Review

Bronchodilator delivery with metered-dose inhaler during mechanical ventilation

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Abstract

The delivery of bronchodilators with metered-dose inhaler (MDI) in mechanically ventilated patients has attracted considerable interest in recent years. This is because the use of the MDI has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing and a lower risk of contamination. A spacer device is fundamental in order to demonstrate the efficacy of the bronchodilatory therapy delivered by MDI. Provided that the technique of administration is appropriate, MDIs are as effective as nebulizers, despite a significantly lower dose of bronchodilator given by the MDI.

Keywords: airway resistance, drug, nebulizer, obstructive lung disease, therapy

Introduction

Bronchodilator therapy is commonly used in mechanically ventilated patients [1]. Bronchodilator drugs significantly decrease airway resistance in patients with obstructive lung disease, as well as in patients with acute lung injury [2••,3••,4]. In patients with obstructive lung disease (chronic obstructive pulmonary disease [COPD] or asthma), these drugs are part of the standard therapy and play an important role in patient management [5••,6••]. By reducing the resistance to airflow, dynamic hyperinflation, a cardinal feature of the pathophysiology in these patients, is decreased. This leads to improved synchrony between the patient and ventilator, less risk of barotrauma and cardiovascular compromise, and enhancement of respiratory muscle performance [5••,6••].

In mechanically ventilated patients bronchodilators may be administered either by the systemic route (ie intravenously) or directly to the target site in the endobronchial tree by inhalation [2••,3••,6••]. Similar to the situation with ambulatory patients, the inhaled route is preferable during mechanical ventilation because the drug efficacy is comparable or even greater than that of the intravenous drug, but the side effects are minimized because of the smaller dose and minimal systemic absorption [2••,3••,6••].

Inhaled bronchodilators in mechanically ventilated patients may be delivered either by a nebulizer or by a MDI [2••]. It is generally believed that nebulizers are superior to MDIs during mechanical ventilation. However, the delivery of bronchodilators with MDI in mechanically ventilated

COPD = chronic obstructive pulmonary disease; FRC = function residual capacity; MDI = metered-dose inhaler; PEEPi = intrinsic positive end-expiratory pressure; Pp = plateau pressure; Ptp = transpulmonary pressure; Rint = Rmin = airway resistance; Rmax = total resistance of the respiratory system; Vtrap = trapped gas volume above passive functional residual capacity.

patients has received considerable interest in recent years [2••,3••]. This is because the use of MDI has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing and a lower risk of contamination [7–10]. Particularly, in the present era of limited financial resources, the cost of therapy is an important issue. Indeed, it has been estimated that substitution of nebulizers with MDIs in a 700-bed hospital could potentially reduce the cost of aerosol therapy by US$300 000 a year [8]. Moreover, the use of nebulizers under certain circumstances may lead to patient/ventilator dyssynchrony [11]. Ineffective efforts have been identified in patients ventilated on assisted modes of support whenever the flow rate of continuous in-line nebulizer exceeded the patient's inspiratory flow rate [11]. This may lead to serious episodes of hypoventilation, which may not be detected by the alarm function because the bias flow introduced into the system by the continuous flow is falsely interpreted by the ventilator as representing minute ventilation. Finally, nebulizers may damage the expiratory transducer of some ventilators, rendering the expiratory volume measurement unreliable [12].

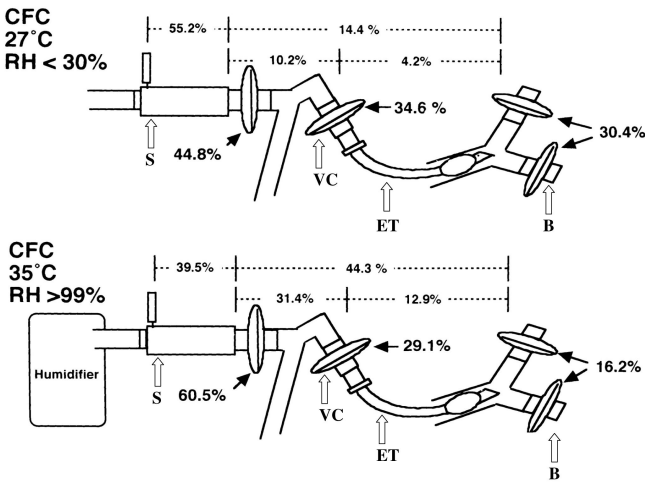
Although bronchodilator delivery with MDI in mechanically ventilated patients has several advantages over nebulizers, the use of MDIs in this group of patients has not gained widespread acceptance among intensive care unit physicians. Indeed, bronchodilator delivery with MDI is considered to be relatively ineffective due to drug deposition in the ventilator circuit and endotracheal tube [13•]. This consideration, however, is not supported by recent scientific data. Provided that a proper technique of administration is used, bronchodilator therapy with MDI is clearly effective [2••,3••]. In this brief review we present data regarding the efficacy of MDI in mechanically ventilated patients, and provide guidelines for proper use of this mode of bronchodilator therapy.

Respiratory tract deposition of bronchodilator delivered by MDI

Several factors may affect respiratory tract deposition of bronchodilator drugs delivered by a MDI during mechanical ventilation. *In vitro* studies [14•,15–22] have shown that aerosol deposition is influenced by the ventilator mode and settings, heat and humidification of inspiratory gas, density of inhaled gas, size of endotracheal tube, and method of connecting the MDI in the ventilator circuit.

Bypassing the humidifier, using a large-bore endotracheal tube and inhalation of less dense gas are associated with increased aerosol deposition. In particular, heat and humidification have a great impact on aerosol deposition; studies [19] have shown that bypassing the humidifier may increase aerosol deposition to target sites by approximately 50% (Fig. 1). Endotracheal tubes with less than 6-mm internal diameter decreases significantly the efficacy

Figure 1



Drug deposition, expressed as a percentage of nominal dose of albuterol from a chlorofluorocarbon formulation (CFC) propelled MDI, in the spacer chamber, the ventilator circuit, the endotracheal tube and on filters at the bronchi under dry (upper panel) and humidified (lower panel) conditions during controlled mechanical ventilation. Under dry conditions 30.4% of the aerosol was deposited at the target sites (bronchi), versus 16.2% in a humidified circuit. RH, relative humidity; S, spacer chamber; VC, ventilator circuit; ET, endotracheal tube; B, filters at the bronchi. From Fink *et al* [19].

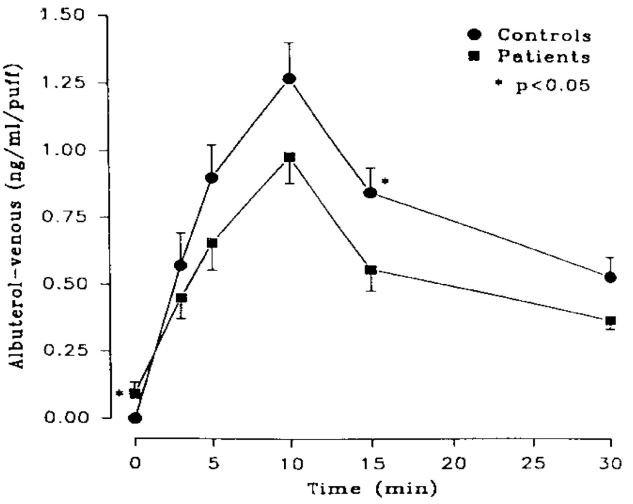
of aerosol delivery, which an important issue when bronchodilator drugs are administered in children [15].

Synchronization of aerosol delivery with the beginning of inspiration, large tidal volume, low inspiratory flow and long duty cycle (T_I/T_{TOT}) are also associated with greater aerosol deposition [14•,19]. Furthermore, active as opposed to passive mechanical ventilation increases considerably the delivery of bronchodilator drugs [14•,23].

Finally, connecting the MDI in the ventilator circuit using a spacer device significantly increases the drug deposition to target sites [20–22]. This is probably among the most important factors. Indeed studies demonstrated that the combination of MDI and spacer device resulted in a four-fold to sixfold greater delivery of bronchodilators compared with MDI actuation into a connector placed directly at the endotracheal tube or into an in-line device without a chamber [20–22]. The aerosol delivery to target sites may approach 30–35% of the nominal dose when a spacer device is used (Fig. 1) [19]. This is much higher than the corresponding values obtained with nebulizers (for review [2••]). Nevertheless, the results of *in vitro* studies should be interpreted with caution because bronchodilatation depends not only on drug dose, but also on several other factors that are mainly related to the patient.

In vivo drug deposition to the lower respiratory tract may be estimated by radionuclide methods and by measuring serum or urine levels of the active drug or its metabolites. Studies using these methods confirmed the *in vitro* findings [22,24,25•]. It is of interest to note that Duarte *et al* [25•] observed that administration of albuterol with MDI combined with a spacer device produces peak serum levels in mechanically ventilated patients that are comparable to those in healthy control individuals, whereas the area under the concentration time curve was lower in ventilated patients than in control individuals (Fig. 2). It follows that bronchodilator delivery with MDI and a spacer in mechanically ventilated patients results in satisfactory drug deposition in the lower respiratory tract, although its duration of action might be somewhat decreased.

Figure 2



Venous serum albuterol, corrected for the number of puffs of albuterol administered, in mechanically ventilated patients (■) and nonintubated control individuals (●). Serum levels were similar in both groups except at baseline and 15 min after drug administration. Note that the groups had similar patterns of systemic absorption, with the peak level occurring at 10 min and a rapid decline in serum levels thereafter. Bars represent standard error. *$P<0.05$ versus controls. From Duarte *et al* [25•].

Assessment of the bronchodilator response

The main outcome variable of bronchodilator therapy is the resistance to airflow [2••,3••]. Measuring the airflow resistance in mechanically ventilated patients is not always an easy task [5••,6••]. In patients with active respiratory efforts in particular, bedside estimation of resistance as well as of respiratory mechanics is rather complicated and imposes unique problems. We briefly review the methods used to assess bronchodilator response in patients ventilated on controlled (ie passive mechanical ventilation) and assisted modes of ventilatory support.

Patients without respiratory efforts (controlled mechanical ventilation)

In these patients the bronchodilator response is usually estimated by measuring inspiratory resistance using the method of rapid airway occlusion at constant flow inflation [26•,27]. Briefly, the airways are occluded at end-inspiration, and there is an immediate drop in airway pressure from a peak to a lower value (P_1), followed by a gradual decay to a plateau pressure (Pp). Airway resistance (Rint or Rmin) is obtained by dividing the difference between peak airway pressure and P_1 by the preceding constant inspiratory flow. By dividing the difference between peak airway pressure and Pp by inspiratory flow, total resistance of the respiratory system (Rmax) is obtained. The difference between Rmax and Rmin represents two phenomena: time-constant inequalities (pendelluft) and viscoelastic behaviour (stress relaxation) [26•,27].

Because reduction in the resistance to airflow decreases the dynamic hyperinflation, the bronchodilator response may also be assessed by measuring indices of dynamic hyperinflation, such as Pp, end-expiratory alveolar pressure (intrinsic positive end-expiratory pressure [PEEPi]) and the trapped gas volume above passive functional residual capacity (FRC; Vtrap) at the end of expiration [5••,6••]. PEEPi is measured by occluding the airways at the end of a tidal expiration and observing the airway pressure [26•,27]. Vtrap is determined by measuring the total exhaled volume during a period of apnoea for a sufficiently long period to visually detect expiratory volume change to cease, thus allowing the patient to reach the passive FRC [28]. This volume represents the volume above passive FRC trapped at end-expiration.

Expiratory resistance may better characterize the bronchodilator response because it greatly influences dynamic hyperinflation [5••,6••]. However, expiratory resistance is difficult to measure in patients with obstructive lung disease, in whom expiratory flow limitation during tidal expiration commonly exists [29]. In this case the driving pressure for flow is not the difference between alveolar and mouth pressure, but between alveolar pressure and total pressure head at the choke point, which is very difficult to measure in humans [30]. Nevertheless, the decrease in expiratory resistance after bronchodilator therapy can be indirectly estimated by measuring expiratory flow at a given elastic recoil pressure (ie Pp) before and after bronchodilator delivery [31]. This technique, however, is cumbersome, time consuming, and necessitates stepwise lung deflation at lung volumes between end-inspiration and passive FRC. Furthermore, the pause time may affect Pp independently of volume [32], making the interpretation of Pp–expiratory flow relationship rather complex. For these reasons, measurement of expiratory resistance is rarely used in order to assess the bronchodilator response.

Patients with respiratory efforts (assisted mechanical ventilation)

In patients ventilated on assisted modes of support, the bronchodilator response cannot easily be assessed. With assist volume, static and dynamic airway pressure may reflect, to a variable extent, respiratory muscle activity, and thus calculation of resistance using the occlusion technique is misleading [5••,6••,33•]. Similarly Vtrap can not be measured in patients with active respiratory efforts. In these patients the response to bronchodilators may be estimated indirectly by clinical examination. Reduction in the number of ineffective efforts and faster response of the ventilator to patient inspiratory efforts may indicate, among other causes, a decrease in dynamic hyperinflation due to a decrease in resistance [5••,6••]. In patients being ventilated on pressure support, the decrease in dynamic hyperinflation and inspiratory resistance may result in higher tidal volume [5••,6••].

Measuring the work of breathing is another index that may by used to assess the bronchodilator response in patients on assisted modes of ventilation [34]. This, however, implies insertion of an oesophageal catheter to measure oesophageal pressure [33•]. This technique is also useful for measuring respiratory mechanics in patients with active respiratory efforts. By recording transpulmonary pressure (Ptp; airway pressure minus oesophageal pressure), flow and volume over a breath, the weighted average of inspiratory and expiratory pulmonary resistance can be estimated as the ratio of change in Ptp over that of flow between two points in the breathing cycle in which lung volume is the same [33•]. Alternatively, inspiratory pulmonary resistance can be measured as the difference between Ptp at mid-inspiration and the corresponding pressure on the Ptp–volume axis (ie relaxation pressure) divided by the inspiratory flow at that point. The Ptp–volume axis is obtained by connecting the points of zero flow on the Ptp–volume curve [33•,35].

In mechanically ventilated patients with active respiratory efforts, PEEPi can be measured as the amount of change in oesophageal pressure preceding the initiation of inspiratory flow [33•]. PEEPi measured with this method is valid provided that expiratory muscles are relaxed. Otherwise, an additional catheter to record gastric pressure simultaneously is needed in order to correct for expiratory muscle activity [33•]. However, detailed description of the methods used to measure respiratory mechanics in patients ventilated on assisted modes is beyond the scope of the present review.

The techniques described above are not practical and are rarely used in every day practice. In the busy and crowded environment of intensive care unit, clinical examination and assessment of the patient–ventilator interaction remains the most widely used method to assess the bronchodilator response in mechanically ventilated patients with active respiratory efforts.

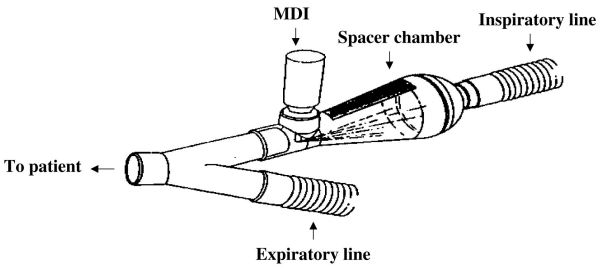
Efficacy of bronchodilators administered with MDI in mechanically ventilated patients

Traditionally, nebulizers have been used for bronchodilator therapy during mechanical ventilation, because bronchodilator delivery with a MDI is considered relatively ineffective. Manthous *et al* [13•] reported no benefit from administration of up to 100 puffs of albuterol (9 mg) with an MDI and elbow adapter in ventilator-supported patients. Other studies, however, using a spacer device instead of elbow adapter [36,37,38••,39•,40•,41••], did not confirm these findings; bronchodilator delivery using an MDI and a spacer device results in significantly decreased airflow resistance. Thus, a spacer device is thought to be fundamental in improving the efficacy of bronchodilator therapy given by MDI. As a rule, in our unit bronchodilator drugs are administered using an MDI and a spacer device. The spacer device we use (Fig. 3) remains in the ventilator circuit, so that disconnection of the ventilator circuit at each bronchodilator treatment is avoided.

In patients with COPD, delivery of bronchodilators with an MDI and a spacer results in approximately 18–25% and 8–15% decreases in Rmin and Rmax, respectively [36,37,38••,39•,40•,41••]. These decreases are comparable to those observed when bronchodilators are delivered with a nebulizer, at a fraction of the drug dose [42]. Although expiratory resistance, the main determinant of dynamic hyperinflation, is usually not measured, indirect evidence suggests an appreciable decrease in expiratory resistance also. Indeed, an approximately 20% reduction in PEEPi has been observed after bronchodilator therapy [39•,40•,41••], indicating a decrease in dynamic hyperinflation as a result of a decline in expiratory resistance.

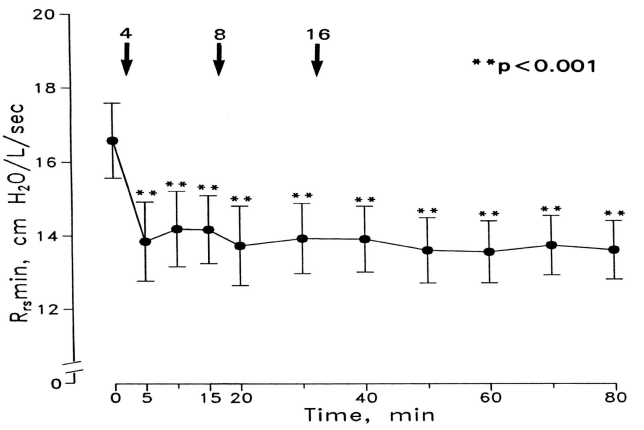
The decrease in total resistance of respiratory system after bronchodilator delivery with an MDI and a spacer is mainly due to a decrease in Rmin decrease (ie airway resistance), whereas the additional resistance due to time-constant inequalities and/or viscoelastic behaviour remains unchanged [37,38••,39•,40•,41••,42]. This indicates that the delivery of bronchodilators with MDI affects the smooth muscle tone of large airways. On the other hand, bronchodilators administered using nebulizers seem to elicit a parenchymal response [42]. Guerin *et al* [42], in a recent study in mechanically ventilated COPD patients, administered a combination of fenoterol–ipratropium bromide either with a nebulizer or with a MDI, and found that total resistance of respiratory system, Vtrap and PEEPi decreased similarly with the two modes of drug administration. With the nebulizer, the reduction in Rmax was due to a decrease in the difference between Rmax and Rmin, whereas with the MDI the decrease was due to Rmin. The authors attributed these results to the higher

Figure 3



Schematic representation of the MDI adapted to the spacer device in the inspiratory limb of the ventilator circuit. Notice that the MDI flume is directed away from the patient. From Mouloudi *et al* [40•].

Figure 4



Airway resistance (R_{rs}min) in mechanically ventilated patients with COPD after four, eight and 16 puffs of albuterol (total dose 28 puffs). The addition of eight and 16 puffs did not cause further bronchodilatation than that observed with four puffs. ** $P < 0.001$ versus baseline. Bars represent standard error. From Dhand *et al* [38••].

alveolar deposition of the total drug mass achieved with the nebulizer, although, as a percentage of the nominal dose, the deposition was greater with the MDI [42].

The optimal dose of bronchodilators delivered with a MDI in mechanically ventilated patients is not clearly established. Manthaus *et al* [13•] found, in patients who had peak pressure–Pp gradient of more than 15 cmH_2O, that five puffs of albuterol (90 μg/puff) decreased resistive pressure significantly. The addition of 10 more puffs reduced the resistive pressure further, but only slightly. Fifteen more puffs did not result in further improvement. Dhand *et al* [38••] showed, in mechanically ventilated patients with COPD, that the decrease in airway resistance with four puffs of albuterol was comparable to that observed with cumulative doses of 28 puffs (Fig. 4). In a recent study [41••] we demonstrated in COPD patients that two puffs of salbutamol resulted in significant bronchodilatation that was comparable to that observed with six puffs.

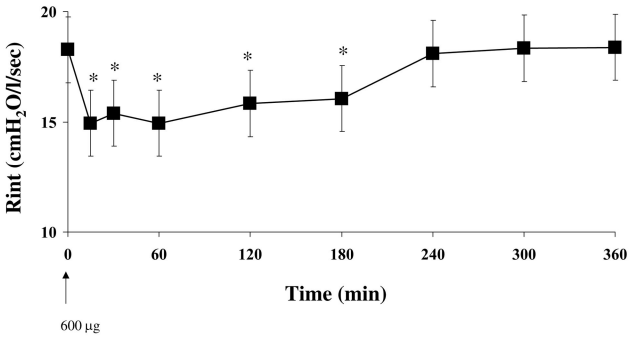
It seems that, in stable mechanically ventilated patients, two to six puffs of short acting β_2-agonist may achieve maximum or near maximum bronchodilatation with no side effects. However, patients with acute bronchospasm (ie status asthmaticus) may require higher doses. Individual titration of the dose so as to achieve the best bronchodilatation with acceptable side effects may be an alternative strategy, rather than using a standard dose [6••]. In our unit four to six puffs of short acting β_2-agonist is delivered initially, and the dose is increased according to the response. The optimal doses of other bronchodilators, such as anticholinergic agents or long-acting β_2-agonists, are not known.

The duration of the bronchodilator response is an important issue, which surprisingly has not been adequately studied. In a recent study [43] we observed, in patients with COPD, that six puffs of salbutamol resulted in significant bronchodilatation lasting approximately 3 h (Fig. 5). Other studies, presented so far in abstract form, concluded that the duration of bronchodilatation in mechanically ventilated patients is decreased compared with that in ambulatory patients. These findings are in accordance with those of Duarte *et al* [25•], who showed that the relative systemic bioavailability of albuterol as measured by serum level was reduced in mechanically ventilated patients. It follows that the dose interval in mechanically ventilated patients might be shorter than that in ambulatory patients. As a rule, in our unit we administer inhaled short-acting bronchodilators every 3–4 h.

The technique of administration of bronchodilators in mechanically ventilated patients using an MDI and a spacer is an important factor thaty determines the efficacy of this therapy. Proper timing of drug delivery, relatively high tidal volumes, low inspiratory flows and application of end-inspiratory pause (breath-hold) are some of the factors that have been suggested to enhance drug delivery to target sites and, thus, bronchodilatation [2••,3••]. However, these suggestions are based, at least as far as the ventilator settings are concerned, on *in vitro* studies.

Recently, in a series of studies [39•,40•,41••], we examined the effects of various ventilator settings on the bronchodilatation induced in mechanically ventilated COPD patients by salbutamol administered using an MDI and a spacer. These studies demonstrated that neither application of 5 s end-inspiratory pause [39•] nor increasing the tidal volume by 4 ml/kg [40•] (strategies that probably enhanced drug delivery [14•,19]) augmented the bronchodilator effect of six puffs of salbutamol. Furthermore, we showed [41••], at constant tidal volume and inspiratory time, that changing the inspiratory flow–time profile from constant (volume controlled) to decelerative flow (pressure controlled) did not have any effect on salbutamol-

Figure 5



Airway resistance (Rint) as a function of time after administration of 600 µg salbutamol with MDI and a spacer device in 10 mechanically ventilated patients with COPD. *$P<0.05$ versus baseline. From Mouloudi *et al* [43].

Table 1

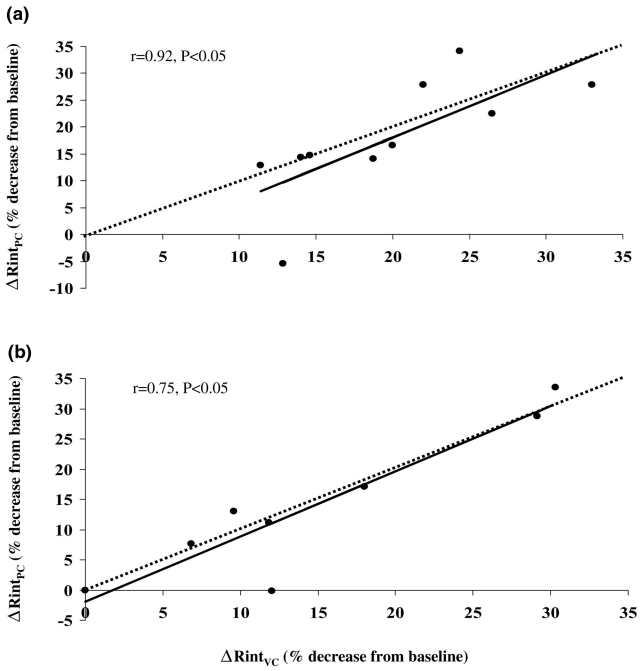
Strategy used in our unit for MDI bronchodilator therapy

Step	Details
1	Place a spacer device in the inspiratory line of the ventilator circuit* (see Fig. 3)
2	Shake the MDI vigorously
3	Adapt the MDI to the spacer device
4	Remove the heat and moisture exchanger† (if used)
5	Do not change the ventilator settings‡
6	Actuate MDI to synchronize with the onset of inspiratory flow
7	Repeat actuation after 20–30 s until the total dose is delivered
8	Start with four to six puffs and observe the response
9	Repeat bronchodilator treatment after 3–4 h§

*The spacer device remains in the circuit so that disconnection and manipulation of the ventilator circuit is minimized. †The effect of the heat–moisture exchanger on the efficiency of bronchodilator therapy has not been studied; if a humidifier is used it should not be bypassed, but the drug dose may need to be increased. ‡If the tidal volume is less that 400 ml, an increased dose may be required; this has not been studied. §A shorter interval may be needed in some patients, particularly those with status asthmaticus.

induced bronchodilation, given by MDI and a spacer [41••]. This was true with both 600 and 200 µg salbutamol (Fig. 6) [41••]. It follows that, in patients with acute exacerbation of COPD, significant bronchodilatation can be achieved both with pressure or volume control, and with doses of salbutamol as low as 200 µg. The similar bronchodilatation observed with both high and low dose of the drug [41••] suggests that the high drug dose used in the other studies [39•,40•] was not responsible for the failure of manipulation of ventilator settings to modify the salbutamol-induced bronchodilatation.

Figure 6



Relationship between the individual mean bronchodilatory response of airway resistance (Rint, percentage decrease from baseline) when **(a)** 200 µg ($n=8$) and **(b)** 600 µg ($n=10$) salbutamol were given with volume control ($Rint_{VC}$) and pressure control ($Rint_{PC}$). The mean bronchodilatory response in each patient was obtained by averaging the Rint response at 15, 30 and 60 min after salbutamol. For clarity of presentation, the mean bronchodilatory response was used instead of data at various time intervals after drug administration. The significant linear relationships did not change by pooling all data. Note that significant bronchodilatation was observed both with 200 and 600 µg salbutamol. Note also that the magnitude of bronchodilatation was not affected by the mode of ventilatory support. The continuous line is the regression line, and the dashed line represents the line of identity. From Mouloudi *et al* [41••].

The findings of the above studies do not support alterations in ventilator settings when bronchodilator drugs are administered in mechanically, passively ventilated patients. For minimizing the importance of manipulation in ventilator settings, the use of an MDI in mechanically ventilated patients is more appealing because it is easier to use. In our unit, the strategy for bronchodilator delivery with an MDI in mechanically ventilated patients is shown in Table 1.

Conclusion

There is evidence in the literature that the delivery of bronchodilators with a MDI and a spacer device in mechanically ventilated patients is effective and results in bronchodilatation that is comparable to that achieved with a nebulizer. MDIs have several advantages over nebulizers, making MDI bronchodilator therapy attractive for use in mechanically ventilated patients.

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