

Clearing the Mist From Our Eyes: Bronchodilators, Mechanical Ventilation, New Devices, Locations, and What You Should Know About Bias Flow

Patients with obstructive lung disease often present with life-threatening respiratory failure, confounded by severe air-flow limitation, dynamic hyperinflation, intrinsic PEEP, reduced pulmonary compliance, hypercarbia, and hemodynamic instability. Inhaled bronchodilators play a vital role in the care of such patients and are one of the most widely prescribed medications in the critical care setting. Despite administration of high doses of bronchodilators and instituting noninvasive ventilation strategies, many patients are incapable of sustaining the high work of breathing that may be required to maintain effective alveolar ventilation. As such, emergency intubation and mechanical ventilation is considered a necessary and “life-saving” intervention.

Mechanically ventilated patients with obstructive airway disease also present as some of the most technically challenging patients to stabilize and then to wean from the ventilator. Airway reactivity and resistance can be affected by infections, changes in lung volume, fluid balance, and other drugs.¹ In addition to these intrinsic factors, there are a number of obscure resistive elements (eg, endotracheal tube [ETT]^{2,3} or exhalation valve⁴) within the ventilator system that can add to causal respiratory failure,⁵ increase the work of breathing,⁶⁻⁹ and potentially prolong ventilation. While little, other than extubation, can be done to avoid these extrinsic factors, bronchoconstriction and air-flow limitation are usually reversible in mechanically ventilated patients. In fact, inhaled bronchodilators have been shown to reduce airway resistance¹⁰ and intrinsic PEEP,^{11,12} improve hemodynamics,¹³ and reduce the work of breathing.¹² Therefore, immediate and effective bronchodilator therapy is pivotal to successful stabilization and weaning of mechanically ventilated patients. But it is not intuitively obvious to clinicians with ICU experience that many bronchodilator treatments given to intubated patients appear to have any clinical effect whatsoever. No one knows for sure, but this probably is often a result of very poor drug delivery to the lungs.

Experimental data obtained from *in vivo* studies have demonstrated poor aerosol delivery to ventilated patients, with approximately 1%¹⁴ and 1–12%¹⁵⁻¹⁷ of the nominal dose being delivered to the peripheral airways of infants and adults, respectively. The paucity of human data makes

it extremely difficult for clinicians to settle on one particular device or method for aerosol delivery. This is an important reason why the elusive practice of bronchodilator administration in ventilated patients has no standards. Thus, techniques and delivery devices differ wildly from one institution to the next.

There are several practical issues complicating the efficacy of drug delivery during mechanical ventilation, including the patient’s lung mechanics, ventilator and ventilation mode, aerosol generator, heating and humidification of the inspired gas, position of the aerosol generator in the ventilator circuit, timing during the respiratory cycle, ETT size, tidal volume, and inspiratory flow rate.¹⁸ The majority of these factors have been described following well designed *in vitro* tests where each of these variables can be independently controlled. However, over the last decade there has been a proliferation of new aerosol delivery devices and a newer generation of microprocessor ventilators introduced into the clinical arenas. Further, humidification practices have changed to include selective use of both passive and active humidification systems during mechanical ventilation. No previous studies have objectively evaluated bronchodilator delivery using currently available devices with the variety of delivery options during mechanical ventilation.

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This issue of *RESPIRATORY CARE* reports 2 original research studies from Ari et al^{19,20} that address several important issues related to medication delivery during mechanical ventilation.

The first study¹⁹ was designed to evaluate drug delivery using all the available types of aerosol generators (jet nebulizer, vibrating-mesh nebulizer, ultrasonic nebulizer, and pressurized metered-dose inhaler [pMDI] with spacer), with and without humidification, with the aerosol generator at 3 locations in the circuit, during simulated adult ventilation.¹⁹ These positions included:

- Position 1: Between the ETT and the Y-piece
- Position 2: 15 cm from the Y-piece in the inspiratory limb of the ventilator circuit
- Position 3: Between the humidifier and the ventilator (15 cm from the gas outlet)

This is the first study to compare all 4 types of aerosol generators under identical ventilation parameters. There are several important clinical implications from these findings:

First, with the exception of the jet nebulizer, medication delivery was most efficient when the vibrating-mesh nebulizer, ultrasonic nebulizer, or pMDI was in position 2, regardless of whether the gas was humidified.

Second, with the aerosol generator at position 2, there were no differences in medication delivery between the vibrating-mesh nebulizer, ultrasonic nebulizer, and pMDI when drug delivery to the filter was expressed as a percentage of the nominal dose. In contrast, the jet nebulizer had the lowest medication delivery at position 2.

Third, all the devices delivered 2-fold more drug under non-humidified conditions than under the heated/humidified conditions, when the aerosol generator was either in position 2 (between the Y-piece and the humidifier) or position 3 (between the humidifier and the ventilator). Additionally, when the pMDI was placed between the ETT and the Y-piece (position 1), it delivered substantially more drug than did the other aerosol generators with non-humidified gas; however, it also had the greatest reduction in medication delivery when a humidified circuit was introduced.

Humidity appeared to be the most important factor affecting aerosol delivery in this study. The problem of reduced aerosol delivery with active humidifier systems is not a new concept. In fact, these data compare well with other studies that support the growing body of evidence that medication delivery is reduced substantially when humidity is applied to the system.^{15,21,22} Data obtained from non-humidified circuits may be particularly exciting and useful to clinicians in institutions that use primarily passive humidification systems (ie, heat-and-moisture exchanger) during mechanical ventilation. These findings also raise the question, for an ongoing clinical debate, about whether active humidifiers should be turned off intermittently or bypassed while aerosolized drugs are being administered through the ventilator system. While this practice cannot be routinely recommended at this time, it encourages additional research. Further, these findings should inspire industry leaders to find more resourceful ways to circumvent the problems associated with poor aerosol efficiency in humidified environments.

The ventilators used in the Ari et al^{19,20} studies are newer-generation microprocessor ventilators with active

exhalation valves that exhaust to the atmosphere during exhalation any gas beyond that required to maintain PEEP. Therefore, since the jet nebulizer is the only aerosol generator that uses an external pressurized continuous gas source, it is likely that a significant proportion of the aerosolized particles are leaving the patient circuit during exhalation, resulting in less medication delivery during the inspiratory phase. In most testing conditions the jet nebulizer delivered less aerosol to the lung model than did any other device. In defense of the jet nebulizer, “continuous flow” jet nebulizer is being applied less frequently because most newer-generation ventilators can provide “intermittent flow” or breath-actuated jet nebulization. Breath-actuated jet nebulizer delivers medication only during the inspiratory phase, and the ventilator automatically adjusts the internal flow to compensate for the additional gas being delivered to the system during inhalation. In vitro and in vivo studies have demonstrated that intermittent breath-actuated jet nebulization provides greater drug delivery than does continuous jet nebulization during mechanical ventilation.²³ The study may have been more clinically relevant if Ari et al had used a ventilator that provides intermittent breath-actuated jet nebulization (in the first study)¹⁹ or enabled the ventilator’s intermittent jet nebulization (in the second study).²⁰ Nonetheless, it is sound research, such as this, that should stimulate scientific inquiry to generate new research questions.

There was a tendency for the jet nebulizer to become more efficient when positioned farther away from the Y-piece and closer to the ventilator (position 3), whereas this finding was not evident with the other aerosol generators. In fact, drug delivery was reduced with the other 3 devices, which do not add additional flow to the system during nebulization. A similar relationship has been described by other researchers using jet nebulizer during mechanical ventilation or when additional circuit length was added to the system.²⁴⁻²⁶ Ari et al discuss the possibility that the inspiratory limb becomes charged with aerosol particles during the expiratory phase and thus acts as an aerosol reservoir, which probably results in greater medication delivery during inhalation.

In this study, Ari et al used a ventilator that applies a bias flow setting, which is an essential component for flow-triggering. Flow-triggering is more commonly used in the clinical setting than is pressure-triggering. Although the efficacy of flow-triggering and pressure-triggering remains controversial in patients, flow triggering is usually the default setting for most ventilators. Ari et al disabled the flow trigger and hence the bias flow, but their reasoning for that is unclear.¹⁹ Only one published study has evaluated the effects of inhaled medication delivery at different bias flow settings. Miller et al²³ observed that there were no major differences in medication delivery at different bias flow settings (10, 15, and 20 L/min), with jet

nebulizer during simulated mechanical ventilation at a single location. So it is presumable that the addition of bias flow would not impact drug delivery with jet nebulizer under those testing conditions. However, it is unclear how medication delivery might be affected by bias flow at different locations when using all of the available aerosol generators described in the present report.

The second paper by Ari et al²⁰ is an elegant follow-up study that was designed to address the issue of bias flow and medication delivery with a jet nebulizer and a vibrating-mesh nebulizer, at 2 positions, with a humidified circuit, during simulated adult and pediatric mechanical ventilation. It is exciting that Ari et al chose these 2 devices, because one adds continuous flow to the system and the other does not, but both nebulize during the entire respiratory cycle. It is probably less important that pMDI/spacer was studied, since bias flow is applied only during exhalation and actuation of pMDI albuterol is applied exclusively during the onset of inhalation.

The placement of the jet nebulizer in this study²⁰ was the same as positions 2 and 3 in the other study,¹⁹ and they used the same adult test lung model. However, they chose to use a different type of jet nebulizer, that uses a lower continuous flow rate (2.5 L/min) than did the model used in the previous study (8 L/min). Another difference is that the vibrating-mesh nebulizer was attached directly to the distal portion of the Y-piece in position 1 (between the ETT and the Y-piece), and directly to the inlet of the humidifier in position 2 (between the humidifier and the ventilator), without the 15-cm length of tubing. Ari et al noted in the previous study that the 15-cm length of tubing prevented the aerosol bolus from moving into the expiratory limb prior to inspiration. Other differences between the studies included the ventilator flow profiles, the set frequency, the ventilator used, and the presence of bias flow. It may also be important to note that the ventilator in the second study (Galileo, Hamilton, Reno, Nevada) uses a proximal flow sensor that is placed at the airway during mechanical ventilation. It is unclear whether the proximal flow sensor was taken out or used during the study. Non-heated-wire flow sensors, such as the type in the Galileo ventilator, have a tendency to accumulate condensation from humidity, which may combine with aerosols resulting in the delivery of large medication particles to the filter medium during inhalation.

There were a number of findings that may be particularly useful for improving the overall understanding of the interaction between aerosol generators and modern micro-processor ventilators. Drug delivery from the vibrating-mesh nebulizer was 2–4-fold greater than that from the jet nebulizer under all conditions in both the adult and pediatric lung models. Unlike the previous study,¹⁹ there did not appear to be any significant difference in the delivery of medication between the 2 positions with the jet nebu-

Table 1. Aerosol Delivery Data From the 2 Studies by Ari et al*

	Aerosol Delivery to the Lung Model (mean \pm SD % of nominal dose)		
	Bias Flow Zero (Study 1) ¹⁹	Bias Flow 2 L/min (Study 2) ²⁰	Bias Flow 3 L/min (Study 2) ²⁰
Jet nebulizer	6.0 \pm 0.1	5.2 \pm 0.2	4.7 \pm 0.4
Vibrating-mesh nebulizer	8.4 \pm 2.1	23.8 \pm 1.0	21.4 \pm 0.4

* During simulated adult mechanical ventilation with humidified gas, with the nebulizer between the ventilator and the humidifier (position 3).

lizer; however, there was nearly a 2-fold increase in drug delivery when the vibrating-mesh nebulizer was placed between the ventilator and the humidifier, in both the adult and pediatric lung models. This is the opposite effect from what was observed with the vibrating-mesh nebulizer in the previous study, where medication delivery was actually lower when the vibrating-mesh nebulizer was placed back at the ventilator, than when it was placed closer to the airway. Table 1 compares the mean \pm SD percent of the nominal dose delivered to the filter in the 2 studies with the vibrating-mesh nebulizer or the jet nebulizer in position 3 (between the ventilator and the humidifier), with humidified gas, during simulated adult ventilation. Comparing data between the 2 studies, there were only small differences in medication delivery when using jet nebulizer at bias flow settings of 0–3 L/min. Additionally, there did not appear to be a substantial reduction in medication delivery when the bias flow was changed from 2 L/min to 5 L/min. These results are similar to findings previously described by Miller et al,²³ who made the observation that drug delivery via jet nebulizer was not significantly reduced at different bias flows. Interestingly, the data obtained from Ari et al^{19,20} are the first ever to describe differences in drug delivery with and without a bias flow setting during mechanical ventilation using all the available types of aerosol generator.

When comparing the results of these 2 studies, the most intriguing finding was the nearly 3-fold increase in medication delivery with the vibrating-mesh nebulizer with bias flow of 2 L/min versus no bias flow (see Table 1). Based on these data it appears reasonable to assume that the delivery of medication is augmented by bias flow when the vibrating-mesh nebulizer is placed back at the ventilator. Ari et al mention in these studies that in most cases the aerosol bolus formed by the vibrating-mesh nebulizer remains in the vicinity of the aerosol device when bias flow is not being used. Therefore, it appears that the movement of the bolus is facilitated further into the inspiratory limb with bias flow during exhalation, to produce a ventilator breath that is possibly “charged” with more aerosolized particles. While this “reservoir-like effect” is the

most likely explanation for the greater drug delivery with the vibrating-mesh nebulizer placed proximal to the ventilator, objective data is needed to confirm this. The complex dynamic interaction between gases in the ventilator circuit and aerosols is a fairly new and complicated topic that has never been previously described.

While these findings may be extremely useful to the care that we provide to our patients, the cautious reader of the Journal should approach them with some trepidation. Ari et al used normal lung mechanics to assess drug delivery. Most patients who receive mechanical ventilation do not have normal lung mechanics. In theory, the amount of drug delivered to the filter, placed distal to the ETT, represents the total mass of available drug delivered to the airways, but it doesn't take into account the amount of respirable drug particles that may be delivered to the peripheral airways of the lungs. Thus, it is extremely important to mention that, despite making every attempt to avoid large droplets of accumulated liquid medication (combined with humidity) from reaching the filter, it is still possible that this fluid can condense in the flow sensor and ETT and be delivered to the filter media during inhalation.

In conclusion, there is so much useful information that can be gained from these studies.^{19,20} These papers do not address clinical efficacy, but they do provide a new foundation on which clinical research should be designed to determine the best ways to deliver bronchodilators. Much of what we do in clinical practice is not supported by objective research, and that is why these studies will provide new tools to add to our armamentarium when treating mechanically ventilated patients. This may not mean that one needs to purchase a whole new line of aerosol generators, but at least it provides good insight on how best to implement the existing devices to optimize medication delivery. For some, just changing the position may make all the difference. For others, the decision of switching from an active to a passive humidification system to improve medication delivery could make all the difference in better achieving the goal of bronchodilator response in patients who need it the most. Ari et al. have provided useful data on a very complicated topic. They have sufficiently "cleared the mist from my eyes" and there is no doubt that this will change the practice and, hopefully, it will improve the care that we provide to our patients.

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REFERENCES

- Smaldone GC. Aerosolized bronchodilators in the intensive care unit: much ado about nothing? *Am J Respir Crit Care Med* 1999; 159(4.1):1029-1030.
- LeSouef PN, England SJ, Bryan AC. Total resistance of the respiratory system in preterm infants with and without an endotracheal tube. *J Pediatr* 1984;104(1):108-111.
- Fontan JP, Heldt GP, Gregory G. Resistance and inertia of endotracheal tubes used in infants during periodic flow. *Crit Care Med* 1985;13(12):1052-1055.
- DiBlasi RM, Salyer JW, Zignego JC, Redding GJ, Richardson CP. The impact of imposed expiratory resistance in neonatal mechanical ventilation: a laboratory evaluation. *Respir Care* 2008;53(11):1450-1460.
- Yoder BA, Martin H, McCurin DA. Lung function measurements in a preterm animal model of respiratory failure: comparison of two different neonatal ventilators. *Pediatr Pulmonol* 2006;41(11):1069-1076.
- Appendini L, Purro A, Patessio A, Zanaboni S, Carone M, Spada E, et al. Partitioning of inspiratory muscle workload and pressure assistance in ventilator-dependent COPD patients. *Am J Respir Crit Care Med* 1996;154(5):1301-1309.
- Guerin C, Milic-Emili J, Fournier G. Effect of PEEP on work of breathing in mechanically ventilated COPD patients. *Intensive Care Med* 2000;26(9):1207-1214.
- Kirton OC, DeHaven CB, Morgan JP, Windsor J, Civetta JM. Elevated imposed work of breathing masquerading as ventilator weaning intolerance. *Chest* 1995;108(4):1021-1025.
- Kirton OC, Banner MJ, Axlerod A, Drugas G. Detection of unsuspected imposed work of breathing: case reports. *Crit Care Med* 1993; 21(5):790-795.
- Dhand R, Duarte AG, Jubran A, Jenne JW, Fink JB, Fahey PJ, et al. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. *Am J Respir Crit Care Med* 1996; 154(2.1):388-393.
- Dhand R, Jubran A, Tobin MJ. Bronchodilator delivery by metered dose inhaler in ventilator-supported patients. *Am J Respir Crit Care Med* 1995;151(6):1827-1833.
- Duarte AG, 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.
- Tzoufi M, Mentzelopoulos SD, Roussos C, Armaginis A. The effects of nebulized salbutamol, external positive end-expiratory pressure, and their combination on respiratory mechanics, hemodynamics, and gas exchange in mechanically ventilated chronic obstructive pulmonary disease patients. *Anesth Analg* 2005;101(3):843-850.
- Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. 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.
- MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. *Crit Care Med* 1985;13(2):81-84.
- Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients. *Am Rev Respir Dis* 1990;141(2):440-444.
- Thomas SH, O'Doherty MJ, Fidler HM, Page CJ, Treacher DF, Nunan TO. Pulmonary deposition of a nebulised aerosol during mechanical ventilation. *Thorax* 1993;48(2):154-159.
- Dhand, R. Bronchodilator therapy. In: Tobin, MJ, editor. Principles and practice of mechanical ventilation, 2nd edition. New York: McGraw-Hill; 2006:1277-1310.

19. Ari A, Areabi H, Fink JB. 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.
20. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. *Respir Care* 2010;55(7):845-851.
21. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med* 1997;156(1):3-10.
22. DiBlasi RM, Coppolo DP, Nagel MW, Doyle CC, Avvakoumova VI, Ali RS et al. A novel, versatile valved holding chamber for delivering inhaled medications to neonates and small children: laboratory simulation of delivery options. *Respir Care* 2010;55(4):419-426.
23. Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med* 2003;168(10):1205-1209.
24. Dhand R. Maximizing aerosol delivery during mechanical ventilation: go with the flow and go slow. *Intensive Care Med* 2003;29(7):1041-1402.
25. Hughes J, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. *Respir Care* 1987;32(12):1131-1135.
26. Harvey C, O'Doherty M, Page C, Thomas S, Nunan T, Treacher D. Effect of a spacer on pulmonary aerosol deposition from a jet nebulizer during mechanical ventilation. *Thorax* 1995;50(1):50-53.

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