Reproducible Dosing With a Jet Nebulizer During Invasive Mechanical Ventilation

The distinct challenges to successful aerosol delivery with jet nebulizers in patients receiving mechanical ventilation are well known.[1] Negotiating the ventilator circuit and narrow artificial airway presents a formidable barrier to aerosolized drug particles.[2] These obstacles are offset to some extent in patients who are ventilator supported because the artificial airway bypasses the upper airway, allowing clinicians to control breathing parameters and synchronize aerosol administration with air flow from the ventilator.[1,3]

Jet nebulizers are readily available and economical aerosol generators that have been widely used for drug delivery in patients receiving ventilator support.[4,5] For clinical effectiveness, an adequate amount of drug must deposit in the lower respiratory tract of patients receiving mechanical ventilation. Futhermore, the dose delivered must be reliable and consistent in various clinical settings.[1,3] In bench models of mechanical ventilation, the ability to control ventilator settings, circuit conditions, and nebulizer operation provides a unique opportunity to enhance the efficiency of drug delivery while also improving the precision of drug dosing.[4-6] In previous bench studies, breath-actuated nebulization and humidity in the ventilator circuit were the most important sources of variability in drug delivery with a nebulizer.[4,6] Compared with continuous nebulization, breath-actuated nebulization resulted in a severalfold increase in drug delivery, whereas humidity in the circuit reduced the amount of drug delivered compared with a non-humidified circuit.[6]

Jet nebulizers have several well-known drawbacks. They require an additional gas flow for operation (generally 6–8 L/min), which influences tidal volume, minute volume, and inspiratory pressures.[1,3] When jet nebulizers are operated continuously, there is a significant drug loss during the exhalation phase, which could account for as much as two thirds or more of the breathing cycle. Intermittent operation of the nebulizer with gas flow from the ventilator avoids such losses.[6,7] However, if the ventilator does not provide adequate gas pressure, then aerosol particle size and efficiency of drug delivery are adversely affected. Integrating nebulizer function in some ventilators facilitates reproducible and consistent dosing but problems with synchronization have been observed.[8] Incorporating a dual-channel volumetric infusion pump with a nebulizer could allow for continuous drug titration over extended periods.[9]

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In this issue of the RESPIRATORY CARE, Cuccia et al[10] describe a novel nebulizer-circuit configuration for aerosol delivery during mechanical ventilation. The new system (i-AIRE, InspiRx, Somerset, New Jersey) provides gases to the nebulizer from 2 separate sources. Aerosol generation is triggered by a pressure-controlled independent breath-actuated circuit that provides wall gases at 50 psi and a low flow (3.5 L/min) to the nebulizer only during inspiration. In addition, all the inspiratory air flow from the ventilator is directed through the top of the nebulizer during active nebulization to enhance aerosol generation. This "breath-actuated and breath-enhanced" system is designed to increase the efficiency of the nebulizer and to minimize aerosol losses during exhalation. In contrast to previous recommendations to place the nebulizer on the ventilator (dry) side of the humidifier,[11] the investigators placed the nebulizer on the patient (wet) side at the humidifier outlet.[10] In their article, they reported their findings in a bench model that tested the effects of this nebulizer system on aerosol delivery with 3 different ventilators and a wide variety of clinically relevant settings with and without active humidification.[10]

Difficulty in achieving reproducible dosing has been a major limitation of nebulizers. Even minor changes in the technique of administration significantly impact the efficiency of drug delivery.[4,12] Cuccia et al[10] showed that the inhaled mass with nebulizers in previous studies varied from 2.7 to 41% of the nominal dose. The variability in dosing efficiency could be attributed to several factors, such as nebulizer type, breathing pattern, nebulizer placement in the circuit, and the presence of humidity in the circuit.[10] The salient feature of the current investigation is that the inhaled mass with the breath-actuated and breath-enhanced nebulizer provided a relatively reproducible dose with

Dr Dhand discloses relationships with GSK Pharmaceuticals, Boehringer-Ingelheim, Bayer, Mylan, Teva, and Astra-Zeneca Pharmaceuticals.

Correspondence: Rajiv Dhand MD FAARC, Department of Medicine, University of Tennessee Graduate School of Medicine, 1924 Alcoa Highway, U-114, Knoxville, TN 37920; E-mail: RDhand@utmck.edu.

DOI: 10.4187/respcare.08279

different ventilators, modes of ventilation, ventilator parameters, bias flows, and PEEPs.[10] Thus, a predictable drug dose could be delivered to patients receiving mechanical ventilation with this novel technology. The consistency of dosing represents a clear advantage for the delivery of drugs, such as antibiotics, that require reproducible delivery of high local concentrations in the lungs for a therapeutic effect.

In previous investigations, the presence of humidity in the ventilator circuit reduced the efficiency of drug delivery with jet nebulizers.[4,6] In contrast, Cuccia et al[10] reported that humidity did not influence the efficiency of drug delivery in their model. In their study, the investigators compared a humidified with a partially humidified circuit, as opposed to a dry one, and they did not report the levels of humidity in the circuit.[10] A major reason for the higher inhaled mass in the presence of active humidification was that a significant proportion of the radioactivity did not leave the nebulizer when dry gases were flowing through the nebulizer.[10] The total air flow through the nebulizer, including 3.5 L/min supplied by wall gases and upward of 40 L/min through the ventilator clearly exceeded the 6 to 8 L/min generally used to run jet nebulizers. The investigators speculated that high air flow of dry gases probably had a dehydrating effect, with more liquid drying on the walls of the nebulizer and failing to be recycled into the nebulizer bowl.[10] However, in the humidified setup, the losses on nebulizer walls were reduced and more liquid was available for nebulization. Based on analysis of these data, the nebulizer system should preferentially be placed at the humidifier outlet instead of the ventilator outlet.[10]

In the humidified versus partially humidified operation of the breath-actuated and breath-enhanced system, the emitted dose from the nebulizer was ~85% in the humidified setup versus ~60% of the nominal dose in the absence of humidification.[10] The aerosol produced in the presence of active humidification had larger particles than those with partial humidification (mass median aerodynamic diameter, 1.34 vs 1.04 μm, respectively) and a correspondingly higher loss in the ventilator circuit (~27 vs ~13%, respectively).[10] The inhaled mass as a proportion of the emitted dose from the nebulizer in the humidified circuit (~0.41, ie, 35/85.4%) was lower than the proportion in the partially humidified circuit (~0.49, ie, 29.4/60.6%). Nevertheless, the efficiency and reproducibility of dosing with the novel nebulizer system in a humidified circuit would argue for maintaining humidity during its operation. Whether the results of this investigation could be reproduced with medications (in contrast to radiolabeled saline solution) needs to be determined. Moreover, further studies could determine whether the reproducibility of drug dosing with the breath-actuated and breath-enhanced system leads to a difference in clinical outcomes for patients receiving mechanical ventilation.

Rajiv Dhand
Department of Medicine
University of Tennessee Graduate School of Medicine
Knoxville, Tennessee

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