

**Effectiveness of Inhaled Albuterol Delivery Methods in Adult Intubated Patients: An
Integrative Review**

Anthony Heidtbrink, SRNA

Bryan College of Health Sciences School of Nurse Anesthesia

Lincoln, Nebraska

Anthony Heidtbrink is a registered nurse and senior student in Nurse Anesthesia at the Bryan
College of Health Sciences in Lincoln, Nebraska. Email:

anthony.heidtbrink@bryanhealthcollege.edu

ABSTRACT

The purpose of this integrative review is to critically appraise the available literature related to effectiveness of albuterol delivery methods for the intubated patient undergoing general anesthesia and to make recommendations for practice. Methods of albuterol delivery commonly utilized by anesthesia providers, such as attaching a metered dose inhaler to an endotracheal tube adapter, have not been proven to reliably deliver albuterol to target tissues. The use of an in-line chambered spacer in conjunction with a metered dose inhaler improves the anesthetist's ability to reliably deliver albuterol to target tissues and achieve measurable reductions in airway resistance. Additionally, a novel method of albuterol delivery, the endotracheal liquid bolus, shows promise as an effective delivery method, especially when tidal volumes are limited. Anesthetists should utilize an evidence based approach rather than relying on convention or personal anecdotes when deciding how to administer needed medications.

Keywords

Albuterol, Metered Dose Inhaler, Intubated, Anesthesia Circuit

EFFECTIVENESS OF INHALED ALBUTEROL DELIVERY METHODS IN ADULT INTUBATED PATIENTS

INTRODUCTION

Bronchoconstriction and Bronchospasm

Bronchoconstriction and bronchospasm are problems that the anesthesia professional is certain to encounter in routine clinical practice. National spirometric surveillance data reveals that 13.5 % of adults in the United States show evidence of obstructive airway disease.¹ Signs of bronchoconstriction as manifested during general anesthesia with an endotracheal tube in place most commonly include an expiratory wheeze and increased inflation pressures during positive pressure ventilation.² Prolonged expiratory phase, decreased oxygen saturations, change in capnography wave form, and change in delivered tidal volume may also indicate a significant degree of bronchoconstriction.³ While acute severe bronchospasm is decidedly less common than mere bronchoconstriction, severe bronchospasm may manifest during anesthesia and is a life-threatening emergency with potentially devastating consequences.^{2,3} Signs of severe bronchospasm are similar to those of bronchoconstriction but airway constriction may be present to such a degree that no wheeze is auscultated and adequate tidal volumes are difficult or impossible to achieve, the so-called silent chest.²

A number of co-morbidities can predispose patients to airway reactivity and increase the risk of bronchoconstriction and bronchospasm. These conditions include asthma, chronic obstructive pulmonary disease (COPD), recent upper respiratory tract infections, chronic bronchitis, heavy smoking and esophageal reflux disease.^{2,3} Patients with these predisposing conditions often present for anesthesia with suboptimal management of their chronic conditions. Even when these conditions are optimally managed and the patient presents with well controlled

symptoms or normal pulmonary function tests, there is no guarantee of an uncomplicated anesthetic course.³

Many factors related to surgery and anesthesia increase the likelihood of a bronchospastic response. Bronchospasm can occur during induction, maintenance, or emergence from anesthesia.² Patients with pre-existing hyper-reactive airways reliably develop increased airway resistance following tracheal intubation.⁴ Additionally, inadvertent bronchial intubation, laryngoscopy, aspiration, extubation, pulmonary edema, trauma, and cold inspired gasses have all been implicated in precipitating bronchoconstriction or bronchospasm.² Bronchospasm is also a common manifestation of anaphylaxis. Many medications commonly utilized in the perioperative arena are frequently associated with anaphylaxis, including antibiotics, beta blockers, neuromuscular blockers, opioids, local anesthetics, and protamine.³

Treatment of bronchial constriction should be prompt and multimodal. Depending on the severity of the clinical situation, there are many treatment options that the anesthetist may consider. These options include delivering 100% oxygen, deepening the plane of anesthesia, utilizing an inhaled anesthetic agent with bronchodilating properties, ceasing noxious stimulation, verifying endotracheal tube position, manually bag ventilating the patient, and administering intravenous epinephrine. Administration of inhaled aerosols of a beta-2 agonist has for decades been a mainstay of treatment for the bronchospastic patient.⁵ The utilization of beta-2 agonist bronchodilator therapy has been proven effective in multiple patient populations, including those with COPD, asthma, and acute bronchial spasm.⁶ Mechanically ventilated patients who exhibit signs of dynamic hyperinflation, increased peak airway pressures, and wheezing should be treated with bronchodilators.⁷ The aerosol route of delivery is “globally

recognized as the preferred route of delivery for bronchodilators”, and carries the advantages of a direct to target tissue delivery and a rapid onset of action.⁸

Purpose and Clinical Problem

The purpose of this integrative review is to critically appraise the available literature related to effectiveness of albuterol delivery methods for the intubated patient undergoing general anesthesia and to make recommendations for practice. An optimal delivery method is a method that maximizes efficacy, safety, and reliability while also considering the ease of administration and overall cost of the treatment.

The foremost reason why it is important to define an optimal delivery method is that utilizing a method that has been proven effective and reliable improves the potential for a clinical response.⁹ Some investigators believe that practitioners do not consistently apply current evidence when administering inhaled bronchodilators to intubated and mechanically ventilated patients in the intensive care setting.¹⁰ This same inconsistency and lack of application of evidence can be observed in anesthesia practice. Anesthesia providers often utilize an MDI attached to an endotracheal tube adaptor, a method of delivery that has been found to be suboptimal in controlled studies.^{5,11,12}

LITERATURE REVIEW

Search Strategy

A literature search was performed utilizing the databases CINAHL, PubMed, Cochrane Collection, and Google Scholar. Search terms included: mechanical ventilation, albuterol, aerosol therapy, metered dose inhaler, and bronchospasm. Articles identified in the initial search were then mined for related relevant articles. Inclusion criteria were primary and secondary peer reviewed sources published in English which addressed the delivery of aerosolized albuterol in

adult intubated subjects. The vast majority of primary literature available originated in the intensive care setting. Articles not available in English were excluded. Research utilizing pediatric subjects or pediatric models were excluded, except for one article which utilized an in vitro pediatric lung model but provided substantial relevant information that was not influenced by the use of the pediatric lung model.¹³ Articles that studied the delivery of an aerosolized medication other than albuterol were excluded with the exception of one article which provided relevant data that was not influenced by the drug chosen.⁴

Bronchodilator Therapy: Albuterol

Albuterol (also known as salbutamol) was introduced in 1968, and as a relatively selective beta-2 agonist, was the first of its kind. Prior to the introduction of albuterol, mainstays of treatment included less selective agents such as isoproterenol, theophylline, aminophylline, ephedrine and epinephrine.¹⁴ Although these other agents were often delivered intravenously, there are case reports from the 1960's citing the use of inhaled isoproterenol in an anesthesia circuit for the treatment of bronchoconstriction.¹⁵ Increased potency and reduction of off-target side-effects were two of the major benefits of the beta-2 selective agent albuterol compared to its less selective predecessors.¹⁴ During modern mechanical ventilation, albuterol is most commonly delivered either by small volume jet nebulizer or by metered dose inhaler (MDI).⁸

The beta-2 adrenoreceptor is a G protein coupled transmembrane receptor classically identified as being located on airway smooth muscle, although it has also been identified in human lungs on epithelial cells, endothelial cells, type II pneumocytes, and mast cells.¹⁶ The mechanism that connects albuterol activation of beta-2 receptors to the relaxation of airway smooth muscle is a complex, multi-step, incompletely understood process.¹⁷ Activation of the receptor causes the release of cyclic adenosine monophosphate (cAMP). This intracellular

messenger then causes the release of protein kinase A (PKA) which in turn causes smooth muscle relaxation by phosphorylation of muscle regulatory proteins and by modification of intracellular calcium stores.¹⁶ Some evidence also suggests the existence of a cAMP independent pathway in which beta receptors couple directly with calcium-dependent potassium channels, thus contributing to smooth muscle relaxation.¹⁷

When appropriate doses of albuterol are effectively delivered to intubated subjects, the bronchodilatory effects of albuterol are measurable within five to ten minutes of aerosol administration, and peak effects have been observed anywhere from 10 to 60 minutes after administration.^{3,18,19} The magnitude and duration of the effects of albuterol are less predictable and are highly variable from one subject to another. A 10% reduction in airway resistance is often utilized to quantify a significant response, although this measure is arbitrarily defined.^{7,20} Reports of mean percent reduction in airway resistance following albuterol administration vary from 13% to 22% with large intersubject variability.^{19,20} The duration of the bronchodilatory response has been measured as significant through the 90 to 120 minute range, with most subjects returning to pre-treatment baseline after 3 to 4 hours.^{19,20} The duration of the response has not been shown to correlate with either the degree of pre-treatment restrictiveness or the magnitude of the bronchodilator response.²⁰

Potential toxicities from albuterol administration include tachycardia, atrial and ventricular arrhythmias, hyperkalemia, tremulousness and nausea.^{5,6} Prolonged or chronic use of albuterol tends to increase the threshold at which patients experience these toxic effects while largely preserving the bronchodilator response, as bronchial smooth muscle has been found to be particularly resistant to beta-2 agonist desensitization.¹⁶ Extremely high doses of albuterol delivered from an MDI have been cited as a theoretical concern for two reasons. First, some MDI

preparations contain oleic acid, and oleic acid is a surfactant reported to cause necrotizing inflammation and ulceration in rabbit tracheas.²¹ Second, the high doses of propellant that accompany MDI actuation may act as an independent airway irritant.^{18,21}

Measurement of Efficacy

Methods typically used to measure bronchodilator efficacy in the awake, ambulatory, spontaneously ventilating patient such as forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) are not possible to measure in intubated mechanically ventilated patients.²¹ There has been no consensus on the most accurate and reliable way to measure airway resistance or changes in airway resistance in this particular population.

One way around this problem is simply to utilize an in vitro model and measure drug deposition at a particular point in the system that is meant to model deposition in lung tissue. In vitro models are often criticized due to the lack of a standard model, the inability to predict actual anatomic drug deposition site, the inability to account for variation in individual airway geometry, and the inability to account for pulmonary disease.⁶ Although imperfect, this method has value. After accounting for differences in the estimated amount of albuterol that subjects exhale, Fink and colleagues were able to reconcile much of the available in vitro data with the in vivo data, thus reinforcing the validity of the in vitro data.²² Some investigators conducting in vivo studies, rather than measuring changes in airway dynamics, instead measured the amount of albuterol and its metabolite that could be recovered in the urine of subjects given aerosolized albuterol.¹¹

When utilizing in vivo techniques and attempting to measure actual dynamic changes in airflow patterns, the majority of investigators chose to report changes airway resistance (R_{aw}) as the primary measure of treatment efficacy.^{5,6,18,19,23-25} R_{aw} is defined as the difference between

the peak inspiratory pressure and the initial occlusion pressure divided by airflow when using a rapid end inspiratory occlusion technique ($(P_{\text{peak}}-P_{\text{init}})/\text{airflow} = R_{\text{aw}}$). This measurement is thought to most accurately represent the “Ohmic” resistance of the conducting airways while minimizing the effect of variables such as the resistance provided by the endotracheal tube and the thorax and the viscoelastic properties of lung tissue.^{7,18}

Delivery Methods

MDI with L-type Adaptor

Administration of albuterol to intubated and ventilated patients utilizing an MDI attached to the ventilator circuit by way of an elbow or L-type adaptor is one commonly used method of albuterol delivery. However, this method has repeatedly been shown as suspect in its ability to deliver therapeutic doses of medication capable of producing a measurable therapeutic effect. The first to call this method into question were Manthous and colleagues in 1993. They conducted a randomized crossover study of 10 mechanically ventilated intensive care subjects with a variety of lung conditions all experiencing increased R_{aw} . The investigators delivered incrementally increasing doses of albuterol utilizing two methods, an in-line jet nebulizer and an MDI attached to an elbow adaptor. After cumulative doses of 100 puffs (9 mg) of albuterol delivered via MDI and elbow adaptor, they detected no significant improvement in resistive airway pressures and no measurable toxicities from albuterol administered by this method. By contrast, when the same 10 subjects received albuterol via jet nebulizer, statistically significant decreases in resistive airway pressures were noted in all 10 subjects and signs of toxicity (most frequently a heart rate increase of greater than 20 beats per minute) were noted in all 10 subjects after the delivery of cumulative nebulized doses ranging from 2.5 to 7.5 mg. The authors concluded that the use of an MDI through an endotracheal tube adapter is not an effective way to

deliver albuterol to intubated subjects, as it does not result in significant objective physiologic improvement.⁵

Marik and colleagues came to a similar conclusion following a comparison of three different delivery methods: the use of an MDI attached to an elbow adaptor; an MDI with an in-line spacer device; and a small volume in-line nebulizer. This group utilized a six hour urine collection to test for albuterol and its sulfate conjugate to determine the bioavailability of albuterol for each of the three methods. Significant differences were found between all three groups with an average of 39 % of drug administered via MDI with a spacer recovered in the urine, 16% of drug delivered via small volume nebulizer recovered in the urine, and only 9% of drug delivered via MDI attached to an elbow adapter recovered in the urine. Notably, 0 mcg of albuterol or its sulfate conjugate were recovered in four of the 10 subjects in the right angle adapter group. The authors concluded that, while the other two methods could reliably deliver albuterol to the lungs, the bioavailability of albuterol delivered via an MDI attached to a right angle adapter was “poor and unreliable” and recommended that this method “should not be used to deliver bronchodilators in mechanically ventilated patients.”¹¹

Additionally, an in vitro study conducted by Rau and colleagues utilized a model of an adult lung ventilated through an endotracheal tube. The investigators compared drug deposition of albuterol delivered via MDI at an endotracheal tube adapter with albuterol delivered via MDI with a chamber type spacer placed at two different locations proximal to the endotracheal tube. They measured drug deposition of albuterol delivered by MDI through the adapter to be only 7.3 % of the administered dose, approximately four fold less than the drug deposition obtained with the other two methods.¹²

MDI with Chambered Spacer

The three studies noted above called into question the efficacy and reliability of attempting to administer albuterol from an MDI through a chamberless endotracheal tube adaptor. Additionally, the latter two studies suggest that when an MDI is actuated using a spacer or chamber device it can reliably provide substantial drug delivery to the target tissues and cause significant reductions in airway resistance.^{5,11,12} Manthous followed up his 1993 article refuting the use of a chamberless adapter by publishing a 1995 study which demonstrated the in vivo efficacy of albuterol delivered by an MDI, this time actuating the MDI via an in-line chambered spacer device.²³ After these results were published, the method of delivering albuterol by attaching an MDI to an in-line chambered spacer device seems to have become the standard method of albuterol administration used in academic research. Subsequent studies seeking to determine the magnitude and duration of response to albuterol, the optimal dose and frequency of administration, and comparing MDI administration of albuterol to nebulized administration of albuterol all utilized Manthous's method. These subsequent studies have repeatedly demonstrated the measurable efficacy, reliability, and safety of delivering albuterol to intubated subjects utilizing an MDI actuated through a chambered spacer device.^{18-20,22,24,26-29}

The use of an MDI with a chambered spacer device, in addition to its reliability and efficacy in drug delivery, presents several other benefits when considering its use in an anesthesia circuit. This method is relatively inexpensive, easy to administer, is not time consuming, provides reliable control of dosage, and is low risk for contamination.³⁰ A benefit not addressed in the literature to date, as the bulk of the data is from the intensive care setting, is that the use of an MDI with a chambered spacer device does not require any additional gas flow to be added to the circuit, and the method can be administered effectively even while utilizing low fresh gas flow rates.

Nebulizer

Another method commonly utilized to deliver aerosolized albuterol to intubated and mechanically ventilated patients is an in-line nebulizer device.¹⁰ The evidence supporting the efficacy of this method in delivering albuterol to lung tissue and producing statistically significant reductions in resistive airway pressures is substantial.^{5,11,19,24,31} A dose of 2.5 mg is most commonly utilized, although some researchers have used stepwise increasing doses with 2.5 mg increments. Despite this being a much higher dose than what is typically used via the MDI with chambered spacer method, the two delivery methods have not been demonstrated to have significant differences in magnitude or duration of response.^{11,19,24} Reviews of the published data seeking to recommend one method over the other have been equivocal.^{8,32} In terms of efficacy and reliability of delivering albuterol to an intubated and mechanically ventilated patient, the two methods appear quite comparable.

Nebulizers, however, present some practical disadvantages when compared to metered dose inhalers, especially when considering their use in an anesthesia circuit. Compared to an MDI with a chambered spacer device, nebulizers are cited as being more costly, more time consuming to administer, and presenting an increased risk of contamination.⁶ Different models of nebulizers may also require different fill volumes and different flow rates.⁷ Flow requirements for effective nebulization are typically in the range of 6 to 8 liters per minute, and it can take several minutes to nebulize a full dose of medication.¹¹ This presents a unique disadvantage when attempting to place an in-line nebulizer in the inspiratory limb of an anesthesia circuit. The added fresh gas flow is certain to dilute the mixture of air, oxygen and anesthetic gas that is already in the patient circuit. With a high downstream flow rate diluting the concentration of anesthetic gases delivered to the patient, it would be especially challenging to

maintain an adequate depth of anesthesia while simultaneously administering a nebulizer treatment of albuterol.

Endotracheal Liquid Bolus

Finally, one novel method of administering albuterol to the intubated and mechanically ventilated patient, the endotracheal liquid bolus, was described in 2015 by Johnston and colleagues. This group studied the effects of an endotracheal liquid bolus of albuterol in 14 subjects, all intubated, mechanically ventilated and in intensive care for respiratory failure with clinical manifestations of bronchoconstriction. Their method was to place the subject in a lateral position, administer 1.25 mg of preservative free albuterol mixed with 3 mL of sterile saline via a liquid bolus down the endotracheal tube, hand ventilate the subject for 1 minute, then turn the subject right lateral and repeat the procedure. Respiratory parameters were measured at five and 30 minutes following treatment, and significant decreases in resistive airway pressures were noted 30 minutes after treatment. This study is unique in that it is the first randomized controlled trial on human subjects identified in the literature in which albuterol is delivered via endotracheal liquid bolus. The authors cite their inspiration for the study as stemming from experience dealing with children presenting with status asthmaticus in a pediatric emergency room. The authors sought to investigate the potential of a method of delivering bronchodilators directly to lung tissue that could be utilized even when bronchoconstriction was so severe that air could not be moved to all or part of the lungs.³³

DISCUSSION

The importance of implementing an evidence-based practice approach in the contemporary healthcare setting cannot be over-emphasized. The delivery of albuterol to the intubated adult patient undergoing general anesthesia is a clinical scenario for which a

substantial body of evidence exists to guide anesthesia practice. However, this evidence does not appear to be routinely implemented in anesthesia practice, and no publication was identified in the literature making recommendations specific to anesthesia practice.

When considering all of the factors that define an optimal delivery method, the evidence suggests that the use of an MDI actuated through a chambered spacer device is likely the most efficacious for routine use. This method has been shown to be safe, reliable and effective in multiple carefully constructed studies.^{5,11,18,19,23} The typical method of delivery utilizing an MDI attached to an endotracheal tube adapter has not been shown to reliably deliver medication to bronchospastic lung tissue and the use of this method is inconsistent with an evidence-based approach.⁵ The use of an in-line nebulizer is time consuming and uniquely problematic in an anesthesia circuit. The use of an endotracheal liquid bolus seems promising, but more investigation of this new method is warranted.

Strengths and Limitations

The value of the existing literature is limited by several factors. The published studies have small sample sizes ranging from 10 to 30 subjects. The clinical studies are often confounded by a variety of co-morbid conditions present in the study subjects. The vast majority of primary literature available originated in the intensive care setting and not the anesthesia setting. No studies were identified in the existing literature that specifically addressed the delivery of albuterol to intubated subjects undergoing general anesthesia. The data on the subject is somewhat dated, with the bulk of the research published between 1990 and 2000. Gaps in the existing literature include a need for studies that specifically address anesthesia practice and a need to further explore the potentially promising new technique of the endotracheal liquid bolus.³³

Despite these limitations, the body of literature available is adequate to make basic recommendations for practice. The evidence is composed of multiple well-conducted in vivo randomized controlled trials that report consistent results. And there are many in vitro studies that corroborate the findings of the in vivo data.^{9,12,22} Although most of the data does originate in the ICU setting, this data can be reasonably applied to the anesthesia setting. Patient characteristics and gas flow dynamics from the ET tube to the target tissues are likely similar enough to allow this extrapolation.

Recommendations for Practice

Given the existing body of knowledge on the subject, it is possible to make practice recommendations regarding albuterol delivery to the intubated adult patient undergoing general anesthesia. The available data clearly precludes the use of an MDI attached to an endotracheal tube adapter for routine use by the anesthesia professional. Multiple studies have called the efficacy of this method into question, and multiple authors have recommended against its routine use.^{5,11,12,18,30} While it remains possible that the method could achieve some drug delivery and physiologic effect for some patients some of the time, the aim of practice should be to utilize a method that reliably results in consistent measurable drug delivery and a significant physiologic response.

The method of albuterol delivery to intubated patients undergoing general anesthesia that most closely meets the definition of optimal would be the use of an MDI via a chambered spacer device. The literature provides some further specific guidance on how to most appropriately and effectively utilize the method. The chambered spacer device is likely most effective when connected in the inspiratory limb of the ventilator circuit at a distance of 10 to 15 cm from the endotracheal tube.^{9,19,23,26} Actuation of the MDI should be synchronized with

inspiration.^{5,11,19,20,22,30} Actuations should occur at 15 to 30 second intervals.^{18,19,22,29} An initial dose of 4 to 6 actuations (320 mcg to 540 mcg) from the MDI is likely appropriate for most patients, but patients with severe underlying disease and patients experiencing severe bronchospastic symptoms may require increased dosage.^{6,11,18,20,23,29,30} Magnitude and duration of effect is highly variable from patient to patient.²⁰ Dosage and frequency should be titrated to physiologic effect and symptoms of toxicity.^{5,23}

The use of an in-line nebulizer is appealing, in that it does seem to meet the goals of efficacy, safety, and reliability. However, certain requirements of nebulizer use cause this method to fall short in terms of ease of administration. When considering use of a nebulizer as a part of an anesthesia circuit, the most salient problem is the high gas flow required to effectively nebulize the medication instilled in the device.^{11,19} Gas flows of this rate introduced downstream from the anesthesia machine are problematic because they alter the concentrations of oxygen, air, and anesthetic agent delivered from the anesthesia machine .

It is worth considering the rare but potentially life-threatening situation of severe acute bronchospasm. The above methods mostly rely on the movement of an effective tidal volume to deliver medication to its therapeutic target in lung tissue. Certainly there are situations in which the movement of a substantial tidal volume is difficult, if not impossible. In these situations, the use of an endotracheal liquid bolus of albuterol should be considered. The data available on this treatment method is quite limited but suggests that the method has efficacy.³³ The potentially devastating consequences of unabated bronchospasm mandate an aggressive approach to treatment, and the research conducted by Johnston and colleagues illuminates a new option for the treatment of this life-threatening condition.

Conclusion

There is a substantial body of evidence to guide anesthesia practice regarding the optimal method of albuterol delivery for the intubated adult patient, but no previous publication was identified making such recommendations. Use of an MDI actuated through an in-line chambered spacer should be the anesthetist's first choice when administering albuterol, provided adequate ventilation is achievable. In the absence of adequate ventilation, the use of an endotracheal liquid bolus of preservative free albuterol may be an emergency alternative, although further study is need to fully ascertain the safety and efficacy of this method.

References

1. Ford E, Mannino D, Wheaton A, Giles W, Presley-Cantrell L, Croft J. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. *Chest*. 2013;143(5):1395-1406.
2. Westhorpe R, Ludbrook G, Helps S. Crisis management during anaesthesia: bronchospasm. *Qual Saf Health Care*. 2005;14(3):7.
3. Woods B, Sladen R. Perioperative considerations for the patient with asthma and bronchospasm. *Br J Anaesth*. 2009;103(1):57-65.
4. Wu R, Wu K, Tan P, et al. Effects of fenoterol and ipratropium on respiratory resistance of asthmatics after tracheal intubation. *Br J Anaesth*. 2000;84(3):358-362.
5. Manthous C, Hall J, Schmidt G, Wood L. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. *Am Rev Respir Dis*. 1993;148(6 Pt 1):1567-1570.
6. Dhand R, Tobin M. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med*. 1997;156(1):3-10.
7. Duarte A. Inhaled bronchodilator administration during mechanical ventilation. *Respir Care*. 2004;49(6):623-634.
8. Holland A. Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units. *Cochrane Database Syst Rev*. 2013;(6).
9. Boukhattala N, Porée T, Diot P, Vecellio L. In Vitro Performance of Spacers for Aerosol Delivery during Adult Mechanical Ventilation. *J Aerosol Med Pulm Drug Deliv*. 2015;28(2):130-136.

10. Ehrmann S, Roche-Campo F, Sferrazza Papa G, Isabey D, Brochard L, Apiou-Sbirlea G. Aerosol therapy during mechanical ventilation: an international survey. *Intensive Care Med.* 2013;39(6):1048-1056.14. Bryan, J. Ventolin remains a breath of fresh air for asthma sufferers after 40 years. *Pharm J.* 2007;279:404-405.
11. Marik P, Hogan J, Krikorian J. A comparison of bronchodilator therapy delivered by nebulization and metered-dose inhaler in mechanically ventilated patients. *Chest.* 1999;115(6):1653-1657.
12. Rau J, Harwood R, Groff J. Evaluation of a reservoir device for metered-dose bronchodilator delivery to intubated adults. an in vitro study. *Chest.* 1992;102(3):924-930.
13. Lange C, Finlay W. Overcoming the adverse effect of humidity in aerosol delivery via pressurized metered-dose inhalers during mechanical ventilation. *Am J Respir Crit Care Med.* 2000;161(5):1614-1618.
14. Bryan, J. Ventolin remains a breath of fresh air for asthma sufferers after 40 years. *Pharm J.* 2007;279:404-405.
15. Fresoli R, Smith R, Young J, Gottshall S. Use of aerosol isoproterenol in an anesthesia circuit. *Anesth Analg.* 1968;47(2):127-132.
16. Johnson M. Beta2-adrenoceptors: mechanisms of action of beta2-agonists. *Paediatr Respir Rev.* 2001;2(1):57-62.
17. Torphy T. Beta-adrenoceptors, cAMP and airway smooth muscle relaxation: challenges to the dogma. *Trends Pharmacol Sci.* 1994;15(10):370-374.
18. Dhand R, Duarte A, Tobin M, et al. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. *Am J Respir Crit Care Med.* 1996;154(2 Pt 1):388-393.

19. Duarte A, Momii K, Bidani A. Bronchodilator therapy with metered-dose inhaler and spacer versus nebulizer in mechanically ventilated patients: comparison of magnitude and duration of response. *Respir Care*. 2000;45(7):817-823.
20. Mouloudi E, Maliotakis C, Kondili E, Kafetzakis A, Georgopoulos D. Duration of salbutamol-induced bronchodilation delivered by metered-dose inhaler in mechanically ventilated COPD patients. *Monaldi Arch Chest Dis*. 2001;56(3):189-194.
21. Dhand R, Tobin M. Bronchodilator delivery with metered-dose inhalers in mechanically-ventilated patients. *Eur Respir J*. 1996;9(3):585-595.
22. Fink J, Dhand R, Grychowski J, Fahey P, Tobin M. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. *Am J Respir Crit Care Med*. 1999;159(1):63-68.
23. Manthous C, Chatila W, Schmidt G, Hall J. Treatment of bronchospasm by metered-dose inhaler albuterol in mechanically ventilated patients. *Chest*. 1995;107(1):210-213.
24. Gay P, Patel H, Nelson S, Gilles B, Hubmayr R. Metered dose inhalers for bronchodilator delivery in intubated, mechanically ventilated patients. *Chest*. 1991;99(1):66-71.
25. Fernandez A, Lazaro A, Garcia A, Aragon C, Cerda E. Bronchodilators in patients with chronic obstructive pulmonary disease on mechanical ventilation. Utilization of metered-dose inhalers. *Am Rev Respir Dis*. 1990;141(1):164-168.
26. Ari A, Areabi H, Fink J. Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. *Respir Care*. 2010;55(7):837-844.

27. Fink J, Dhand R, Duarte A, Jenne J, Tobin M. Aerosol delivery from a metered-dose inhaler during mechanical ventilation. An in vitro model. *Am J Respir Crit Care Med.* 1996;154(2 Pt 1):382-387.
28. Mouloudi E, Prinianakis G, Kondili E, Georgopoulos D. Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of flow pattern. *Eur Respir J.* 2000;16(2):263-268.
29. Waugh J, Jones D, Aranson R, Honig E. Bronchodilator response with use of OptiVent versus Aerosol Cloud Enhancer metered-dose inhaler spacers in patients receiving ventilatory assistance. *Heart Lung.* 1998;27(6):418-423.
30. Georgopoulos D, Mouloudi E, Kondili E, Klimathianaki M. Bronchodilator delivery with metered-dose inhaler during mechanical ventilation. *Crit Care.* 2000;4(4):227-234.
31. Miller D, Amin M, Palmer L, Shah A, Smaldone G. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med.* 2003;168(10):1205-1209.
32. Dolovich M, Ahrens R, Guyatt G, et al. Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines. *Chest.* 2005;127(1):335-371.
33. Johnston D, Gilmore T, Gosselin K. A comparison of metered-dose inhaled albuterol versus endotracheal liquid bolus albuterol for the treatment of bronchoconstriction. *Respir Care.* 2015;60(5):627-635.