High Impact Aerosol Technology Offers Higher Efficiency, But Is Not Ready for Prime Time

The therapeutic administration of medical aerosols has been a standard adjunct to treatment of critically ill patients since positive-pressure mechanical ventilators were introduced over 60 years ago, and most ventilators can operate a jet nebulizer in synchrony with mechanically delivered breaths. However, for the first 40 years, little was known about the efficiency of aerosol delivery during mechanical ventilation.[1]

Most of what we know about the science of aerosol delivery in critical care environments has been brought to light since 1987. At that time, several investigators reported scintigraphic studies demonstrating that in mechanically ventilated patients, aerosol deposition (1–3%)[2–4] can be an order of magnitude less than that achieved in ambulatory patients (10–30%).[5,6] Subsequent research identified substantial barriers to efficient and consistent aerosol delivery, related to the presence of artificial airways, and the range of variables associated with mechanical ventilation caused diminishing expectations that perceived barriers could be overcome.[7,8]

Much of what we now know about aerosol delivery during mechanical ventilation has come from in vitro models,[9,10] which allow researchers to isolate variables and to determine the roles of those variables in reducing or improving aerosol delivery efficiency, in a way that would be difficult or impossible under clinical conditions. Bench testing allows rapid iterative evaluation of specific variables, at low cost, and in increments and ranges that would not be practical or well tolerated in patients.

In vitro models have yielded information that has resulted in substantial benefits in vivo. Bench studies of variables associated with jet nebulizers during mechanical ventilation of adults have led to order-of-magnitude improvements, through changes in clinical practices, increasing aerosol efficiency to 15–22% in vivo.[11–12] This was accomplished with a nebulizer that creates very small particles, with a relatively low inspiratory flow, high tidal volume, and a nonhumidified ventilator circuit, for administration times of up to 40 min. The desire for more efficient pulmonary delivery may be balanced by clinicians' concerns about the impact of the required ventilatory parameters. Other research has suggested that large tidal volume[13] and administration of dry and cold gas to the lungs when bypassing the upper airway[14] may have adverse effects.

Whether or not these new techniques were widely adopted, the successful application of principles learned from in vitro testing demonstrated pioneering techniques to improve clinical aerosol delivery and break the 10% barrier, showing that aerosol delivery to adults during mechanical ventilation could be as efficient as aerosol delivery to ambulatory patients.

The challenge of efficient aerosol delivery to low-birthweight infants is even greater than with adults.[15] The only scintigraphic study in low-birthweight infants[16] found deposition of $< 1\%$ when using either jet nebulizer or metered-dose inhaler in both spontaneously breathing and mechanically ventilated infants. This confirmed animal models (2 kg rabbits) of infant ventilation that reported similar pulmonary delivery.[17] Fok and colleagues also demonstrated that this low level of deposition efficiency was sufficient for clinical response to bronchodilators in both infants and rabbits.[18,19] These studies demonstrated that mechanical ventilation does not necessarily decrease aerosol delivery efficiency, compared to nonintubated spontaneously breathing patients. However, this finding elevates the challenge to improve aerosol deposition efficiency for infants both on and off the ventilator.

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To that end, in their report in this issue of RESPIRATORY CARE, Quong and colleagues[20] recognize that $> 90\%$ of the aerosol generated with a nebulizer flow rate of 6 L/min never has a chance to be inhaled by a mechanically ventilated infant with a minute ventilation of 0.5 L/min. The authors, a group of engineers and clinicians, describe the physics and method required to reclaim and recycle a portion of the aerosolized drug escaping past the patient into the expiratory limb of the ventilator circuit. The use of a gas jet to create an area of turbulence increases impaction of larger particles, which are collected as liquid returned to the nebulizer reservoir to be renebulized. This technique increased aerosol delivered by a factor of 1.6, which may have the potential to shatter the 1% efficiency barrier with jet nebulizers during mechanical ventilation.

Quong et al point out that use of newer vibrating-mesh aerosol-generation technology has resulted in $> 10\%$ deposition in animal models of infant ventilation,[21] so why is this new study[20] so important? Simply because, no matter what the efficiency of a specific aerosol generator, as long as the total flow of the ventilator exceeds the patient's

minute volume, this new aerosol recycling method suggests the possibility of the same 1.6-fold increase.

This is the first report[20] of a successful attempt to collect and recycle aerosol to improve the efficiency of aerosol drug delivery during mechanical ventilation. If this technique can increase drug delivery by 60% with a jet nebulizer, it should offer similar efficiency improvements with more efficient aerosol technology during infant ventilation.

Don't try this at home. Quong et al clearly state that this technique is not ready for "prime time." As any neonatal therapist can attest, the addition of gas flow into an infant circuit can increase expiratory resistance and intrinsic positive end-expiratory pressure, with potential for deleterious impact on the patient. This report[20] does not justify placing infants at risk with experimentation at the bedside. However, the lessons learned with this study may surface in products we can all safely use in the future. Once the principle of increasing turbulence to create expiratory-limb aerosol-particle impaction for aerosol recycling has been established, it is the engineer's role to find alternative methods to create such turbulence without affecting the pressure or volume in the ventilator circuit.

Such innovation is not justified for delivery of low-cost drugs such as albuterol. However, for expensive medications, such as "boutique" antibiotics, prostacyclins, surfactants, and protease inhibitors that cost > $200 per dose, a 1.6-fold increase in dose-delivery efficiency could prove enabling for drug delivery and drug development for this patient population.

For now it should be sufficient for the reader to understand that this innovative aerosol waste-reduction technique, though not yet suitable for patient application, can redefine our perceived limits of aerosol delivery during mechanical ventilation of infants, and may lead to advances that can lead to even greater promise for the future.

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