

New Technology Offers New Opportunities: Continuous Bronchodilator Therapy
During Mechanical Ventilation

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Introduction

Patients with severe exacerbations of asthma, refractory to standard dose and frequency of inhaled bronchodilators may benefit from continuous bronchodilator therapy (CBT). CBT is commonly described in the literature for treatment of non-intubated patients little has been written about appropriate techniques for CBT during mechanical ventilation. Historically, lower respiratory tract deposition with standard nebulizers is diminished in mechanically-ventilated patients compared to ambulatory patients. Appropriate selection of techniques and devices can result in deposition and efficacy during mechanical ventilation that equals or exceeds delivery of aerosols in nonintubated spontaneously breathing patients. Multiple factors -- including the type of aerosol generating device, particle size, placement in the ventilator circuit, circuit humidity, flow rates and duty cycle -- influence the efficacy of aerosol delivery and deposition in mechanically-ventilated patients. Use of CBT in spontaneously breathing patients should serve as a basis for similar application during mechanical ventilation.

The Need for Bronchodilator Resuscitation

Patients often arrive at the Emergency Department with severe exacerbation of asthma or acute bronchospasm. Many of these patients have been taking their beta agonist and failed to respond to standard doses prior to presenting in the ED or clinic. A common response is to order another nebulizer treatment with standard dose of bronchodilator, and if the patient continues not respond, to ordering treatments at a high frequency until the patient responds. This strategy requires several hours of delay in giving the patient relief, and hours of additional staff time treating the patient. (1)

Role of CBT

Several alternative strategies for bronchodilator resuscitation have been advocated including high dose MDI with holding chamber, administration of undiluted bronchodilators and high dose continuous nebulization. As we speak of high dose bronchodilator administration, it is important to remember that bronchodilators *relieve* symptoms such as severe airway obstruction, with the goal to provide the patient relief of their respiratory distress, with the greatest improvement in airflow in the shortest period of time and a minimum of toxic side effects, often while waiting for systemic anti-inflammatory agents to affect the underlying pathology. In the absence of symptom relief, the more severe patients become exhausted and require ventilatory support. This also

exacerbates the challenges of aerosol delivery in that standard jet nebulizers are less effective during mechanical ventilation. Best methods for providing both intermittent and continuous bronchodilator therapy (CBT) during mechanical ventilation have not been well defined.

Clues to effective CBT during mechanical ventilation come from the literature describing CBT in non-ventilated patients. A standard SVN treatment with 2.5 mg of albuterol takes 10 - 15 minutes to administer. When the patient fails to respond, end on end treatments may be ordered until the patient "opens up". With severe exacerbation, a patient may receive up to 4 - 6 treatments in an hour, equivalent to a nebulizer nominal dose of 10 - 15 mg of albuterol in an hour. To be fair, the literature is mixed on the benefits of continuous vs high frequency intermittent nebulizer therapy (1) The one clear benefit with CBT, is the decreased requirement for personnel at the bedside during administration. And in the case of mechanical ventilation, the reduction of disruptions in mechanical ventilation required to periodically remove and fill the SVN jet nebulizers.

CBT in non-ventilated patients

Candidates for CBT are patients who, despite frequent beta-agonist treatments, remain in extremis with bronchospasm, dyspnea, cough, chest tightness, and diminished breath sounds.

Papo et al (2) described a method of continuous nebulization in which a Harvard pump is adjusted to inject an albuterol/saline mixture into a SVN. A blender and humidifier were incorporated to control oxygen concentration with higher than ambient humidity. Papo found that continuous nebulization with pediatric patients compared to standard intermittent treatments with SVN reduced the duration of hospital stay ($p < 0.04$), duration of therapy, therapist time ($p < 0.001$) and provided greater reduction in asthma score within one hour of therapy. Moler et al. (3) described an SVN system using an infusion pump to continuously fill the nebulizer, with a valved O₂ mask and reservoir bag (figure 1).

Large volume nebulizers such as the HEART (Westmed) or Hope (Band B) nebulizers have become commercially available to deliver CBT. A 20 ml bottle of albuterol solution is mixed with 180 ml of .09% NaCl with dose regulation by changes in the flow rate driving the nebulizer (10 lpm \approx 10 mg/hr and 15 lpm \approx 15 mg/hr). There is great variability in flow rate between individual nebulizers of the same model, so dosing can vary a great deal (4). During CBT patients are commonly placed in monitored beds with EKG and pulse oximetry. If treatment extends beyond 3 hours, serum K⁺ should be monitored, with repetition q 4h. Linn et al (5.) studied the effects of such dosage levels and found minimal toxicity in treatment of acute exacerbation of asthma. The patient must be observed for adverse drug responses, including worsening tachycardia, palpitations, and vomiting. In these situations, the attending physician must be contacted immediately.

A positive response is indicated by an increase in PEFR of at least 10% after the first hour of therapy. The goal is to achieve a PEFR of at least 50% of predicted. For small children, improved oxygenation (oxygen saturation by pulse oximeter [SpO₂] >92% on room air) with evidence of decreased work of breathing indicates a favorable response. Once the patient “opens up,” intermittent bronchodilator therapy can be resumed on a prn basis.

If you accept the premise that all of these methods of high dose administration of albuterol have similar clinical effectiveness and safety, the choice of method should be based on other criteria such as disruption of mechanical ventilation, infection risk and personnel time.

CBT during mechanical ventilation

Many patients undergoing mechanical ventilation receive aerosolized medications, with variable effects.(6) In cases in which bronchospasm does not resolve with standard intermittent bronchodilator therapy CBT has been initiated. To date, this has been most commonly relied on jet SVN, with a port to allow infusion of broncodilator into the nebulizer from an IV type infusion pump. This allows refilling of the nebulizer without removing it from the ventilator circuit and interruption of PEEP or ventilation.

Although in vitro models demonstrate up to 40% higher aerosol delivery in a dry ventilator circuit, the risks of increased airway irritability and bronchospasm associated with administering cold dry gas through an endotracheal tube has been well established. When performing CBT, do not turn off humidification. Heat moisture exchangers (HMEs) act as a barrier to aerosol, and should be removed from between the nebulizer and the patient airway.

Use of SVN During Mechanical Ventilation

Aerosol administered by common jet SVNs to intubated patients receiving mechanical ventilation tends to be deposited mainly in the tubing of the ventilator circuit and expiratory limb or filter. Under normal conditions with heated humidification and standard jet nebulizers, pulmonary deposition ranges between 1.5% and 3.0%. (ref: Egan chapter) When nebulizer output, humidity level, tidal volume, flow, and I:E ratio are optimized, deposition can increase to as much as 15%. There are several disadvantages with SVN use during mechanical ventilation in that they add additional flow through the circuit,

The addition of gas flow into the ventilator circuit may change parameters of flow and delivered volumes requiring changes to ventilator parameters and alarm settings both during and after nebulization. The smaller the patient, the greater the impact of this additional flow into the ventilator circuit where 6 L/min of additional gas flow can more than double tidal volumes and inspiratory pressures, placing the patient at risk. Perhaps the greatest risk is the tendency

for condensate and secretions to drain into the nebulizer reservoir, contaminating medication being delivered to the lungs. It is not uncommon for a nebulizer with 3 mL of drug to run for 30 minutes and be found to contain 4 mL of fluid. This additional fluid is contaminated condensate which is then aerosolized and delivered to the lungs of the patient.

Use of a VM Nebulizer During Mechanical Ventilation

The Aeorneb Pro and Solo (Aerogen) are vibrating mesh (VM) nebulizers with a small plate that contains 1,000 funnel shaped apertures or holes. This plate (or mesh) is domed and attached to a washer. The mesh is vibrated by a piezo ceramic element that is also attached to the washer, moving the plate up and down by about 1 micron at 128kHz (or 1/10th the frequency of an ultrasonic nebulizer). Liquid medication is extruded or pumped through the narrow end of the apertures, about 3 micron in diameter, creating very small, consistent particles. These apertures are so narrow, that gas from the ventilator does not leak out during ventilation (even with heliox) and liquid placed in the reservoir does not leak through the holes unless the nebulizer is actuated. This allows the VM nebulizer to be refilled without removal from the ventilator circuit or interruption of ventilation. The VM does not add gas into the ventilator circuit, so no changes in ventilator parameters occur, even in neonates.

The Aeroneb® Pro is a multi-patient, autoclavable VM nebulizer, designed to deliver aerosol for periods of 15 or 30 minutes. The Aeroneb Pro has been shown to deliver between 10 - 20% of nominal dose past the endotracheal tube

during mechanical ventilation of both adults and infants without the addition of gas into the ventilator circuit. The low residual drug volume and small particle size are associated with higher efficiency. The Aeroneb Pro can be operated properly in the ventilator circuit for up to one week without requiring removal from the circuit for cleaning. The nebulizer reservoir can be opened without interrupting ventilation, even with heliox administration.

The Aeroneb® Solo is a single patient use disposable nebulizer that can be operated continuously for CBE. The inlet port as an adapter that can be attached to a standard IV infusion set, and connected to an infusion or syringe pump to allow filling of the nebulizer over extended periods of time. Testing with the nebulizer has shown that it has similar performance and efficiency as the Pro.

Unlike both jet and ultrasonic SVNs, the medication reservoir of Aeroneb Pro and Solo nebulizers is superior (above) the ventilator tubing, reducing the risk of contamination from circuit condensate to the medication in the reservoir.

Use of CBT

In order to use any nebulizer for CBT during mechanical ventilation it is important the maximum rate infusion of medication into the nebulizer does not exceed the minimum output rate of the nebulizer. Overflow of the nebulizer with SVNs obstruct the ventilator circuit and patient airway while compromising ability of the nebulizer to function, reducing drug delivery. With the vibrating mesh nebulizer,

overflowing the reservoir does not affect the ventilator circuit or nebulizer function, but wastes medication and can be messy.

Nebulizer manufacturers should provide minimum output rates for their products under standard operating conditions, however individual units, even of the same type of nebulizer may vary. Nebulizer output rate can be quantified by placing a known volume of medication into the nebulizer reservoir, and noting the time from turning on the nebulizer and the point that aerosol is no longer produced.

SVNs have residual drug volumes as high as 1.5 mL, so larger volumes should be used for testing. Since SVNs begin to stutter and output decreases near the end of dose, output rates should be determined gravimetrically. For SVNs, weigh the loaded nebulizer prior to aerosol generation, run for one minute, weigh again and determine the difference in weight. For water or albuterol sulfate, 1mg is equivalent to 1 mL. This will provide the mL/min.

With the Aeroneb Solo, place a known volume of liquid in the nebulizer (100 μ l, 0.5 mL or 3.0 mL). Measure time from beginning to end of aerosol generation. Output rate does not vary with dose volume and it is easy to determine when aerosol generation is complete since there is no period of sputtering, and aerosol output simply stops. Determine output by dividing dose volume by time of operation.

Once the minimum output rate of the nebulizer is determined, the rate of flow into the nebulizer should be determined by the amount of bronchodilator you wish to nebulize each hour (e.g., 10, 15 or 30 mg/hour). Keep in mind that pulmonary deposition efficiency will vary between types of nebulizer and differences in ventilator parameters. Consequently, dose rate should be titrated based on patient response. For beta- agonists, changes in heart rate or presence of tremor suggest that the rate is too high and should be lowered.

Techniques for assessing the response to a bronchodilator in intubated patients undergoing mechanical ventilation differ from those used in the care of spontaneously breathing patients because (1) expiration is passive during mechanical ventilation, (2) forced expiratory values (PEFR, FVC, FEV₁) cannot normally be obtained. Additional techniques can be used for mechanically ventilated patients because (1) a change in the differences between peak and plateau pressures (the most reliable indicator of a change in airway resistance during continuous mechanical ventilation) can be measured, (2) automatic positive end-expiratory pressure (auto-PEEP) levels which may decrease in response to bronchodilators (see Chapter 41), and (3) breath-to-breath variations make measurements more reliable when the patient is not actively breathing with the ventilator.

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Table 1: Factors affecting respiratory tract deposition during mechanical ventilation

Physicochemical properties of medication

Aerosol generating characteristics of delivery device

Delivery device position in circuit

Mechanical ventilator settings

Ventilator circuitry and endotracheal tube

Relative humidity of inspired air

Airway Anatomy

Neb	MMAD ± GSD	FPF (<5µm)	Residual Volume (ml)	Dose (µg) Deposited	% Dose Deposited
AN Pro	2.1 ± 2.2	83.2%*	0.4 mL*	315 µg*	13%*
Salter	3.1 ± 2.4	62 %	1.7 mL	19 µg	0.8%
MistyNe	2.5 ± 2.1	73%	1.1 mL	68 µg	2.7%
PB Drop	2.7 ± 2.4	67%	1.3 mL	52 µg	2.1%

Table 2 - Comparison the Aeroneb Pro (continuous) and three common jet nebulizers during adult mechanical ventilation. Particle size, fine particle fraction, residual volume and dose of albuterol sulfate delivered to the distal tip of an 8.0mm endotracheal tube are shown.

Figure 1: OnQ vibrating mesh technology. The Aerogen OnQ™ aerosol generator (left) with a microscopic view of tapered apertures (upper middle), and cross section of apertures (upper right). High speed microscopic photograph of aerosol generated from a single aperture (lower right).

Figure 2: Aeroneb® Solo Nebulizer