

Inhaled Bronchodilator Administration During Mechanical Ventilation: How to Optimize It, and For Which Clinical Benefit?

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ABSTRACT

Bronchodilators are frequently used in ICU patients, and are the most common medications administered by inhalation during mechanical ventilation. The amount of bronchodilator that deposits at its site of action depends on the amount of drug, inhaled mass, deposited mass, and particle size distribution. Mechanical ventilation challenges both inhaled mass and lung deposition by specific features, such as a ventilatory circuit, an endotracheal tube, and ventilator settings. Comprehensive *in vitro* studies have shown that an endotracheal tube is not as significant a barrier for the drug to travel as anticipated. Key variables of drug deposition are attachments of the inhalation device in the inspiratory line 10 to 30 cm to the endotracheal tube, use of chamber with metered-dose inhaler, dry air, high tidal volume, low respiratory frequency, and low inspiratory flow, which can increase the drug deposition. *In vivo* studies showed that a reduction by roughly 15% of the respiratory resistance was achieved with inhaled bronchodilators during invasive mechanical ventilation. The role of ventilatory settings is not as clear *in vivo*, and primary factors for optimal delivery and physiologic effects were medication dose and device location. Nebulizers and pressurized metered-dose inhalers can equally achieve physiologic end points. The effects of bronchodilators should be carefully evaluated, which can easily be done with the interrupter technique. With the non-invasive ventilation, the data regarding drug delivery and physiologic effects are still limited. With the bilevel ventilators the inhalation device should be located between the leak port and face mask. Further studies should investigate the effects of inhaled bronchodilators on patient outcome and methods to optimize delivery of inhaled bronchodilators during non-invasive ventilation.

INTRODUCTION

BRONCHODILATORS ARE FREQUENTLY USED in ICU patients receiving invasive mechanical ventilation (IMV) and commonly delivered through the inhalation route.⁽¹⁾ The main advantage of in-

halation route is to enhance the therapeutic/toxicity index of the agent. However, a drawback is lack/variability in efficiency. Because the clinical/physiological efficiency largely depends on amount of drug available at its site of action, namely β_2 or muscarinic receptors in the smooth

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muscular cells in the wall of the bronchial tree, and given that there are numerous causes of drug losses in intubated patients, it has long been thought that inhaled bronchodilators are ineffective or exhibited markedly variable clinical effects. Bench studies have shown that it should be not the case if the drug inhaled mass and deposited mass are properly measured^(2,3) and ventilator-related key factors involved in the drug delivery carefully controlled.^(2,4) A substantial amount of nebulized drug may actually reach its target in patients,⁽⁴⁾ and guidelines have been developed to optimize the administration of agent during IMV.^(3,5) With increasing use of noninvasive ventilation (NIV) in ICU,⁽⁶⁾ the issue of the efficiency of inhaled bronchodilators in this setting has also to be examined. This review will go over pharmacological concepts of the aerosol administration, devices used to generate aerosol, ventilator-related factors for an optimal delivery of drug inhaled during IMV and NIV, indications and effects of inhaled bronchodilators in ICU patients during mechanical ventilation.

Pharmacological concepts of aerosolization during mechanical ventilation

During mechanical ventilation, the aerosolized drug travels the inspiratory line and the endotracheal tube then deposits in the lungs, while some amounts flows out with the next expiration (Fig. 1). By applying the mass balance law, it comes that the amount of drug inhaled minus the amount of drug exhaled is equal to the amount of drug deposited in the lungs. The setup shown in Figure 1^(2,4,7-9) depicts these components relative to the initial amount of active drug filled in the nebulizer (nebulizer charge). The inhaled fraction is the ratio of the amount of drug captured by the filter A (Fig. 1) to the nebulizer charge. It reflects the amount of drug available for inhalation by the patient because it takes into account the amount of drug lost into the nebulizer, the ventilator circuit and the endotracheal tube. But the drug can also be directly exhaled without being inhaled or exhaled from the lungs after inhalation, and this amount is captured on the filter B (Fig. 1). O'Riordan et al.⁽⁴⁾ combined *in vitro* (Fig. 1) and *in vivo* experiments in seven mechanically ventilated patients, computed the exhaled fraction and found that: (1) the inhaled fraction averaged 31%, and (2) the lung deposition averaged 15%

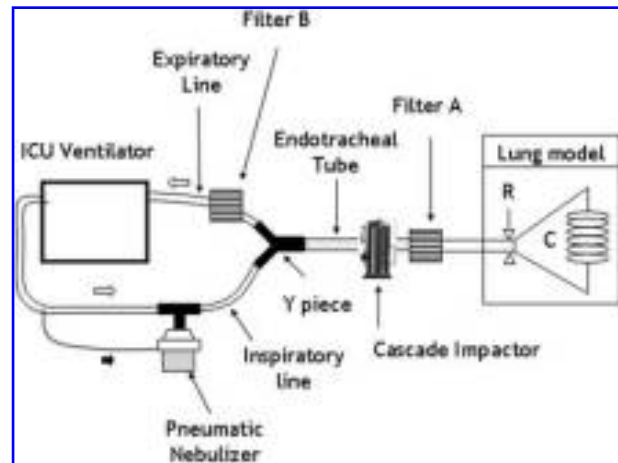


FIG. 1. Schematic drawing of the experimental setup to measure the pharmacological determinants of aerosol deposition and to test the effects of various ventilator-related factors on the drug lung deposition applied to invasive mechanical ventilation. The pneumatic nebulizer is filled by the active drug and fed by the gas from the ICU ventilator at the recommended specific flow (usually 6–8 L/min). The nebulizer is activated during the inspiratory phase (black-filled arrow), the tidal volume being kept constant. The gas reaches filter A where the inhaled mass of the drug is determined. During inspiration some amount of nebulizer charge can be exhaled without being inhaled, and is captured in filter B. In separate experiments, a cascade impactor can be inserted to measure the particle size distribution of the aerosol. The resistance (R) and/or compliance (C) of the lung model can be changed to mimick various clinical scenarii.

of the nebulizer charge and 53% of the inhaled fraction.⁽⁴⁾

Furthermore, by accommodating a cascade impactor in the setup (Fig. 1) during a separate experiment, the mass median aerodynamic diameter (MMAD) can be determined. Particles with MMAD > 5- μm impact the endotracheal tube and the ventilatory circuit during IMV and the pharynx during NIV. Particles with MMAD between 1 and 5 μm mainly deposit in the airways by sedimentation while particles with MMAD between 1 and 3 μm have the potential to reach the alveoli by diffusion.

Devices to generate aerosols during mechanical ventilation

In patients receiving mechanical ventilation inhaled bronchodilators can be administered by nebulizer or pressurized metered-dose inhaler (MDI) devices. A nebulizer device is characterized by a function curve that relates the cumulative output of the drug against time. The nebu-

lizer function curve has an initial slope and a plateau. The time interval to the plateau is the time during which the inhaled mass increases. Once the plateau is reached the amount of inhaled drug no longer increases and, hence, there is no advantage to continue nebulization further. In clinical practice there is a good correlation between plateau onset and sputtering. Depending on the function curve of the nebulizer, both treatment time and amount of inhaled drug may vary between devices.⁽²⁾ The nebulizer fill volume can also influence inhaled mass: the higher the volume fill the greater the inhaled mass for a given nebulizer.⁽¹⁰⁾ The performance of jet or pneumatic nebulizers depends on the powering flow of the gas, which is usually between 6–8 L/min (Fig. 2). Ultrasonic nebulizers can also be used during mechanical ventilation.⁽¹¹⁾ Contrary to pneumatic nebulizers, their performance is independent on the ventilatory settings (Table 1). Devices that utilize a vibrating mesh or plate may be interesting because they are highly efficient to deliver aerosol.⁽¹²⁾

In ambulatory spontaneously breathing patients, MDIs require training to ensure coordination for optimal delivery. However, up to 70% of these patients fail to use MDIs properly.⁽³⁾ For ICU patients receiving mechanical ventilation, it is caregivers' responsibility to optimize MDI administration. Of notice, MDI canister has to be shaken vigorously, and must be connected to an inhalation chamber with the drug delivery port of the canister placed bottom up (Fig. 2). The use of chamber with a MDI increases the drug depo-

sition⁽¹³⁾ with differences among the spacers.^(14–16) The MDI actuation should be synchronized with the inspiratory phase of the ventilator to increase the delivery.⁽¹⁷⁾ Performing an end-inspiratory pause after actuation has been recommended.⁽¹⁾ Compared to chlorofluorocarbon, gas propellant hydrofluoroalkane protects environment better,⁽¹⁸⁾ and MDIs powered by the latter are as efficient as those propelled by the former.

Ventilator-related factors of inhaled drugs deposition during mechanical ventilation

Comprehensive *in vitro* studies have investigated the role of ventilator-related factors to the lung deposition during mechanical ventilation (Table 1). Ventilatory settings, location of the device in the circuit, density, and humidity of the gas powering the device, the endotracheal tube, are the most important ones.

Among the ventilatory settings, low inspiratory flow, high tidal volume, low respiratory frequency, and long duty cycle applied during the inhalation have been shown to increase lung deposition with both nebulizer and MDI. The location of nebulizer in the ventilatory circuit influences deposition,^(10,19) the manifold location being more efficient than Y piece placement (Table 1). This is also true using MDI with a chamber.⁽²⁰⁾ During NIV, the optimal position of the nebulizer is between the leak port and the patient connection to maximize the delivery of nebulized albuterol.⁽²¹⁾

The modern ICU ventilators can directly power the nebulizer, making the nebulization synchro-

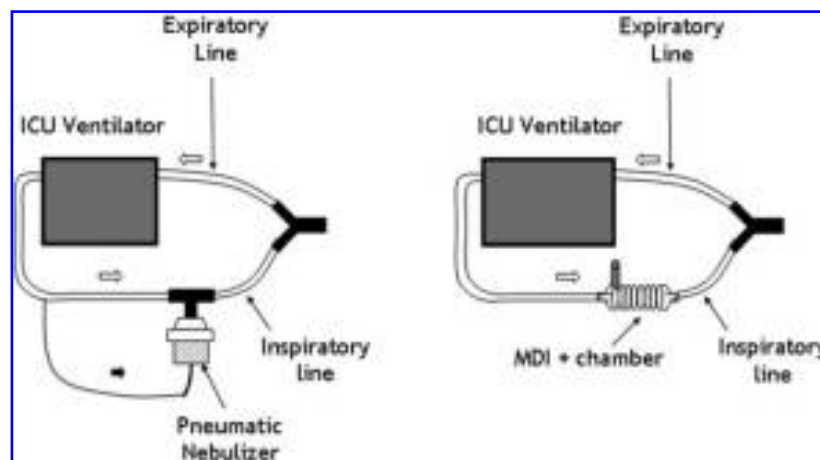


FIG. 2. Proper installation of pneumatic nebulizer (left panel) and pressurized metered-dose inhaler (MDI) (right panel) in the ventilatory circuit. Both devices should be located 20–30 cm upstream from the Y piece. The pneumatic nebulizer should be powered with optimal gas flow. The MDI-canister should be actuated using a chamber.

TABLE 1. VENTILATOR-RELATED FACTORS OF LUNG DEPOSITION AFTER DRUG INHALATION: *IN VITRO* STUDIES

<i>Factors tested</i>	<i>Factors increasing the deposition</i>	
	<i>Pneumatic nebulizer</i>	<i>Metered-dose inhaler</i>
Ventilatory settings		
Inspiratory flow	Low inspiratory flow ^(2,10)	
Tidal volume	High tidal volume ⁽²⁾	High tidal volume ⁽²⁴⁾
Respiratory frequency	Low respiratory frequency ^(2,10)	
Duty cycle	High duty cycle i.e., long inspiratory time ^(2,10)	High duty cycle, i.e., long inspiratory time ⁽²⁴⁾
Inspiratory flow pattern	No difference between constant and decelerating ⁽⁶¹⁾	Sinusoidal and decelerating versus constant ⁽²⁴⁾ No difference between constant and decelerating ⁽⁶¹⁾
Ventilator mode	Pressure controlled versus volume controlled ⁽⁶¹⁾	CPAP relative to CMV, AC, PS for same V_T of 800 mL ⁽²⁴⁾ No difference between pressure and volume controlled ⁽⁶¹⁾
Trigger		No difference between pressure and flow triggering systems ⁽²⁴⁾
Position of the device in the circuit	Manifold relative to the Y piece ^(10,19)	
Driving gas		
Humidity	Dry air increases the deposition relative to humidified air ⁽²⁾	Dry air increases the deposition relative to humidified air ⁽²⁴⁾
Density	Deposition increased with helium ⁽²²⁾ Inhaled mass decreased with helium ⁽²³⁾	Deposition increased with helium ⁽²²⁾ Inhaled mass decreased with helium ⁽²³⁾
Noninvasive mechanical ventilation	Nebulizer between leak port and patient adaptor, respiratory rate 20/min, increasing inspiratory pressure and decreasing expiratory pressure ⁽⁵⁸⁾	

CPAP, continuous positive airway pressure; CMV, controlled mechanical ventilation; AC, assisted controlled mechanical ventilation; PS, pressure support; V_T , tidal volume.

nized with the inspiration and, hence, enhancing its efficiency by as much as four times more than a continuous administration.⁽⁸⁾ The flow diverted from the ventilator to the nebulizer is automatically compensated to maintain tidal volume and minute-ventilation constant. Use of helium-oxygen mixture may be attractive to increase the inhaled mass by reducing impaction in ventilator circuit and promoting a more peripheral deposition. *In vitro*, with MDI, albuterol deposition increased by 50% with 80% helium-20% oxygen compared to oxygen feeding the ventilator.⁽²²⁾ However, the performance of the nebulizer was impaired with heliox compared to oxygen at same flow.⁽²²⁾ Finally, the maximal drug deposition was obtained by powering the nebulizer with oxygen and feeding the ventilator with heliox.⁽²²⁾ This situation combines the maximal energy supply to the nebulizer and the facilitation of drug transport to the airways. However, this result

does not mean that the inhaled mass of the drug is increased with helium. The humidity of air has a major impact on lung deposition during mechanical ventilation. Lung deposition may be reduced by as much as 40% with wet air compared to dry air with either nebulizer^(7,8,10) or MDI.⁽²⁴⁾ Taken together, the above data provide the ICU physician with recommendations to optimally deliver inhaled bronchodilators during mechanical ventilation (Table 2).

Endotracheal tube has long been viewed as a significant barrier to the deposition of inhaled medications.⁽²⁵⁾ *In vitro*, the delivery to filter decreased with the reduction of the inner diameter of the endotracheal tube.⁽¹⁷⁾ *In vivo*, however, the endotracheal tube was not a significant barrier to the deposition because it was found that only 2.6% and 7% of the nebulizer charge deposited in the endotracheal tube during inspiration and expiration, respectively.⁽⁴⁾

TABLE 2. THE 10 STEPS TO OPTIMIZE AND SECURE THE AEROSOL DELIVERY WITH MDI OR NEBULIZER IN PATIENTS RECEIVING INVASIVE MECHANICAL VENTILATION IN VOLUME-CONTROLLED MODE

<i>Procedure</i>	<i>Metered-dose inhaler</i>	<i>Nebulizer</i>
Choose the device	MDI plus a cylinder chamber	Small volume nebulizer
Locate the device	In the inspiratory line between 10 to 30 cm from the Y piece	
Minimize humidity of the air	Bottom-up in the chamber	Horizontal
Clear the airways		Stop the heater-humidifier before and during inhalation
Protect exhalation valve of the ventilator		Suction endotracheal tube and proximal airways
Adjust ventilator settings		Adapt a low resistance filter on the expiratory line before the exhalation valve
Proceed inhalation	<ul style="list-style-type: none"> a. V_T 500 mL: make sure that plateau pressure if measurable ≤ 32 cm H_2O b. Duty cycle ≥ 0.30 and/or inspiratory flow 30–50 L/min: make sure that intrinsic PEEP does not rise c. No change in applied PEEP and F_{iO_2} 	<ul style="list-style-type: none"> a. Fill the nebulizer with optimal volume. If unknown fill with 4–6 mL. b. Select optimal flow to power the nebulizer. If unknown, choose 6–8 L/min. c. Adjust minute ventilation if required to keep V_T constant. d. Set the optimal duration of nebulization. If unknown, choose 30 min.
Observe inhalation	Observe emitted aerosol cloud for adequate aerosol generation	Observe nebulizer volume for adequate aerosol generation until sputtering
Monitor patient	<ul style="list-style-type: none"> a. Heart rate, SpO_2, blood pressure 	<ul style="list-style-type: none"> a. Heart rate, SpO_2, blood pressure b. Patient–ventilator synchronization
Return to baseline after inhalation		<ul style="list-style-type: none"> a. Disconnect MDI plus chamber or nebulizer b. Reset previous ventilatory settings c. Heater-humidifier or heat and moisture exchanger ON

Adapted from refs 1, 2, and 10.

MDI, metered-dose inhaler; V_T , tidal volume, PEEP, positive end-expiratory pressure; SpO_2 , transcutaneous oxygen saturation.

Indications of inhaled bronchodilators in mechanically ventilated ICU patients

The medications usually employed for inhalation therapy in France are provided in Table 3. Inhaled bronchodilator therapy has been graded as level B, that is, of probable value, in patients receiving mechanical ventilation and exhibiting bronchospasm or asthma.⁽²⁶⁾ Wheezing, intrinsic PEEP, elevated airway resistance, difficult to wean, ventilator dependence are also indications

for using inhaled bronchodilators in the ICU setting. The studies supporting this level of recommendation are essentially physiologic and short term. No controlled study to date in asthma or chronic obstructive pulmonary disease (COPD) evaluated the impact of inhaled bronchodilators on clinical outcomes as duration of mechanical ventilation or weaning process. In a single ICU, it has recently been observed that: (1) one-third of patients did receive inhaled bronchodilating agents for unclear reason, (2) mechanical ventila-

TABLE 3. BRONCHODILATOR AGENTS USED VIA INHALATION ROUTE DURING MECHANICAL VENTILATION IN FRANCE

<i>Molecule</i>	<i>MDI</i>				<i>Nebulization</i>	
	<i>Dose per puff</i>	<i>Nominal dose</i>	<i>Frequency</i>	<i>Dose per vial</i>	<i>Nominal dose</i>	<i>Frequency</i>
β -adrenergic Albuterol-Salbutamol sulfate (Ventoline [®])	100 μ g	1-2 puffs	Every 4-6 h ^a	1.25-2.5-5 mg/2.5 mL 5 mg/mL	1-2 vials 1-2 mL	Every 4-6 h ^a
Terbutaline sulfate (Bricanyl [®])	500 μ g	1-2 puffs	Every 4-6 h ^a	5 mg/2 mL	1-2 vials	Every 4-6 h ^a
Anticholinergic Ipratropium Bromide (Atrovent [®])	20 μ g	1-2 puffs	Every 4-6 h	0.50 mg/1 mL 0.50 mg/2 mL	1-2 vials	Every 4-6 h ^a

^aFor adults. Higher doses, that is, more frequent administrations, may be required in patients experiencing severe acute bronchospasm.

TABLE 4. EFFECTS OF INHALED BRONCHODILATORS ON RESPIRATORY MECHANICS IN PATIENTS RECEIVING INVASIVE MECHANICAL VENTILATION IN ICU: IN VIVO STUDIES

<i>Studies</i>	<i>Patients</i>	<i>Molecule</i>	<i>Dose/device</i>	<i>Effects</i>
Gay ⁽⁶²⁾	18 AO	albuterol	270 μ g MDI vs. 2.5 mg NEB	↑ Expiratory iso-flow 0.1 L/sec with MDI or NEB Rrs ↓ 16% PEEPi ↓ 28% vs. Rrs ↓ 9% PEEPi ↓ 21% Rrs ↓ 12% PEEPi → with IP alone Rrs ↓ 16% PEEPi ↓ 24% with IP-fenoterol Raw ↓ 16%, PEEPi ↓ 15% Rrs, Raw Δ Rrs ↓ 10%, 18%, 6% PEEPi ↓ 17% with MDI Rrs, Raw, Δ Rrs ↓ 16%, 17%, 16% PEEPi ↓ 14% with NEB Rrs ↓ 14% after 400 μ g MDI, ↓ 18% after 1000 μ g MDI ↓ 14% after 2.5 mg NEB Maximal ↓ Rrs 37%, Raw 43% PEEPi 56% ↓ Pres 24% No effect of MDI vs ↓ Pres 10% NEB
Fernandez ⁽⁶³⁾	20 COPD	IP vs. albuterol	40 μ g MDI vs. 200 μ g MDI	
Fernandez ⁽⁶⁴⁾	12 COPD	IP alone	40 μ g MDI vs. 40-100 μ g MDI	
Dhand ⁽³⁸⁾	7 COPD	vs. IP-fenoterol	900 μ g MDI	Maximal ↓ Rrs 5.6-40.4% and Raw 4.6-43% ↓ Rrs 17% and Raw
Guérin ⁽⁶⁵⁾	18 COPD	albuterol	80-200 μ g MDI vs. 500-1.25 mg NEB	
Duarte ⁽³²⁾	13 COPD	IP-fenoterol	400 μ g or 1000 μ g MDI vs. 2.5 mg NEB	
Bernasconi ⁽³³⁾	7 COPD	albuterol	400, 800, 1200 μ g NEB	
Manthous ⁽³⁷⁾	10	fenoterol	450, 900, 1350 μ g MDI	
Manthous ⁽³⁶⁾	10	albuterol	900, 1800, 2700, 3600 mg MDI vs. 2.5, 5.0, 7.5 mg NEB	
Dhand ⁽³⁵⁾	12 COPD	albuterol	360, 720, 1440 μ g MDI	
	7 COPD	albuterol	360 μ g MDI	

AO, airway obstruction; MDI, pressurized metered-dose inhaler; NEB, nebulizer; Rrs, total resistance of the respiratory system; Raw, airway resistance; Pres, resistive pressure of the respiratory system; IP, ipratropium bromide.

tion duration was longer in patients who were treated with inhaled bronchodilators than in those who were not; and (3) related cost was greater in the former.⁽²⁷⁾

Promising findings have been obtained in patients with the acute respiratory distress syndrome (ARDS) in whom intravenous albuterol was able to reduce extravascular lung water and plateau pressure compared to placebo.⁽²⁸⁾ Because nebulization can achieve relevant concentrations of albuterol in the edema fluid of patients with ARDS,⁽²⁹⁾ the efficacy of this route to increase the alveolar clearance of lung edema should be assessed in this setting.

Effects of inhaled bronchodilators in mechanically ventilated ICU patients

Physiologic effects. The primary objective of bronchodilator treatment in intubated and mechanically ventilated COPD patients is to reduce pulmonary dynamic hyperinflation and resistance of the respiratory system to reduce the work of breathing.⁽³⁰⁾ Respiratory mechanics was essentially assessed from the interrupter technique during constant-flow inflation.⁽³¹⁾ This technique is very popular in the ICUs because it is easy and quick to perform at the bedside and allows partitioning of total inspiratory resistance into its airway (R_{aw}) and tissue components. It requires, however, fully relaxation of the patient during the manoeuvre. A reduction of respiratory system resistance, mostly stemming from a decline in R_{aw} , and of intrinsic PEEP, has consistently been documented after administration of inhaled bronchodilators in intubated COPD patients by roughly 15% on average (Table 4).

Duration of effects. The beneficial effects of albuterol inhalation on respiratory mechanics were no longer observed after 240 min in stable mechanically ventilated COPD patients, suggesting that this drug may be administered every 4 h.⁽³²⁾ However, 120 min after fenoterol inhalation the resistance of the respiratory system did not significantly differ from the baseline.⁽³³⁾ Furthermore, the time course of respiratory mechanics after inhaled albuterol was highly variable among patients, which precludes any fixed standardization of dosage schedule.⁽³⁴⁾ This lack of predictability is an additional argument to thoroughly evaluate the clinical response to the drug.

Dose. Contrasted dose–response effects on respiratory mechanics have been observed with MDI and nebulizer. Dhand et al.⁽³⁵⁾ found that maximal reduction of R_{aw} was obtained after 4 puffs of albuterol administered via an MDI with no further reduction up to 16 puffs. Bernasconi et al.⁽³³⁾ found that nebulized fenoterol resulted in significantly greater reduction of R_{aw} than nebulized saline but no dose–effect relationship with fenoterol. Manthous et al.⁽³⁶⁾ found no dose–response relationship with albuterol administered via an MDI but a 10% decline in resistive pressure while delivering the same molecule at 2.5, 5, and 7.5 mg via a nebulizer. In this study⁽³⁶⁾ the modest reduction of respiratory resistance may be attributed to the case mix because only two patients were COPD. The lack of effect of MDI in this work⁽³⁶⁾ may result from an administration not optimized because the device was attached directly to the endotracheal tube via an elbow without any chamber. In this connection, the same group found, in a further study,⁽³⁷⁾ a significant reduction of respiratory resistance with the same molecule delivered by an MDI located 10 cm to the endotracheal tube.

Increasing the dose of the molecule may also increase the risk for cardiac arrhythmias. Above 4 puffs of albuterol, any further reduction of respiratory resistance was obtained while heart rate significantly increased.⁽³⁵⁾ In a previous study, the same group did not observe any significant change in heart rate with 10 puffs of albuterol via an MDI.⁽³⁸⁾

Administration. It has been shown *in vitro* (Table 1) that it was possible to optimize the delivery of inhaled medication by accommodating the ventilator and its adjuncts. Accordingly, recommendations were provided for patients receiving IMV (Table 2). However, Mouloudi et al.⁽³⁹⁾ demonstrated that some of these ventilator-related factors were no longer significant in the real life. The authors studied the effects on respiratory mechanics of albuterol delivered via an MDI in intubated and mechanically ventilated COPD patients. Although albuterol induced a significant reduction of respiratory resistance, the accommodation of tidal volume (8 vs. 12 mL/kg)⁽³⁹⁾ or inspiratory flow rate (0.6 vs. 1.2 L/s)⁽⁴⁰⁾ or pattern (decelerating versus constant)⁽⁴¹⁾ or end-inspiratory pause (none or 5 sec)⁽⁴²⁾ at the time of inhalation did not influence the reduction of respiratory resistance and intrinsic PEEP. These re-

sults demonstrated that once dosage was adequate (200–600 μg albuterol^(39–42)) and administration optimized (MDI plus spacer), manipulation of the ventilator settings did not produce additional measurable effects on respiratory mechanics.

The application of external PEEP in COPD patients under invasive mechanical ventilation has been largely investigated in the last years.^(43–50) As far as the patient is sedated and receives passive mechanical ventilation the use of external PEEP is not necessary. If it is nevertheless used, its level should be less than 85% of the static intrinsic PEEP to avoid any hemodynamics compromise.⁽⁴⁹⁾ However, there may be a rationale for using low levels of PEEP in passively ventilated COPD patients to reopen small airways closed during the tidal breathing.^(51,52) Furthermore, by maintaining small airways patency, external PEEP may facilitate the distribution and physiological effects of inhaled bronchodilators medication. *In vitro* studies have shown that inhaled mass was not reduced with external PEEP.^(9,53) The interaction between external PEEP and inhaled bronchodilator was recently investigated in two studies on COPD patients who received INV, which gave discrepant results. In 10 COPD patients, Guérin et al.⁽⁵⁴⁾ studied the time course of the effects on respiratory mechanics of nebulized fenoterol either on zero external PEEP (ZEEP) or external PEEP amounting to 85% intrinsic PEEP. They found that after fenoterol administration respiratory mechanics improved with ZEEP but remained unchanged with external PEEP. The authors explained the results by the fact that intrinsic PEEP declined with fenoterol, and once its level became lower than external PEEP dynamic hyperinflation increased as did respiratory resistance. Tzoufi et al.⁽⁵⁵⁾ in 10 COPD patients, measured respiratory mechanics during five conditions: (1) baseline ZEEP, (2) 30 min after nebulization of 5 mg albuterol on ZEEP, (3) 8 h after albuterol inhalation on ZEEP, (4) 30 min after application of PEEP equal to intrinsic PEEP, (5) 30 min after nebulization of 5 mg albuterol on the same level of PEEP as in condition 4. The authors found that PEEP and albuterol had additive beneficial effects on intrinsic PEEP which went from 7 cm H₂O at baseline to 4.8 cm H₂O with albuterol alone, to 3.7 cm H₂O with external PEEP alone and to 2 cm H₂O with both interventions. Furthermore, hemodynamics and gas exchange

were improved with the combination of PEEP and albuterol.

Nebulizer or MDI. Both devices were equally effective to improve respiratory mechanics in most studies (Table 4). Therefore, other arguments than effectiveness should be taken into account to prefer one device to the other. MDI are easier to use. Nebulizers are cumbersome and more costly. Whatever the device, the physician has to be familiar with the one she/he uses routinely and, of notice, with particle size distribution generated and optimal powering flow in the case of a nebulizer.

Noninvasive ventilation

Although NIV is increasingly used in ICUs, the data regarding the effects of bronchodilators in this setting are still scanty. NIV may be a method to increase the deposited mass in adults with acute bronchospasm⁽⁵⁶⁾ or in children with cystic fibrosis.⁽⁵⁷⁾ The mechanisms by which NIV can increase deposited mass are: dry air, larger tidal volume than during unassisted spontaneous breathing, improvement of efficiency of the nebulizer,⁽⁵⁷⁾ combination with external PEEP,⁽⁵⁵⁾ absence of endotracheal tube. *In vitro*, significant increase in inhaled mass was obtained during NIV by locating the nebulizer between the leak port of the single limb circuit and the patient^(58,59) and by using high inspiratory or expiratory pressures.^(58,59) In a randomized controlled study in 18 stable COPD patients, Nava et al.⁽⁶⁰⁾ found that salbutamol delivered via an MDI and a chamber during NIV exhibited a greater bronchodilating effect than placebo, but might be less efficient than during spontaneous breathing.

CONCLUSIONS

The administration of bronchodilators in ICU patients receiving mechanical ventilation is possible and efficient, using either nebulizer or MDI. Based on *in vitro* studies, practical recommendations have been issued to help clinicians in optimization of this therapy. Future studies should assess the effects of inhaled bronchodilators on patient outcome as duration of mechanical ventilation/weaning/ICU stay/cost-effectiveness and determine how to optimize the delivery of

inhaled bronchodilators during NIV in the acute care setting in large-scale trials

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