluted in saline. The starting concentration of histamine diphosphate was 0.075 mg/ml, which was trebled on each subsequent inhalation up to a maximal concentration of 18 mg/ml. The time interval between inhalations of

increasing histamine concentrations was kept constant. One to two min after inhalation of each aerosol dose FEV₁ was measured three times and the largest FEV₁ was accepted.

Challenges were discontinued if the subject had symptoms of chest tightness or difficulty in breathing, a decrease in FEV₁ of at least 20% from the prechallenge baseline, or had received the maximal concentration of histamine diphosphate. The histamine threshold concentration necessary for a 20% decrease in FEV₁ (PC20) was calculated for each subject.¹⁰

Lidocaine, Dyclonine, Salbutamol, and Saline Inhalation

Lidocaine and dyclonine were diluted in saline without additives. Aerosols were produced by a nebulizer driven by compressed air at 30 psi (DeVilbiss No. 646, Somerset, PA). The start of nebulization was triggered (Spira elektro 2 flow meter; Respiratory Care Center, Hämeenlinna, Finland) after inhalation of 100 ml air.

The volunteers took deep tidal breaths with a nebulization time of 2 s with each breath and they were advised to perform a 5 s breath hold at the end of each inspiration. The inhalation was continued until the complete solution was aerosolized.

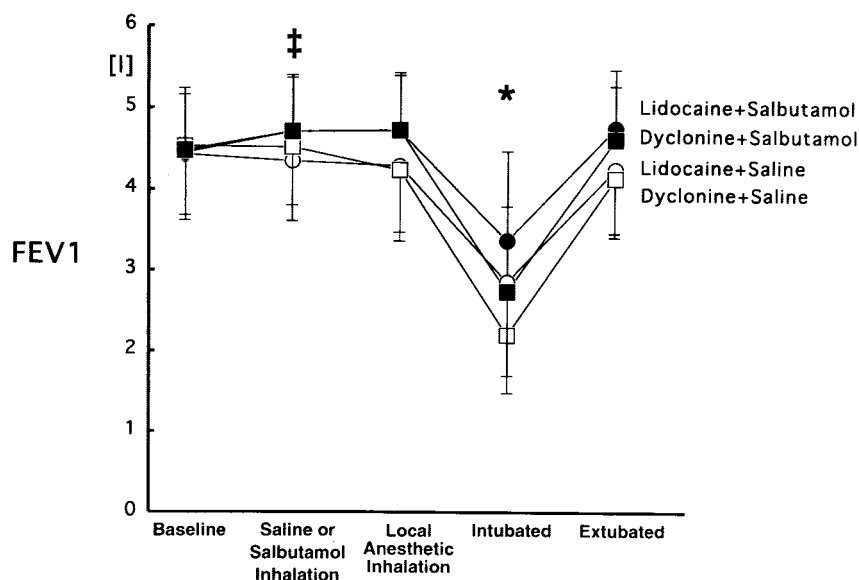
Protocol

On each study day baseline lung function was assessed. Further measurements were postponed, if the actual FEV₁ differed by more than 7% from the initial baseline obtained on the day of the screening visit.

On four different study days, in random order and in a double-blind fashion, the subjects inhaled lidocaine (4%) and dyclonine (1%), each on two study days. The total dose was 2.0 mg/kg for lidocaine and 0.5 mg/kg for dyclonine, respectively.

On one of the two days volunteers were pretreated with salbutamol inhalation (1.5 mg in 1.5 ml), while on the corresponding other day they were pretreated with

Fig. 1. FEV₁ of 10 asthmatic volunteers (mean \pm SD) at baseline, after salbutamol (black symbols) or saline (open symbols) inhalation, following lidocaine (4%; circles) or dyclonine (1%; squares) inhalation, while endotracheally intubated, and after extubation, respectively. Intubation under topical anesthesia with lidocaine causes significantly less airway irritation than with dyclonine. Pretreatment with salbutamol significantly improves FEV₁ compared with baseline (§) and attenuates the response to tracheal intubation without outweighing the difference between lidocaine and dyclonine. (§, **P* < 0.05)



saline (1.5 ml). Thus, the volunteers always inhaled a volume of 0.05 mg/kg. Directly after salbutamol or placebo were administered and after the local anesthetic inhalation was given, lung function was measured.

Subsequently, to enforce topical anesthesia the subjects gargled 2.0 ml of the local anesthetic solution of the respective day, and after rinsing 1.0 ml of the respective local anesthetic solution on the epiglottis *via* a bronchoscope three times, the volunteers were orally intubated using a bronchoscope. For intubation of each volunteer an endotracheal tube of the same size (7.5 or 8.0 mm ID) was used.

Lung function was measured again 2 to 3 min after intubation. After 10 min the volunteers were extubated and lung function measurements were repeated 3 to 4 min after extubation.

Venous blood was drawn from an antecubital vein prior to the start of the inhalation and every 5 min for 15 min, after intubation, and after extubation. Heart rate and blood pressure were measured every 5 min during salbutamol and local anesthetic inhalation.

Data Analysis

Data are presented as mean \pm SD. The following *a priori* null hypotheses were tested: (1) Intubation does not decrease FEV₁; (2) lidocaine or dyclonine inhalation did not affect FEV₁ differently; and (3) salbutamol pretreatment does not outweigh any differences between lidocaine or dyclonine. Comparisons were made by ANOVA and *post hoc t* test with Bonferroni correction of the α -error for multiple comparisons. Null hypotheses were rejected and significant differences assumed with *P* < 0.05/*n* as indicated. Power analysis was based on repeated measurements in the same subjects, with an α -error of 5%, a β -error of 20%, and a change to be detected in FEV₁ of 20%.

Results

Awake fiberoptic intubation significantly decreased FEV₁. Intubation under topical anesthesia with dyclonine decreased FEV₁ significantly more than intubation under lidocaine anesthesia. Salbutamol pretreatment significantly attenuated reflex bronchoconstriction with either local anesthetic but did not compensate for the difference between the effects of dyclonine and lidocaine.

Salbutamol significantly increased FEV₁ from baseline on both days compared with placebo (4.45 ± 0.76 vs. 4.71 ± 0.61 l, *P* = 0.0034 and 4.48 ± 0.62 vs. 4.71 ± 0.61 l, *P* = 0.0121, respectively; fig. 1), while neither lidocaine nor dyclonine inhalation *per se* changed FEV₁ significantly from baseline after placebo inhalation (4.43 ± 0.67 vs. 4.29 ± 0.72 l and 4.53 ± 0.63 vs. 4.24 ± 0.80 l, respectively; fig. 1).

After fiberoptic tracheal intubation FEV₁ significantly decreased under lidocaine topical anesthesia from 4.29 ± 0.72 to 2.86 ± 0.87 l (*P* < 0.0001), but after dyclonine FEV₁ decreased significantly more from 4.24 ± 0.80 l to 2.20 ± 0.67 l (*P* < 0.0001 and *P* < 0.0001 for lidocaine vs. dyclonine; fig. 1).

This decrease in FEV₁ evoked by intubation was significantly attenuated by salbutamol pretreatment both in combination with lidocaine (FEV₁ from 4.72 ± 0.62 l to 3.37 ± 1.03 l; *P* = 0.0011) as well as in combination with dyclonine (FEV₁ from 4.73 ± 0.62 l to 2.74 ± 0.98 l; *P* = 0.0003). The difference in FEV₁ response between topical anesthesia provided by lidocaine *versus* dyclonine remained significant even after salbutamol pretreatment (*P* = 0.0004).

Two to five min after extubation FEV₁ increased to values close to those following placebo or salbutamol administration (4.25 ± 0.74 l for lidocaine, 4.76 ± 0.64 l for lidocaine with salbutamol, 4.14 ± 0.61 l for dyclo-

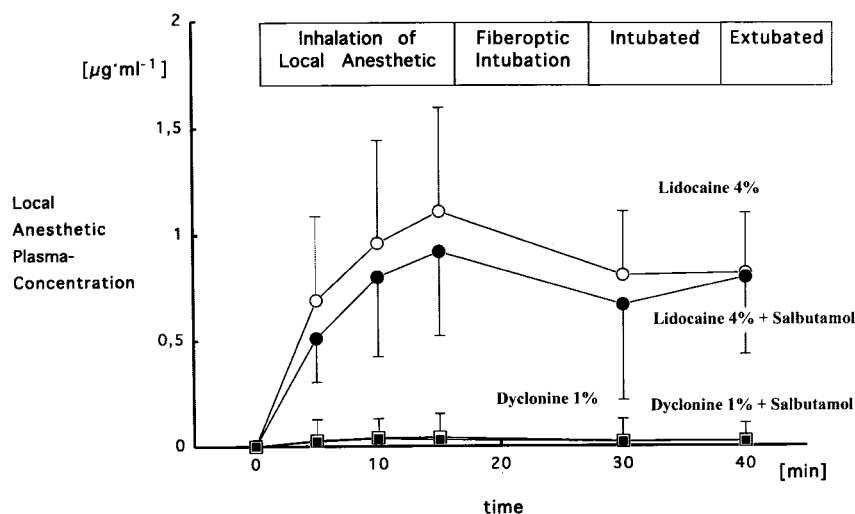


Fig. 2. Time course of local anesthetic plasma concentrations following inhalation of lidocaine (circles) or dyclonine (squares) with (full symbols) or without (open symbols) salbutamol pretreatment (mean \pm SD). With comparable topical anesthesia lidocaine has a fast onset of absorption while dyclonine is barely absorbed at all.

nine, and 4.62 ± 0.58 l for dyclonine with salbutamol, respectively; fig. 1). There was no significant difference between FEV₁ values after extubation *versus* the respective FEV₁ baseline.

Local anesthetic plasma concentrations reached a peak directly at the end of inhalation attaining 1.11 ± 0.48 $\mu\text{g/ml}$ for lidocaine but only 0.04 ± 0.02 $\mu\text{g/ml}$ for dyclonine (fig. 2). Salbutamol pretreatment did not change peak concentrations significantly (0.92 ± 0.38 $\mu\text{g/ml}$ for lidocaine and 0.04 ± 0.02 $\mu\text{g/ml}$ for dyclonine; fig. 2). Even with supplementation of topical anesthesia *via* the bronchoscope prior to intubation plasma concentrations were well below the toxic threshold of 5.0 $\mu\text{g/ml}$. The inhalation of the local anesthetics took 16.0 ± 4.3 min for lidocaine and 15.1 ± 3.0 for dyclonine and including all preparations additional 12.6 ± 4.7 and 13.7 ± 4.0 min later the volunteers were intubated. Furthermore, 4 of 10 volunteers spontaneously mentioned a much more intense topical anesthesia following dyclonine inhalation compared with lidocaine.

Heart rate and blood pressure did not change significantly during salbutamol or placebo inhalation. Two subjects showed a mild increase in heart rate (13 and 16 beats/min, respectively) on both of the days of salbutamol inhalation, in contrast to the days were placebo was inhaled.

Discussion

Awake tracheal intubation evoked significant bronchoconstriction. The degree of bronchoconstriction was influenced by the choice of the local anesthetic, with significantly greater bronchoconstriction following dyclonine, and could be significantly attenuated by preceding salbutamol inhalation. However, even salbutamol pretreatment did not compensate for the difference in FEV₁ decrease between the two local anesthetics.

These results were obtained from volunteers with mild bronchial hyperreactivity, all in stable clinical condition

while taking their current medication or during their symptom free interval. Since mechanical airway irritation elicited by intubation and by the endotracheal tube in place can not be modelled by or titrated as a histamine or methacholine challenge, only volunteers with mild asthma and defined bronchial reactivity were chosen so as to minimize the risk of severe uncontrolled bronchoconstriction. All measurements were made by the same investigator at the same time of day. Due to its low day-to-day variability, FEV₁ was chosen to analyze the responses to inhalation and intubation on the different study days.¹¹⁻¹³

A salbutamol dose of 1.5 mg was chosen to minimize cardiac side effects while achieving bronchial dilation. In fact, the response to intubation was significantly attenuated by salbutamol, and two subjects showed a mild increase in heart rate. Thus, the salbutamol dose chosen for pretreatment attenuating bronchial hyperreactivity and carrying a low risk for cardiac complications, can be considered appropriate. A higher dose might have shown a greater effect attenuating bronchoconstriction but also more side effects.

An inhaled lidocaine concentration of 4% has been shown to provide effective topical anesthesia with moderate or little airway irritation, while a dyclonine concentration of 1% has been shown to be as effective for topical airway anesthesia as lidocaine 4%.^{7,9}

Lidocaine inhalation, even with a supplemental dose administered *via* the bronchoscope, led to a peak mean plasma concentration of only 1.1 ± 0.5 $\mu\text{g/ml}$. This concentration is far below the presumed toxic threshold of 5 $\mu\text{g/ml}$ for lidocaine and well within the range (0.25–1.7 $\mu\text{g/ml}$) reported after lidocaine inhalation.¹⁴⁻¹⁷

Dyclonine plasma concentrations of only 0.04 ± 0.05 $\mu\text{g/ml}$ indicate a low absorption rate. This might help to explain why after dyclonine inhalation reflex bronchoconstriction was less attenuated than after lidocaine inhalation.

Several mechanisms may explain the attenuation of bronchoconstriction by lidocaine. First, lidocaine has a direct effect on nerve conduction at concentrations already achieved after intravenous administration.¹⁸ While the attenuating effect of intravenous lidocaine on histamine evoked bronchoconstriction is dose-dependent, lidocaine inhalation leads to the same attenuation at significant lower plasma concentrations. Accordingly, additional local mechanisms must be responsible.¹⁹ This may involve local neural tissue, with lidocaine blocking impulse conduction in parasympathetic afferent or efferent nerve fibers.¹⁸ Second, Kai *et al.* have shown that lidocaine in high tissue concentrations (20–200 $\mu\text{g/ml}$) directly depresses smooth muscle cell contraction.²⁰ With aerosol concentrations of 40 mg/ml such concentrations might be reached in bronchial tissue. Third, lidocaine in clinically relevant concentrations alters muscarinic signaling after stimulation of m_1 as well as m_3 muscarinic receptors and might attenuate parasympathetically mediated smooth muscle constriction.^{21,22} All of these potential mechanisms might explain why dyclonine might not be as effective. Finally, lidocaine and dyclonine, in addition to providing topical anesthesia, might block different airway receptors, as speculated after showing different effects of lidocaine and dyclonine on cough and bronchial constriction.²³ However, these findings cannot be supported by our results because under topical anesthesia we did not see any difference in the cough response, either with lidocaine or with dyclonine.

Overall, none of these mechanisms is proven *in vivo* and cannot be proven using our study protocol. Accordingly, how these various mechanisms contribute to attenuation of reflex bronchoconstriction can only be speculated.

Increased airway resistance and decreased FEV_1 following tracheal intubation in awake volunteers free of pulmonary disease have been shown earlier.²⁴ However, the effect on resistance of the endotracheal tube itself and the amount of bronchial constriction in “normals” have been difficult to define.^{25–28} On the one hand the endotracheal tube bypasses the upper airway which makes up for up to 50% of total airway resistance and compensates for some of the resistance.²⁵ On the other hand, its resistance is flow dependent and measurements of endotracheal tube resistance *in vitro* cannot simply be added to measurements with a dynamically changing flow during *in vivo* breathing.^{26,27} In fact, such measurements grossly overestimate the increase in resistance by endotracheal tubes in intubated patients.²⁸ However, Gal *et al.* demonstrated in awake healthy volunteers that awake tracheal intubation under lidocaine topical anesthesia causes a 20% decrease in FEV_1 .²⁴ Nevertheless, even in volunteers with no history of bronchial hyper-

reactivity an endotracheal tube can be expected to cause some bronchoconstriction in response to this strong stimulus. Because, even awake fiberoptic bronchoscopy alone, as a pure airway irritation, decreases FEV_1 . After awake bronchoscopy nonasthmatic patients respond with a 8 to 9% decrease in FEV_1 while asthmatic patients show a decrease of 20–26%.^{29,30}

Overall, tracheal intubation in nonasthmatic patients causes a 20% decrease in FEV_1 but is most likely not only caused by the rather fixed obstruction by the tube but also to a (so far not quantified) mild bronchoconstriction.

In our volunteers with mild asthma the decrease in FEV_1 following intubation under topical anesthesia averaged 35% after lidocaine, but 51% after dyclonine. Since our volunteers had mild asthma the FEV_1 decrease in subjects with moderate or severe bronchial hyperreactivity can only be assumed to be significantly greater. Interestingly, reflex bronchoconstriction had resolved almost completely 5 min after extubation. This underlines the clinical observation that bronchospasm is mainly an intraoperative, rather than postoperative, complication of tracheal intubation.

In patients with bronchial hyperreactivity, undergoing general anesthesia pretreatment with a β_2 -adrenoceptor agonist significantly mitigates the bronchoconstrictive response to tracheal intubation.^{2,3} Furthermore, salbutamol and lidocaine inhalation when combined attenuates the response to a histamine challenge even more than each of the drugs alone.⁸ In accordance with these findings intubation after salbutamol and lidocaine inhalation evoked a significantly lesser decrease in FEV_1 than lidocaine alone. Still, awake tracheal intubation caused a decrease of about 24% even in this combination.

However, although salbutamol pretreatment mitigated the decrease in FEV_1 following intubation with dyclonine as well, it failed to compensate for the difference between lidocaine or dyclonine. Therefore, combined treatment with lidocaine and salbutamol can be recommended for awake intubation while the use of dyclonine, despite its excellent and longer lasting topical anesthesia, must be considered relatively contraindicated in patients with bronchial hyperreactivity.

In conclusion, awake fiberoptic intubation in mild asthmatics can evoke a more than 50% decrease in FEV_1 in asthmatics, which is less under lidocaine anesthesia and further attenuated by salbutamol pretreatment. While combined pretreatment with lidocaine and salbutamol is recommended to minimize reflex bronchoconstriction awake tracheal intubation is still associated with a decrease in FEV_1 by 24% in volunteers with mild asthma. Considering resolution of reflex bronchoconstriction within minutes after extubation the effect of mechanical irritation by intubation may often be underestimated in patients with bronchial hyperreactivity.

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