Innovation in Aerosol Drug Delivery During Adult Mechanical Ventilation

Drug delivery during mechanical ventilation in adult patients is a complex process. Many variables affect the efficiency of drug delivery, including tidal volume, inspiratory time, inspiratory flow, method of humidification, type of aerosol generator, position of nebulizer in the ventilator circuit, volume load, and others.[1]

For many years, vibrating mesh nebulizers have been studied and used to deliver aerosols during invasive mechanical ventilation.[2-3] Other devices such as ultrasonic nebulizers are now rarely used, and jet nebulizers with continuous output are inefficient. The use of vibrating mesh nebulizers has been limited by poor performance with some formulations (eg, tobramycin and hypertonic saline) and reported problems with reliability.[4-5] There has been a paucity of technological development in the area of drug-delivery devices intended to be used with patients receiving mechanical ventilation. Cuccia et al[6] recently reported a new type of nebulizer that operates using a breath-enhancement mechanism and is placed before the inspiratory limb. This novel breath-enhanced nebulizer uses an external low flow to generate the aerosol and takes advantage of a solenoid system that allows the whole tidal volume to enhance aerosol delivery during inspiration while diverting the bias flow away from the nebulizer during exhalation, adding a breath-actuation mechanism.

In this issue of RESPIRATORY CARE, Ashraf et al[7] compared drug delivery during mechanical ventilation of 3 nebulizers using different operating principles: jet nebulizer, vibrating mesh nebulizer, and breath-enhanced nebulizer. The breath-enhanced nebulizer is similar to the device reported by Cuccia et al[6] except that it is not breath-actuated. The authors utilized radiolabeled aerosols to perform an extensive evaluation of the drug delivery achieved with the 3 devices with different humidification systems (humidifier vs no humidification), different ventilator modes (volume control vs pressure control), and varying tidal volumes during volume control mode. The authors also tested different loading volumes (3 mL vs 6 mL), and performed a mass balance study and a particle size distribution analysis.

SEE THE ORIGINAL STUDY ON PAGE 1419

The drug delivery of this novel breath-enhanced nebulizer was less efficient than breath-enhanced nebulizers and breath-actuated nebulizers previously reported.[6] This was expected because the novel breath-enhanced nebulizer continues producing aerosol during exhalation.[7] When using the humidifier system, the authors placed the nebulizer after the humidification chamber as previously published.[3,6] When not using humidification, they placed the nebulizer 15 cm after the ventilator outlet right before the inspiratory limb.

Although volume control and pressure control modes were studied, no specific data are provided. Others have reported that the use of volume control modes resulted in higher aerosol deposition than pressure control modes.[8] The authors' finding of increasing deposition with increasing inspiratory time is consistent with previous reports.[9]

The mass balance analysis with the humidifier configuration had the following findings. First, the amounts of aerosol lost before entering the inspiratory limb (ie, nebulizer + humidifier) were similar for both breath-enhanced nebulizers and vibrating mesh nebulizers (27.6% and 23.3%, respectively) but lower than the amounts lost with the jet nebulizers (70%, almost all in the nebulizer). Second, the addition of closed-system suction minimally affected drug delivery. Third, the breath-enhanced nebulizers and vibrating mesh nebulizers had similar amounts of aerosol deposited in the filter ($\sim$ 45%). Operating the ventilator without humidification resulted in similar drug delivery for breath-enhanced nebulizers and vibrating mesh nebulizers, but the lack of humidification improved the jet nebulizer performance, making it similar to breath-enhanced nebulizers. However, in an in vivo study, Moustafa et al[10] reported no difference in drug delivery related to humidification. These conflicting results need to be reconciled in future studies.

Ashraf et al[7] reported a variable effect of humidification on drug delivery efficiency. The jet nebulizer was the only nebulizer that exhibited a significant increase when humidification was discontinued (5.5% vs 10.9%, respectively).

Dr Berlinski has disclosed relationships with AbbVie, Allergan, Anthera, DCI, Cempra, Cystic Fibrosis Foundation, National Institutes of Health, Novartis, Therapeutic Development Network, Trudell Medical International, Vertex, Vivus, and the International Pharmaceutical Aerosol Consortium on Regulation and Science.

Correspondence: Ariel Berlinski MD FAARC, 1 Children's Way, Slot 512–17, Little Rock, AR 72202. E-mail: berlinskiariel@uams.edu.

DOI: 10.4187/respcare.08470

However, doubling of the loading dose for jet nebulizers when using the humidifier (16.3%) resulted in a 60% increase in drug delivery compared to the low loading volume without humidification (10.9%).

The reported particle size is in agreement with previous measurements from our laboratory (unpublished data) and others.[10] The aerosol impacts the walls of the endotracheal tube as it travels through it, resulting in size selection at the exit. The tube acts as a size equalizer with similar particle sizes reported for the 3 tested devices.

The increase in drug delivery noted with jet nebulizers and breath-enhanced nebulizers when the loading dose was increased from 3 mL to 6 mL was expected because of their residual volumes. Increasing the loading volume in the vibrating mesh nebulizers did not increase output, and resulted in less consistent delivery (coefficient of variation of 71%). This coefficient of variation is significantly higher those previously reported in adult and pediatric studies and is most likely related to device failure.[2,3,5] With a higher volume load, the breath-enhanced nebulizers outperformed the vibrating mesh nebulizers and was matched by the jet nebulizers when using humidification. The effect of fill volume was different when no humidification was used, resulting in the breath-enhanced nebulizers and the jet nebulizers outperforming the vibrating mesh nebulizers.

The reported data confirm that drug-delivery efficiency during adult invasive mechanical ventilation is influenced by multiple variables, including device selection and placement in the ventilator circuit, loading volume, and type of humidification systems used.[1,7] Optimization of drug delivery has to be individualized to the specific setup being used.

A limitation of this and other studies is its in vitro nature.[1-7,11] For some drugs with a flat dose-response curve, a more efficient device might not be better; for other drugs with a narrow therapeutic window, a low coefficient of variation will be of paramount importance for safety. The next step is to determine whether these differences in drug-delivery efficiency are clinically important. The end points of these trials will vary with the drug being studied (eg, bronchodilators, pulmonary vasodilators, antibiotics, and others).

This new technology offers the advantage of providing aerosol delivery while enhancing drug delivery during the inspiratory cycle, which potentially may avoid contamination of the humidifier's reservoir. The retail cost will significantly affect its ability to gain market share. The efficiency of this new device has not been studied under pediatric conditions. Previous reports have indicated that changes in tidal volume do not affect drug delivery.[11] Therefore, its pediatric application remains to be proven.

We hope to see more new developments in drug-delivery devices that are designed for use in patients receiving mechanical ventilation and other forms of ventilatory support.

Ariel Berlinski
Pediatric Aerosol Research Laboratory
Arkansas Children's Research Institute
University of Arkansas for Medical Sciences
Little Rock, Arkansas

REFERENCES

1. Dhand R. How should aerosols be delivered during invasive mechanical ventilation? Respir Care 2017;62(10):1343-1367.
2. 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.
3. Berlinski A, Willis JR. Albuterol delivery by 4 different nebulizers placed in 4 different positions in a pediatric ventilator in vitro model. Respir Care 2013;58(7):1124-1133.
4. Mashat M, Clark BJ, Assi KH, Chrystyn H. In vitro aerodynamic characterization of the dose emitted during nebulization of tobramycin high strength solution by novel and jet nebulizer delivery systems. Pulm Pharmacol Ther 2016;37:37-42.
5. Gowda AA, Cuccia AD, Smaldone GC. Reliability of vibrating mesh technology. Respir Care 2017;62(1):65-69.
6. Cuccia AD, Ashraf S, McPeck M, Samuel J, Smaldone GC. Wet-side breath-enhanced jet nebulization: controlling drug delivery during mechanical ventilation. Respir Care 2020;65(8):1077-1089.
7. Ashraf S, McPeck M, Cuccia AD, Smaldone GC. Comparison of vibrating mesh, jet, and breath-enhanced nebulizers during mechanical ventilation. Respir Care 2020;65(10):1419-1426.
8. Dugernier J, Reychler G, Wittebole X, Roeseler J, Depoortere V, Sottiaux T, et al. Aerosol delivery with two ventilation modes during mechanical ventilation: a randomized study. Ann Intensive Care 2016;6(1):73.
9. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145(5):1117-1122.
10. Moustafa IOF, Ali MRA, Al Hallag M, Rabea H, Fink JB, Dailey P, Abdelrahim MEA. Lung deposition and systemic bioavailability of different aerosol devices with and without humidification in mechanically ventilated patients. Heart Lung 2017;46(6):464-467.
11. Berlinski A, Willis JR. Effect of tidal volume and nebulizer type and position on albuterol delivery in a pediatric model of mechanical ventilation. Respir Care 2015;60(10):1424-1430.