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Comparison of Albuterol Delivery between High Frequency Oscillatory Ventilation and Conventional Mechanical Ventilation in a Simulated Adult Lung Model using Different Compliance Levels

Waleed A. Alzahrani
KSAU-HS

COMPARISON OF ALBUTEROL DELIVERY BETWEEN HIGH FREQUENCY OSCILLATORY VENTILATION AND CONVENTIONAL MECHANICAL VENTILATION IN A SIMULATED ADULT LUNG MODEL USING DIFFERENT COMPLIANCE LEVELS

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By

Waleed Awdhah Alzahrani

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ACCEPTANCE

This thesis, COMPARISON OF ALBUTEROL DELIVERY BETWEEN HIGH FREQUENCY OSCILLATORY VENTILATION AND CONVENTIONAL MECHANICAL VENTILATION IN A SIMULATED ADULT LUNG MODEL USING DIFFERENT COMPLIANCE LEVELS, by Waleed Awdhah Alzahrani was prepared under the direction of the Master's Thesis Advisory Committee. It is accepted by the committee members in partial fulfillment of the requirements for the degree Master of Science in the College of Health and Human Sciences, Georgia State University.

The Master's Thesis Advisory Committee, as representatives of the faculty, certifies that this thesis has met all standards of excellence and scholarship as determined by the faculty.

Arzu Ari, Ph.D., RRT, CPFT, PT
Committee Chair

Robert Harwood, MSA, RRT
Committee Member

Lynda T. Goodfellow, Ed.D. RRT, FAARC
Committee Member

December 14, 2010
Date

AUTHOR'S STATEMENT

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Waleed Awdhah Alzahrani

Local Address:
3605 Noble Creek Dr. NW
Atlanta, GA 30327

International Address:
B. O. Box 66566
City: Dammam. Zip: 31586
Saudi Arabia

The director of this thesis is:

Arzu Ari, Ph.D., RRT, CPFT, PT
College of Health and Human Sciences
Georgia State University
Atlanta, Georgia 30303-3083

VITA

Waleed Awdhah Alzahrani

Address:

Local Address:
3605 Noble Creek Dr. NW
Atlanta, GA 30327

International Address:
B. O. Box 66566
City: Dammam. Zip: 31586
Saudi Arabia

EDUCATION:

B.S. 2005 King Faisal University, Dammam, Saudi Arabia
Respiratory Care

PROFESSIONAL EXPERIENCE:

October 2007 – present:	Faculty Member King Saud Bin Abdul-Aziz University for Health Science, Dammam, Saudi Arabia
September 2005 – August 2007:	Respiratory Therapist I (ICU therapist) King Fahad National Guard Hospital / King Abdul-Aziz Medical City

PROFESSIONAL SOCIETIES AND ORGANIZATIONS:

June 2009 – Present	American Association for Respiratory Care

ABSTRACT

COMPARISON OF ALBUTEROL DELIVERY BETWEEN HIGH FREQUENCY OSCILLATORY VENTILATION AND CONVENTIONAL MECHANICAL VENTILATION IN A SIMULATED ADULT LUNG MODEL USING DIFFERENT COMPLIANCE LEVELS

By

Waleed A. Alzahrani, BSRT

BACKGROUND: Delivery of aerosol by pMDI has been described with conventional mechanical ventilation (CMV) but not with high frequency oscillatory ventilation (HFOV). The purpose of this study was to compare aerosol delivery to a simulated 75 kg adult with low compliance during both CMV and HFOV. Since actuation of pMDI with inspiration is not feasible with HFOV, we investigated the impact of actuation timing only during CMV.

METHOD: CMV (Respironics Esprit) and HFOV (Sensor Medics 3100B) ventilators with passover humidifiers and heated circuits were connected by 8 mm ID ETT and filter (Respirgard II, Vital Signs) to a test lung (TTL) with compliance settings of 20 and 40 ml/cm H_2O in order to simulate a non compliant lung. Settings for CMV (V_T 6 ml/kg, I:E 1:1, PEEP 20 cm H_2O, and RR 25/min), and HFOV (RR 5 Hz, IT 33%, ΔP 80 cm H_2O and mPaw 35 cm H_2O) were used, with similar mPaw on CMV and HFOV. Parameters were selected based on ARDSnet protective lung strategy (Fessler and Hess, Respiratory Care 2007) Eight actuations of albuterol from pMDI (ProAir HFA, Teva Medical) with double nozzle small volume spacer (Mini Spacer, Thayer Medical) placed between the "Y" adapter and ETT at more than 15 sec intervals for each condition (n=3). During CMV, pMDI actuations were synchronized (SYNC) with the start of inspiration at more than 15 s, and nonsynchronized (NONSYNC) with actuations at 15 s intervals. Drug was eluted from the filter and analyzed by spectrophotometry (276 nm). Repeated measures ANOVA, pairwise comparisons and independent t- tests were performed at the significance level of 0.05.

RESULTS: In all cases, aerosol delivery was greater with HFOV than CMV ($p<0.05$). Synchronizing pMDI actuations with the beginning of inspiration increased aerosol deposition significantly at compliance levels 20 ml/cm H_2O and 40 ml/cm H_2O ($p=0.011$ and $p=0.02$, respectively). Lung compliance and aerosol delivery are directly related. Increasing lung compliance to 40 ml/cmH_2O improved aerosol delivery during CMV and HFOV ($p<0.05$).

CONCLUSION: Albuterol deposition with pMDI was more than two fold greater with HFOV than CMV in this in-vitro lung model. Changing lung compliance has almost 2 fold impact on aerosol delivery during both modes of ventilation. Furthermore, synchronizing pMDI actuations during CMV improved aerosol delivery up to 4 fold.

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Abbreviations

ARDS: Acute Respiratory Distress Syndrome.

ARDSNet: ARDS Network Trial.

ALI: Acute Lung Injury

CMV: Conventional Mechanical Ventilation.

CMV-VC: Conventional Mechanical Ventilation with Volume control Mode.

COPD: Chronic Obstructive Pulmonary disease.

Delta-P: Pressure Amplitude.

ETT: Endotracheal Tube.

f (Frequency)

FiO_2: The Fraction of Inspired Oxygen.

HFOV: High Frequency Oscillatory Ventilation.

HFV: High-Frequency Ventilation.

ICU: Intensive Care Unit.

T_I: Inspiratory Time.

LPS: Lung Protective Strategy.

ME: Minute Ventilation.

mPaw: Mean Airway Pressure.

MV: Mechanical Ventilation.

OI: Oxygenation Index.

$PaCO_2$: Partial Pressure of Carbon Dioxide in Arterial Blood.

PaO_2: Partial Pressure of Oxygen in Arterial Blood.

PASW: The Predictive Analysis Software.

PCV: Pressure Control Ventilation.

PEEP: Positive End-Expiratory Pressure.

PIP: (Peak Inspiratory Pressure)

pMDI: Pressurized Metered Dose Inhalers.

Raw: Airway Resistance.

RCT: Randomized Controlled Trial.

RR: Respiratory Rate.

TTL: Training/Test Lung.

V_T: Tidal Volume.

VILI: Ventilator-Induced Lung Injury.

Chapter I

Introduction

Pulmonary diseases with low lung compliance such as acute respiratory distress syndrome (ARDS), pneumonia, acute respiratory failure, atelectasis, and aspiration pneumonia are common reasons for admission to an adult intensive care unit (ICU) for mechanical ventilatory support. These diseases have one particular characteristic in common: all of them are characterized by having low lung compliance. Low lung compliance in adults can occur for many reasons such as the aspiration of fluids into the lungs, the loss of surfactant, or the collapse of the alveoli. Aspiration occurs when oropharyngeal or gastric material is misdirected into the lower respiratory tract. Following aspiration, the inhaled secretions are colonized by pathogens resulting in the development of pneumonia during which an acute inflammatory reaction occurs, which can result in granulomatous lesions or bronchiolitis (Müller, 2003). Eventually, the inflammatory reaction will cause a disease that will reduce the lung compliance such as ARDS.

ARDS is a disease associated with low lung compliance that frequently requires admission to the ICU and the subsequent use of conventional mechanical ventilation (CMV) and/or high frequency oscillatory ventilation (HFOV). ARDS is characterized by activation of inflammation and coagulation that induces changes in the permeability of the alveolocapillary membrane. As a result protein-containing fluid shifts into the interstitial and alveolar space (David, et al., 2003). This leads to degradation of alveolar surfactant and to atelectasis formation, which results in increased intrapulmonary shunting and hypoxemia (Ragaller & Richter, 2010). Mismatch of ventilation and perfusion is further aggravated by microthrombosis of alveolar capillaries, resulting in increased partial pressure of carbon dioxide in the blood ($PaCO_2$) and alveolar dead space (David, et al., 2003).

CMV support is one of the initial therapeutic modalities used to manage patients who have low lung compliance due to diseases such as ARDS, pneumonia, or atelectasis. Early CMV support strategies in these patients include increasing inspiratory time (T_I), positive end-expiratory pressure (PEEP), and the use of large tidal volumes (V_T). The high pressures and high V_T in ventilation are associated with increased transpulmonary pressure that results in a reduction of right ventricular preload (Jardin & Vieillard-Baron, 2003). These strategies may produce barotrauma and volutrauma, which may damage the pulmonary capillary endothelium and thus allow fluid and protein to accumulate in the interstitial space and alveoli (Brower & Brochard, 2006). In recent years, CMV strategies have emerged to reduce these complications. These strategies, which include the acute lung injury (ALI) and ARDS management protocol that uses CMV with high respiratory rate (RR) and low V_T (Brower & Brochard, 2006), are used to prevent further lung injury and to avoid lung collapse and atelectasis caused by high PEEP levels. This strategy also uses low V_T to avoid overdistension of the lung. Additionally, static pressure volume curves are used to determine lower and upper inflection points in order to apply the appropriate level of PEEP and end-inspiratory pressures (Wunsch & Mapstone, 2005).

However, these approaches have limitations, especially when the pressure range between the upper and lower inflection points is too small to provide sufficient alveolar ventilation. Studies have shown that compartments with very long time constants (more than 8 seconds) may exist in patients with ARDS, and that such “slow” compartments may comprise more than 10% of aerated lung volume (Fessler & Hess, 2007). Presently, avoiding high peak inspiratory pressures (PIP), large V_T, and high inspiratory oxygen concentration is recommended (Malik, 2003). Even with optimal use of CMV, progression of hypoxia and respiratory acidosis frequently occur (Fessler & Hess, 2007).

Another strategy to manage patients with low lung compliance diseases is through the use of HFOV, a type of ventilation developed to limit mechanical ventilator-induced lung injury (VILI) or damage (Derdak, et al., 2002). In HFOV, a diaphragm superimposes pressure oscillations on the mean airway pressure (mPaw) provided by continuous gas flow. This results in small V_T at high RR with active exhalation. Lung injury is reduced by avoiding over inflation of compliant segments of the lung and collapse of less compliant lung segments (Mehta, et al., 2004). Furthermore, HFOV improves oxygenation, reduces the need for supplemental oxygen, and improves outcomes (survival with or without severe chronic lung disease) in adults (Derdak, 2003; Derdak, et al., 2002; Fort, et al., 1997; Mehta, et al., 2001).

As this literature review shows, both CMV and HFOV have advantages and disadvantages in the management of ARDS. Usually, lung compliance is worsened with the severity of the lung disease, which makes it more difficult to manage. Exacerbating problems include overdistension of the lungs due to the stiffness and the low compliance of the lung. Thus, to protect the lungs, strategies for lung-protective ventilation have begun to emerge. HFOV appears to be ideal to support principles of lung-protective ventilation and provides a relatively high mPaw, which may recruit the lung more effectively than PEEP as typically set on a CMV (Ritacca & Stewart, 2003). It also provides small V_T, which minimizes the risk of overdistension during inspiration and minimizes the opportunities for derecruitment during expiration. However, controversy about HFOV and its ability to achieve the goals of lung-protective ventilation still remains. One of the reasons behind this debate is the fact that the V_T cannot be measured during HFOV (Fessler & Hess, 2007).

Some studies have compared HFOV and CMV in cases of low and different levels of lung compliance, though these comparisons have never been fully investigated. However, one study showed a statistically significant difference between the intervention and control groups in the total length of ventilator days (Wunsch & Mapstone, 2005). Overall, current studies have not provided enough evidence to conclude that high-frequency ventilation (HFV) reduces mortality or long-term morbidity in patients with ARDS when compared to CMV (Wunsch & Mapstone, 2005). Furthermore, lung-protective CMV strategies are structured to limit alveolar overdistension through the use of small V_T and low end-inspiratory pressures, and to avoid repeated end-expiratory alveolar collapse by using adequate PEEP (Downar & Mehta, 2006). This strategy has been associated with a 9% absolute reduction in mortality compared with a strategy that employed a higher V_T (ARDSNet, 2000).

Research shows that patients with low levels of compliance, such as adult patients with ARDS, also often receive inhaled bronchodilators (Garner, Wiest, & Bradley, 2000), although their benefits has not been well established. Because effectiveness of inhaled medications is dependent on delivery to the lung, it is important to determine how HFOV and CMV affect the delivery of inhaled medications in patients with low lung compliance. No studies have thoroughly investigated the use of a pressurized meter dose inhaler (pMDI) during HFOV or CMV to treat diseases that have low levels of lung compliance such as ARDS. The amount of aerosol deposition during HFOV and CMV in a simulated model will be determined in this study. Currently, ventilator manufacturers recommend disconnecting the patient from HFOV and applying manual ventilation during inhaled drug administration. This could potentially be detrimental to ARDS patients because the disconnection from HFOV in order to deliver pMDI medications may result in lung derecruitment (Garner, et al., 2000).

The purpose of this study is to compare albuterol delivery between HFOV and CMV in a simulated adult lung model with different compliance levels.

Upon reviewing the literature, four important research questions arose:

1. What is the amount of aerosol delivered from pMDI at two levels of compliance during HFOV?
2. What is the amount of aerosol delivered from pMDI at two levels of compliance during CMV?
3. Is there any difference in aerosol delivery between HFOV and CMV in a simulated adult lung model with different levels of compliance?
4. What is the difference in aerosol delivery between synchronized puffs and unsynchronized puffs in a simulated adult lung model with different levels of compliance in the CMV groups?

Chapter II

Review of Literature

This literature review focuses on areas relevant to HFOV in adult patients, CMV in adult patients with ARDS, comparisons between HFOV and CMV in the management of ARDS, the relation of lung compliance to ARDS, how to manage ARDS with lung protective strategies (LPS), aerosol delivery using pMDI in CMV, and aerosol delivery using pMDI in HFOV. The studies and reviews collected for this review come from the following databases: Medline, Science Direct, Proquest, Ebsco Host, Web of Science, and PubMed. The search terms used were HFOV, CMV, ARDS, adult, aerosol delivery, pMDI, albuterol, and lung compliance. No published studies were found that compared aerosol delivery with HFOV versus CMV in the adult population. However, one published study was found that explored aerosol delivery in a pediatric HFOV model. Additionally, very few studies compared HFOV and CMV in the adult population with ARDS or low lung compliance diseases.

ARDS

Brower et al. (2001) published an article about the treatment of ARDS that improved the understanding of the pathogenesis of ARDS. They indicated that one of the clinical hallmarks of ARDS is the decrease in lung compliance that is caused by the flooding of alveoli, which increases surface tension at air-fluid interfaces and eventually causes atelectasis. The authors suggested that the standard supportive care for ALI/ARDS should now include a protective ventilatory strategy with low V_T ventilation. They also indicated that results of anti-inflammatory strategies have been disappointing in clinical trials.

HFOV in Adults

Mehta et al. (2004) reviewed patients treated with HFOV at three academic university-affiliated ICUs since 1998 in three medical-surgical ICUs in Toronto, Canada. A total of 156 adults were involved in the study. The mean partial pressure of oxygen in arterial blood (PaO_2) / the fraction of inspired oxygen (FiO_2) ratios and mean oxygenation index (OI) improved significantly with the application of HFOV. Significant changes in hemodynamics following HFOV initiation included an increase in central venous pressure, a reduction in cardiac output, and an increase in pulmonary artery occlusion pressure. The study concluded that HFOV has beneficial effects on PaO_2/FiO_2 ratios and OI, and may be an effective rescue therapy for adults with severe oxygenation failure. The study suggested that early institution of HFOV may be advantageous.

Another study by Metha et al. (2001) evaluated the safety and efficacy of HFOV in adult patients with the ARDS and oxygenation failure. In an ICU and burn units of two universities teaching hospitals. Twenty-four adults were included in the study. The authors indicated observed the occurrence of changes in hemodynamic variables following HFOV initiation, these included an increase in pulmonary artery occlusion pressure and central venous pressure, and a reduction in cardiac output throughout the course of the study. They also indicated that there were no significant changes in systemic or pulmonary pressure associated with initiation and maintenance of HFOV. The authors concluded that HFOV has beneficial effects on oxygenation and ventilation, and may be a safe and effective rescue therapy for patients with severe oxygenation failure. Also they indicated that early institution of HFOV may be advantageous.

Chan et al. (2007) reviewed randomized controlled trials (RCT) and case series about HFOV and adult patients with ARDS. The authors found that what makes HFOV unique is its rapid delivery of small V_T of gas and the application of high mPaw. This concept makes HFOV an ideal lung-protective ventilatory mode for the management of ARDS, as the high mPaw prevents cyclical derecruitment of the lung, and the small V_T limits alveolar overdistension. In their review, Chan et al. identified two RCTs and 12 case series evaluating HFOV in adults with ARDS. In these studies, HFOV appeared to be safe and consistently improved oxygenation when used as a rescue mode of ventilation in patients with severe ARDS. The two RCTs comparing HFOV to CMV had encouraging results that led to an increasing use of HFOV in adults with ARDS. However, their study failed to show a mortality benefit of HFOV over CMV.

David et al. (2003) examined whether ARDS patients who failed to maintain oxygenation and CO_2 removal on CMV can be safely transitioned to HFOV. They also examined whether HFOV use is efficacious. Their study was observational and included a 14-bed ICU of a university hospital. A total of 42 patients with ARDS were enrolled in the study. The study showed that at baseline the median PaO_2/FiO_2 ratio was 95. However, after 24 hours of HFOV, the PaO_2/FiO_2 ratio increased significantly to 165. Of the 42 patients, 18 (43%) had died by Day 30. The study showed a significantly higher 30-day mortality rate in patients with at least 3 days of mechanical ventilation (MV) prior to HFOV (64%) and in patients without oxygenation improvement after 24 hours on HFOV (71%). It also showed that failure to improve oxygenation within 24 hours of HFOV is associated with high mortality. The study concluded that HFOV is an effective and safe method to ventilate ARDS patients.

Ragaller and Richter (2010) examined different MV strategies for treating patients with ALI or ARDS. They emphasized on experimental and clinical data that can be applied to clinical practice. The authors indicated that one of the ARDS symptoms is substantial reduction in pulmonary compliance. They focused on VALI and how to reduce it using the protective ventilation strategy. The goals of this strategy are directed towards the prevention of further harm to the lungs through the use of a low V_T and a high RR to prevent overdistension, barotraumas, and atelectasis. Furthermore, their study showed that protective MV is beneficial not only for the lungs but also for the heart. Their article concluded that the simple procedure of lung-protective ventilation, using reduced V_T, a pressure limit, and a FiO_2 as low as possible is the only known effective therapy that does not incur excessive risk. Thus, using lung-protective ventilation can effectively reduce the mortality rate of patients with ALI/ARDS.

Downar and Mehta (2006) reviewed the use of HFOV in adults with ARDS and found that MV for ARDS patients can exacerbate lung damage because of VILI. However, they suggested that HFOV may improve oxygenation in patients with ARDS, while limiting further lung injury associated with high ventilatory pressures and volumes delivered during CMV. They also indicated that no mortality benefit was established when using HFOV over CMV. Nevertheless, their review suggested that HFOV, compared with CMV, is a safe and effective ventilation strategy for adults with ARDS. They also indicated that HFOV may improve outcomes if used early in the course of ARDS or if used in certain populations. Downar and Mehta focused on the evidence supporting the use of HFOV in adults with ARDS including the goals of a lung-protective strategy. Their review indicated that a higher sustained mPaw would increase alveolar recruitment, which, in turn, would improve ventilation–perfusion matching and oxygenation.

Another review about the use of HFOV with adults, conducted by Ritacca and Stewart (2003), indicated that strategies aimed at preventing VILI, such as ventilating with low V_T, can reduce mortality in patients with ARDS. The review also suggested that HFOV is ideal as a LPS for adult patients with ARDS. The authors indicated that the amount of gas that enters and exits the lung with each oscillation is frequently below the anatomic dead space. Despite this, gas exchange still occurs, and potential adverse effects of CMV, such as overdistension and the repetitive opening and closing of collapsed lung units, are arguably mitigated. Ritacca and Stewart reviewed the principles and practical aspects of HFOV, as well as the current evidence of the application of HFOV in adults with ARDS. They concluded that when HFOV is used early in ARDS, it will have, at least, an equivalent effect to that of CMV and may reduce mortality.

Derdak, et al. (2002) conducted a multicenter, RCT study to compared the safety and effectiveness of HFOV with CMV in adults with ARDS. The authors indicated that ARDS patients managed by HFOV showed improvement in PaO_2 / FiO_2 when compared with patients managed by CMV. Their study also showed an improvement in the mortality rate with the HFOV group. The study concluded that HFOV is a safe and effective mode of ventilation for the treatment of ARDS in adults.

Another review by Derdak (2003) indicated that using HFOV improved oxygenation in neonatal and pediatric respiratory failure and reduced the occurrence of VILI, without increasing barotrauma. The author also indicated that HFOV in patients failing CMV strategies have improved oxygenation in adult patients with severe ARDS. The review suggested that early (2 days) initiation of HFOV is more likely to result in survival than delayed initiation (>7 days). The author indicated that HFOV is as effective and safe as CMV.

HFOV vs. CMV

Wunsch and Mapstone (2005) compared HFOV with CMV for the treatment of ARDS by examining the outcomes of using the two ventilation therapies to treat ALI and ARDS in children and adults. They found two trials that fit their inclusion criteria: the first included 58 children, and the second recruited 148 adults. Both trials used HFOV as the intervention and included variable use of lung-volume recruitment strategies. Wunsch and Mapstone's review indicated that the intervention groups showed a trend toward 30-day less mortality. However, the authors also found that neither study had a statistically significant difference. Similarly, there was no statistically significant difference between the intervention and control groups for total number of ventilator days. The pediatric study showed a statistically significant reduction in the need for supplemental oxygen among survivors at the 30 days trend. Wunsch and Mapstone determined that there is not enough evidence to conclude HFOV reduces mortality or long-term morbidity in patients with ARDS.

Another review, conducted by Fessler and Hess (2007), compared HFOV and CMV in adult patients with ARDS and found that HFOV can support gas exchange with much smaller V_T than can be achieved with CMV. Additionally, the review found that HFOV provides more effective lung recruitment than CMV and may improve PaO_2 in some patients as compared to CMV, although this improvement is often transitory. Nevertheless, the authors concluded that there is not enough evidence to indicate that survival in adults with ARDS is improved by HFOV. The available evidence does not support that pulmonary inflammation is reduced with HFOV in adult ARDS. Fessler and Hess suggested that the use of HFOV as a lung protective ventilator strategy needs more clinical trials to determine whether this approach is superior to lung protective ventilation using CMV.

Lung Protective Mechanical Ventilator Strategy for ARDS

Meade et al. (2008) studied the ventilation strategy using low V_T, recruitment maneuvers, and high PEEP in ALI and ARDS. The purpose of the study was to compare an established low-V_T ventilation strategy with an experimental strategy based on the original "open-lung approach," combining low V_T, lung recruitment maneuvers, and high PEEP. The RCT involved 30 ICU in Canada, Australia, and Saudi Arabia and was conducted between August 2000 and March 2006 and included 983 consecutive patients with ALI. At enrollment, 85% (n = 983) of the patients met the criteria for ARDS. The study concluded that using a multifaceted protocolized ventilation strategy designed to recruit and open the lung resulted in no significant difference in hospital mortality or barotrauma compared with an established low V_T protocolized ventilation strategy in patients with ALI and patients with ARDS.

Brower and Brochard (2006) reviewed the use of LPS with CMV for the management of ALI and ARDS and found that CMV can cause VILI, which may delay or prevent recovery in some patients. They discussed clinical trials that demonstrated improved clinical outcomes in patients who received lower V_T and inspiratory airway pressures to prevent VILI from overdistension. The authors also indicated that experimental models suggest that VILI may occur from cyclic opening and closing of small bronchioles and alveoli, and that this can be reduced by applying PEEP. They indicated that some clinical studies suggested that clinical outcomes may be improved with the use of higher levels of PEEP, especially when compared to the outcomes of using CMV strategies. However, in these studies, higher PEEP was combined with lower V_T and inspiratory airway pressures. Brower and Brochard also indicated that the physiologic rationale for using HFV is strong, but clinical trials are needed to demonstrate improved clinical outcomes with HFV when compared to lung-protective MV strategies.

Koutsoukou et al. (2009) investigated the effect of CMV on respiratory mechanics and blood gases using a LPS before the onset of ARDS. Nineteen patients with ARDS were stratified into two groups according to ARDS onset relative to the onset of MV. In group A, MV was applied at the onset of ARDS. In group B, MV was initiated before ARDS. The study showed that in group A, the PaO_2/FiO_2 ratio increased and respiratory system resistance decreased from early to late ARDS. In group B, static elastance of the respiratory system increased in the late stage. In both groups, PEEP application resulted in PaO_2/FiO_2 ratio and respiratory system resistance improvements. Their study concluded that ARDS patients ventilated using a LPS will show late alteration of respiratory mechanics if they were ventilated before ARDS onset. Their result suggests that history of MV affects subsequent progress of ARDS even when using a LPS.

Pressurized Metered Dose Inhalers and CMVs

Hess, Dillman, and Kacmarek (2003) studied aerosol bronchodilator delivery during MV. They compared the delivery of aerosol pMDI in both pressure control ventilation (PCV) and volume control ventilation. The objective of their study was to determine the effect of T_I and inspiratory flow patterns on albuterol delivery by aerosol during MV using both a nebulizer and a pMDI. Their study evaluated two different levels of lung compliance, two different resistance levels, two different T_I, and three different inspiratory flow patterns. Their study concluded that the nebulizer showed a significant difference in albuterol delivered for T_I, flow pattern, and lung mechanics, which means that albuterol delivery by nebulizer is affected by T_I and inspiratory flow patterns. For the pMDI, there were no significant differences in the amount of albuterol delivered for T_I, flow pattern, or lung mechanics. These results indicate that when pMDI is used, the amount of albuterol delivered is not affected by the inspiratory flow pattern or T_I. Thus, the pMDI is much more stable than a nebulizer when used with CMV.

Another study, conducted by Marik, Hogan, and Krikorian (1999), compared bronchodilator therapy delivery by nebulization and pMDI in 30 mechanically ventilated patients. Marik et al. studied albuterol delivery using a nebulizer, a pMDI, a spacer, and a right-angle pMDI adaptor in MV patients. Urinary analysis was used to measure drug levels. First, five puffs of albuterol were delivered by pMDI with a small volume spacer. Second, five puffs of albuterol were delivered by pMDI using a right-angle adaptor. And third, 2.5 mg of albuterol was delivered by a nebulizer. Their study concluded that the three delivery systems varied markedly in their efficiency of drug delivery to the lung. However, this study confirmed that using a pMDI and spacer is an efficient method for delivering inhaled bronchodilators to the lung.

Dhand et al. (1996) explored the efficacy of pMDIs in mechanically ventilated patients and sought to determine its optimal dose. They studied the response to increasing doses of albuterol administered by a pMDI and cylindrical spacer to 12 mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). In the study, four, eight, and 16 puffs of albuterol were administered at 15-minute intervals. Rapid airway occlusion was performed before and at 5-minute intervals after albuterol administration for 80 minutes. Respiratory mechanics were measured for 60 minutes in another group of seven patients with COPD who received four puffs of albuterol. Their study found a significant decrease in airway resistance (Raw) after the administration of albuterol. The decrease in Raw with four puffs of albuterol was comparable to that observed with cumulative doses of 12 puffs and 28 puffs. The study indicated that the heart rate increased significantly after a cumulative dose of 28 puffs. The decrease in Raw was sustained for 60 minutes in the group that received four puffs of albuterol. They concluded that four puffs of albuterol given by a pMDI and spacer provided the best combination of bronchodilator effect and safety in stable mechanically ventilated patients with COPD.

Dhand and Tobin (1997) discussed inhaled bronchodilator therapy in mechanically ventilated patients. They concluded that the administration of inhaled drugs to mechanically ventilated patients is complicated by deposition of the aerosol particles in the ventilator circuit and the endotracheal tube (ETT). Their study showed that aerosol deposition in the lower respiratory tract of mechanically ventilated patients is lower than that of ambulatory patients. They also indicated that aerosol delivery involves several variables that might affect the delivery to mechanically ventilated patients. These include the type of nebulizer used, actuation of pMDI into an in-line chamber spacer, timing of actuation, ventilator mode, V_T, circuit humidification, and duty cycle. Dhand and Tobin suggested that the bronchodilator effect obtained with four puffs of albuterol from a pMDI is comparable to that obtained with 6 to 12 times the same dose given by a nebulizer and is likely to be far more cost-effective.

Gay et al. (1991) investigated pMDI for bronchodilator delivery in intubated mechanically ventilated patients. They studied the efficacy of two bronchodilator aerosol delivery methods in 18 intubated mechanically ventilated patients with airway obstruction. In the first group, a pMDI was used to deliver albuterol. In the second group, a nebulizer with an updraft inhaler was used to deliver albuterol. The study was a single blind, randomized crossover design. The results revealed that treatment sequence, severity of obstruction, and bronchodilator responsiveness had no effect on relative efficacy. Albuterol caused a small but significant increase in heart rate that was similar following both delivery methods. Gay et al. concluded that bronchodilator aerosol delivery with pMDI provided a viable alternative to nebulizer therapy in intubated mechanically ventilated patients and may result in a cost savings to hospitals and patients.

Ari, Areabi, and Fink (2010) evaluated drug delivery from four aerosol generator devices—jet, vibrating mesh, ultrasonic nebulizers, and pMDI with spacer—at three locations in the circuit; between the ETT and the Y-piece, 15 cm from the Y-piece, and 15 cm from the ventilator in humidified and non-humidified circuits during adult CMV. Their study indicated that the vibrating-mesh nebulizer, ultrasonic nebulizer, and pMDI with spacer were most efficient when positioned 15 cm from the Y-piece with both non-humidified and heated/humidified circuits. They also found that all devices delivered approximately twofold more of the drug under non-humidified than under heated/humidified conditions when positioned 15 cm from the Y-piece and 15 cm from the ventilator. The researchers also found that pMDI deposited a higher proportion of medication than the other aerosol generators in the non-humidified circuit, and when they positioned it between the ETT and the Y-piece under humidified conditions, the percentage of drug delivered sharply decreased. Their study concluded that the optimal drug delivery efficiency during CMV depends on the aerosol generator used, the ventilator circuit, and the aerosol generator position.

Aerosol Delivery With HFOV in a Pediatric Model

Garner et al. (2000) assessed albuterol delivery by pMDI in a pediatric lung model ventilated by HFOV. The researchers used a set-up consisting of a HFOV and a pediatric lung simulator and used ventilator settings, lung compliance, and resistance values that were consistent with a pediatric patient with pulmonary disease. They administered albuterol pMDI with a spacer and actuator, which were placed proximal to the ETT. They placed a circuit filter proximal to the lung simulator and another filter in the circuit's expiratory limb. The filters collected the albuterol exiting the ETT and any albuterol lost in the expiratory limb, respectively. Albuterol administration was repeated at different operating frequencies and T_I using both an

actuator and a spacer. The study showed that albuterol delivery to the lung simulator was <1% of the administered dose regardless of the operating frequency (f), T_I, or use of a spacer or actuator. Albuterol lost in the expiratory limb ranged from 3.28% to 14.89% of the administered dose. The study concluded that albuterol delivery by pMDI in a pediatric model of HFOV is negligible, regardless of the operating f, T_I, or use of a spacer or actuator.

After reviewing the literature, it is clear that ARDS affects lung compliance and Raw due to the etiology of the ARDS disease. Lung compliance is directly related to the severity of ARDS: if the disease gets worse, lung compliance will decrease, and if the patient gets better, the lung mechanics will improve. In respiratory diseases with low lung compliance and high Raw such as ARDS, a lung protective ventilatory strategy with low V_T should be implemented to avoid damaging the lungs. As the literature shows, studies that have compared CMV support and HFOV support in the management of ARDS in adults have shown incongruent results. One review article failed to prove that the use of HFOV improves survival rates among patients with ARDS (Ritacca & Stewart, 2003). Additionally, available evidence does not support the claim that HFOV reduces pulmonary inflammation in ARDS patients (Fessler & Hess, 2007). Another study indicated that using HFOV is as effective and safe as the use of CMV (Derdak, 2003). Overall, the literature indicated that HFOV is an effective lung protective ventilatory strategy and a safe method to ventilate ARDS patients with low lung compliance. Studies have shown that HFOV consistently improves oxygenation and may reduce mortality. Combining this strategy of ventilation with effective delivery of aerosolized respiratory medications could help in improving the condition. During the review of literature, no studies were found that examined the effectiveness of aerosol delivery using pMDI with HFOV in the adult population with ARDS. However, the effectiveness of aerosol delivery with CMV has been explored and

according to studies discussed in this chapter, nebulized albuterol with CMV is affected by the T_I, inspiratory flow pattern, and lung mechanics, including lung compliance and Raw. In comparison, the literature shows that when using pMDI with CMV, the amount of albuterol delivered is not affected by inspiratory flow pattern or T_I, which indicates that pMDI is much more stable when compared to a nebulizer. The literature also indicated that using pMDI and spacer with CMV is an efficient method for delivering inhaled bronchodilators to the lung.

Chapter III

Methods and Materials

Research Design

This in vitro study utilized a quasi-experimental design. The study consisted of three main groups: the unsynchronized CMV, the synchronized CMV, and the HFOV groups. In all groups, two different levels of compliance (20 L/cm H_2O and 40 L/cm H_2O) were used. The methods and materials utilized in this study were used to answer the following questions:

1. What is the amount of aerosol delivered from pMDI at two levels of compliance during HFOV?
2. What is the amount of aerosol delivered from pMDI at two levels of compliance during CMV?
3. Is there any difference in aerosol delivery between HFOV and CMV in a simulated adult lung model with different levels of compliance?
4. What is the difference in aerosol delivery between synchronized puffs and unsynchronized puffs in a simulated adult lung model with different levels of compliance in the CMV groups?

Lung Model

A portable dual test lung (Training/Test Lung [TTL] PneuView systems, dual adult lung simulator, Michigan Instruments, Grand Rapids, MI, United States) was used to simulate the breathing parameters of an adult patient. The TTL simulates adult lungs that can hold a residual capacity typical of adult human lungs. The TTL uses a steel alloy spring, which is stretched

during inflation of the lung, to set and adjust the two levels of lung compliance (20 ml/cm H_2O and 40 ml/cm H_2O). The Raw was simulated by using a fixed-orifice flow resistor that was placed in the two branches of the TTL tubes. A resistance of 20 cm H_2O/L/sec was used in this study. The resistors offer accurate simulation at both upper and lower Raw in exact accordance with the American Society for Testing and Materials standards. The resistors represent the parabolic flow characteristics of the human airway. This resistance was constant during all runs and consistent with the resistance levels reported for adult patients who are candidates for HFOV.

Study Groups

Three groups of tests were included in the study. In the unsynchronized CMV and the synchronized CMV groups, a CMV with a volume control mode (CMV-VC) was used (Respironics Esprit Ventilator Philips/Respironics, Murrysville, PA) with a standard heated wire circuit and a humidification chamber (Fisher & Paykel, Auckland, New Zealand), connected to a 8 mm ETT (Mallinckrodt, PA, United States) that was attached to the TTL lung simulator using a collecting filter (Respirgard II™ Filter, Vital Signs, Totowa, NJ). Figure 1 shows the pMDI spacer and how it is set-up in the study.

Figure 1. The placement of the pMDI spacer in the patient-ventilator circuit in all groups (Modified with permission from Thayer Medical).

The HFOV group of tests used the HFOV (Sensormedics 3100B, Loma Linda, CA, United States) with a HFOV patient-ventilator circuit and a humidification chamber (Fisher & Paykel, Auckland, New Zealand), connected to a 8 mm ETT (Mallinckrodt, PA, United Sates) that was attached to the TTL lung simulator using a collecting filter.

Figure 2 shows the experiment set-up of the study.

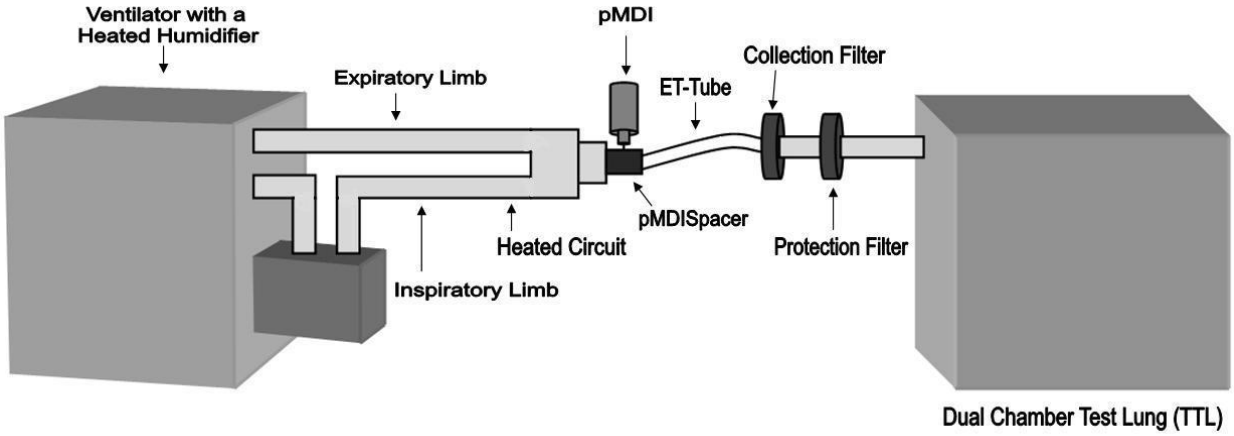

Figure 2. A diagram of the experimental set-up of the study used with CMV and HFOV.

Ventilators Settings

The Unsynchronized and Synchronized CMV groups settings. The ventilator settings used for the CMV group were obtained from the recommendations in Fessler and Hess (2007). They included using an ideal body weight of 75 kg with a delivered V_T of 6 ml/kg on a volume control mode, I:E of 1:1, PEEP 20 cm H_2O, a rate of 25 breaths per minute, and a humidified temperature of 37°C.

The HFOV group settings. The settings used for the HFOV were obtained from the guidelines in Fessler and Hess. (2007).These guidelines were implemented to direct routine clinical care for operating HFOV. Fessler and Hess recommended these guidelines to optimize

lung-protective characteristics of HFOV. The settings they used included a pressure amplitude (delta-P) of 80 cm H2O, a 33% T_I, a f of 5 Hz, and a mPaw of 35 cm H2O, at bias gas flow of 30 L/min at 50% oxygen. The present study used the following HFOV settings: a f of 5 Hz, a T_I of 33%, and a delta-P of 80 cm H_2O. Usually, patients are started with an mPaw either the same or 2 – 3 cm H_2O above the mPaw found during CMV. For the purpose of comparison, this study used an mPaw of 35 cm H_2O. The humidified FiO_2 was set at 50%, the T_I was 33%, and the humidified temperature was 37°C. The delta-P used in this study provided an excellent chest wall movement simulation with the TTL.

Data Collection

The ventilators in all groups were allowed to stabilize for 15 minutes before data collection, and circuit calibration was performed before each test run. The pMDI canister (Proair HFA, TEVA Pharmaceuticals, Horsham, PA) was inserted into a pMDI spacer (Mini spacer, Thayer Medical, uscan, AZ), which was placed between the ETT and the Y adaptor of the ventilator circuit. The collecting filter was placed between the TTL lung and the ETT to collect any albuterol aerosol particles. The collecting filters were replaced with each test. Albuterol delivery was determined by rinsing the circuit filter with 0.1 N HCl. The filter was manually rinsed for 3 minutes to elute the drug. The albuterol concentration was then detected with a spectrophotometer (Beckman UV & Visible Light Spectrophotometer, Fullerton, CA) at 276 nm.

pMDI Delivery

The administration of eight albuterol pMDI puffs (one puff every 15 seconds) was repeated three times, with each ventilator group at each level of compliance (n=3). Each canister

was primed before administering aerosolized albuterol. All drug administration in all runs during the experiment was performed by one investigator to assure consistency.

Unsynchronized pMDI actuations with CMV. In the unsynchronized CMV group, the administration of the pMDI puffs was performed every 15 seconds regardless of the phase of respiration that was occurring at the time. There was no synchronization between the pMDI puffs and the inspiratory phase in this group.

Synchronized pMDI actuations with CMV. In the synchronized CMV group, administration of the pMDI puffs was synchronized with the inspiratory phase by allowing more than 15 seconds between puffs.

pMDI actuations with HFOV. In the HFOV group, the administration of the pMDI puffs was performed every 15 seconds.

Data Analysis

The amount of drug deposited on the filter was quantified as a percentage of the emitted dose. The descriptive statistics including the means and standard deviations were calculated for each condition tested in the study. An independent sample t-test was conducted to evaluate differences in the mean inhaled percentage of the dose delivered by pMDI between two compliance levels. A repeated measure ANOVA was utilized to determine differences among the means for unsynchronized CMV, synchronized CMV, and HFOV. A pairwise comparison among the means for unsynchronized CMV, synchronized CMV, and HFOV at each compliance level was used in this study. All data analysis was performed using the predictive analysis software (PASW) statistics (version 18), and statistical significance was defined as $p < 0.05$.

The research methods were directed by the study questions: What is the amount of aerosol delivered from pMDI at two levels of compliance during HFOV? What is the amount of aerosol delivered from pMDI at two levels of compliance during CMV? Is there any difference in aerosol delivery between HFOV and CMV in a simulated adult lung model with different levels of compliance? What is the difference in aerosol delivery between synchronized puffs and unsynchronized puffs in a simulated adult lung model with different levels of compliance in the CMV groups? The HFOV used in this study was the sensormedics 3100B and it is considered the only adult HFOV available in the market. A lung simulator with ability to control lung compliance and Raw was used in this study. Aerosol deposition was measured using a spectrophotometer and the analysis was performed using PASW statistics (version 18).

Chapter IV

Results

This study compared CMV with HFOV in order to quantify the amount of aerosol delivery to a patient receiving those types of MV modalities. In this chapter, the aerosol deposition results of all groups are shown first, comparing the two levels of lung compliance within the groups. Second, a comparison of the aerosol deposition results between the corresponding levels of lung compliance from all groups will be explored. Table 1 shows the descriptive statistics of the three comparison test groups.

Table 1

The Mean and Standard Deviation of Inhaled Drug Mass Percent Obtained From pMDI With Each Ventilator at Each Level of Compliance (20 ml/cm H_2O and 40 ml/cm H_2O)

Compliance Level (ml/cm H_2O)	**CMV Unsynchronized**	**CMV Synchronized**	**HFOV**
20	3.14 ± 0.62	7.44 ± 0.44	19.80 ± 3.64
40	3.73 ± 1.27	14.37 ± 2.46	35.08 ± 4.20
p value	.506	.009	.009

The Unsynchronized CMV Group

The independent t-test shows that there was no significant statistical difference between compliance level 20 ml/cm H_2O and compliance level 40 ml/ H_2O (p = .506) when there was no synchronization of pMDI delivery with the inspiratory phase in the unsynchronized CMV group. As shown in Table 1, the mean aerosol deposition in the unsynchronized CMV group with a compliance level of 20 ml/cm H_2O was 3.14 ± 0.62 %, while the mean aerosol deposition at a compliance level of 40 ml/cm H_2O was 3.73 ± 1.27%.

The Synchronized CMV Group

The independent t-test shows that there was a significant statistical difference between compliance level 20 ml/cm H_2O and compliance level 40 ml/cm H_2O (p = .009) when there was synchronization of pMDI delivery with the inspiratory phase in the synchronized CMV group. As shown in Table 1, the mean aerosol deposition in the synchronized CMV with a compliance level of 20 ml/cm H_2O was 7.44 ± 0.44%, while the mean aerosol deposition with a compliance level of 40 ml/cm H_2O was 14.37 ± 2.46%.

The HFOV Group

The independent t-test shows that there was a significant statistical difference between compliance level 20 ml/cm H_2O and compliance level 40 ml/cm H_2O (p = .009). The mean aerosol deposition in the HFOV group with a compliance level of 20 ml/cm H_2O was 19.80 ± 3.64%, while the mean aerosol deposition with a compliance level of 40 ml/cm H_2O was 35.08 ± 4.20%.

Comparison of the HFOV, the Synchronized CMV, and the Unsynchronized CMV Groups at Compliance Level 20 ml/cm H_2O

The repeated measures ANOVA results showed that there was a statistical significance (p = .014) in the comparison of the HFOV, the synchronized CMV, and the unsynchronized CMV groups at the 20 ml/cm H_2O compliance level.

As shown in Figure 3, the post-hoc multiple comparisons showed that at the 20 ml/cm H_2O compliance level, there was a significant statistical difference between the unsynchronized CMV group and the synchronized CMV group (p = .011). Comparing the unsynchronized CMV

group and the synchronized CMV group with the HFOV group showed a significant statistical difference (p = .014 and p = .022, respectively).

Comparison of the HFOV, the Synchronized CMV, and the Unsynchronized CMV Groups at Compliance Level 40 ml/cm H_2O

Comparing the level 40 ml/cm H_2O compliance from the HFOV, the synchronized CMV, and the unsynchronized groups using the repeated measures ANOVA showed that there was a statistical significance (p = .01). Post-hoc multiple comparisons showed that at the 40 ml/cm H_2O compliance level, there was a significant statistical difference between the unsynchronized CMV group and the synchronized CMV group (p = .020). Additionally, a comparison of the unsynchronized CMV group with the HFOV group showed a significant statistical difference (p = .010). Furthermore, comparing the synchronized CMV group with the HFOV group showed a significant statistical difference (p = .019). Figure 3 shows the results of the independent t-test and the post-hoc multiple comparisons at compliance levels 20 ml/cm H_2O and 40 ml/cm H_2O.

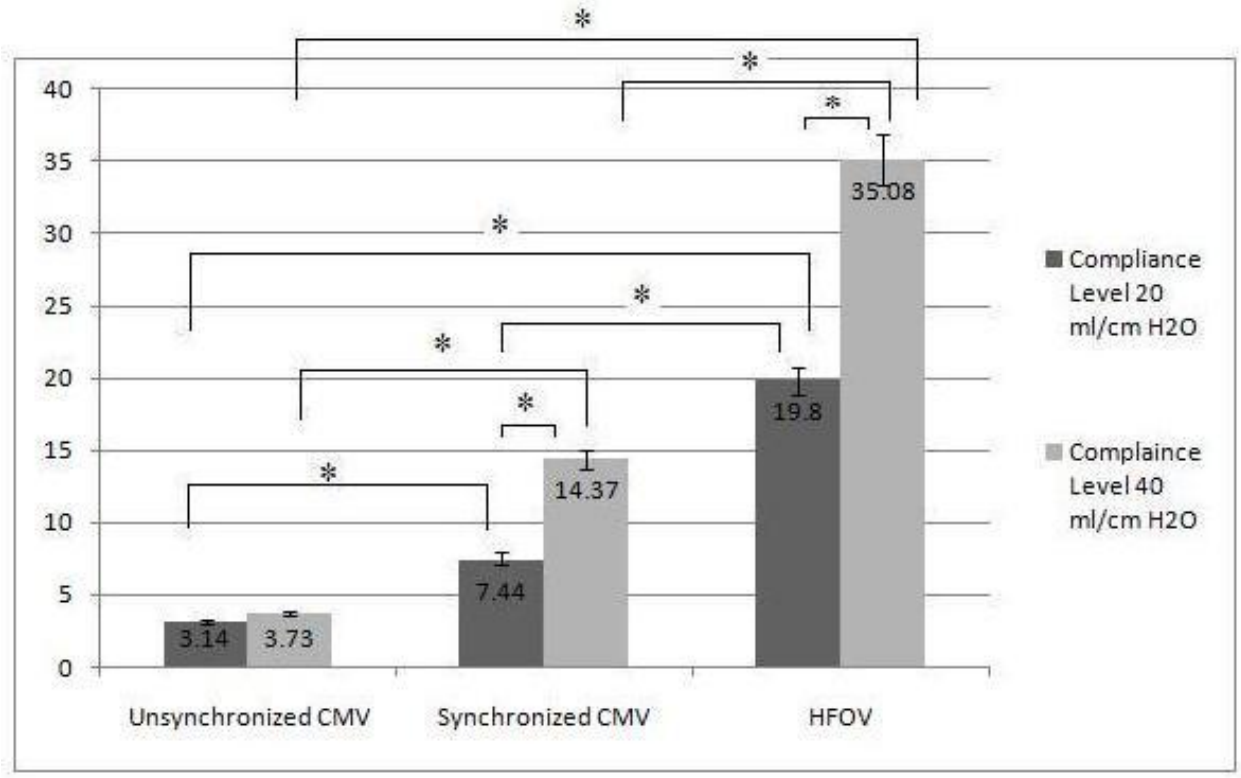

Figure 3. The inhaled dose percent obtained from the unsynchronized CMV, Synchronized CMV and HFOV groups at lung compliance level of 20 ml/cm H_2O and 40 ml/cm H_2O.

Chapter V

Discussion

The main purpose of this study was to investigate the aerosol delivery with HFOV and compare it to the aerosol delivery with CMV at different compliance levels. The questions that were investigated in this study are: What is the amount of aerosol delivered from pMDI at two levels of compliance during HFOV? What is the amount of aerosol delivered from pMDI at two levels of compliance during CMV? Is there any difference in aerosol delivery between HFOV and CMV in a simulated adult lung model with different levels of compliance? What is the difference in aerosol delivery between synchronized puffs and unsynchronized puffs in a simulated adult lung model with different levels of compliance in the CMV groups? The study results revealed significantly different amounts of aerosol deposition when using pMDI albuterol with HFOV when compared with CMV. The following discussion will look more closely at observations made during the study and will evaluate how this study compares with results found in the literature. This chapter concludes with a discussion of the limitations of this study, the future research needed, and a conclusion for this study.

Observations

After all comparisons, this study showed that there was no significant statistical difference between compliance level 20 ml/cm H_2O and compliance level 40 ml/ H_2O in the unsynchronized pMDI delivery during the inspiratory phase of the unsynchronized CMV group. The mean aerosol deposition at compliance level 20 ml/cm H_2O was 3.14 %, while the mean aerosol deposition at compliance level 40 ml/cm H_2O was 3.73 %. This was expected due to the fact that unsynchronization with the inspiratory phase may cause the delivery of pMDI to occur

during the expiratory phase, thus making the aerosol travel away from the patient. This was proven when the synchronization of pMDI delivery during the inspiratory phase in the synchronized CMV group was conducted.

In the synchronized delivery of pMDI during the inspiratory phase of the CMV group, the study showed that there was a significant statistical difference between 20 ml/cm H_2O and 40 ml/cm H_2O. The mean aerosol deposition in the synchronized CMV group with a compliance level of 20 ml/cm H_2O was 7.44%. This is more than double the amount of deposition that occurred when the delivery of pMDI was not synchronized with the inspiratory phase. Furthermore, the mean aerosol deposition at compliance level 40 ml/cm H_2O was 14.37%, which is more than triple the deposition recorded for the unsynchronized CMV group. These results are not surprising because aerosol was delivered during the inspiration phase only, thus ensuring that aerosol particles would be carried towards the lung and not away from it.

Furthermore, the results of this study is different than those of other researchers who synchronized pMDI delivery with CMV (Ari, et al., 2010). Ari and her colleagues had a mean deposition of albuterol sulfate distal to the ETT of 7.6 ± 1.3%. In this study, the mean deposition was 7.44 ± 0.44% and 14.37 ± 2.46% at compliance levels 20 ml/cm H_2O and 40 ml/cm H_2O, respectively. The differences are contributed to factors related to the settings used in both studies including the flow rate, minute ventilation (VE) and I:E ratio. In this study, a flow rate of 50 liters per minute was used while Ari et al. used a flow rate of 60 liters per minute. The slower flow used in this study caused more aerosol deposition to occur. Other factors that contributed to this difference in aerosol deposition between the two studies are the VE and I:E ratio used in both studies. In this study, a VE of 11.250 liters per minute and I:E ratio of 1:1 were used while Ari et al. used a VE of 7.5 liters per minute and I:E ratio of 1:3. The higher VE and I:E ratio used

in this study allowed for more volume of air to be delivered in a single minute thus contributing to the increase in aerosol delivery.

The difference in the amount of deposition between 20 ml/cm H_2O and 40 ml/cm H_2O in both the unsynchronized CMV and synchronized CMV groups can be explained by the status of the lungs. At compliance level 20 ml/cm H_2O, the lung is stiffer and air has more difficulty reaching the lungs. Volumes measured by the ventilator at a compliance level of 20 ml/cm H_2O were lower than those measured during a compliance level of 40 ml/cm H_2O. This finding indicates that aerosol deposition is affected significantly by the level of lung compliance and by the respiratory phase in which the medication is delivered. This result is confirmed by comparing the amount of aerosol deposition that occurs between levels 20 ml/cm H_2O and 40 ml/cm H_2O of lung compliance. In both groups, the amount of aerosol deposition was larger at the compliance level of 40 ml/cm H_2O and smaller at the compliance level of 20 ml/cm H_2O. This can be explained by the amount of air entering the lungs during each level of compliance. Even though expired V_T was not measured during the lab tests for this study, upon observation, the expired V_T was higher when the lung was more compliant and lower when the lung was less compliant. This was consistent in all test runs performed with CMV. These tests confirm that the level of lung compliance has a major impact on the aerosol deposition for the reasons mentioned earlier.

In the HFOV group, there was a significant statistical difference in aerosol delivery between compliance level 20 ml/cm H_2O and compliance level 40 ml/cm H_2O. The mean aerosol deposition in the HFOV group with a compliance level of 20 ml/cm H_2O was 19.80%, while the mean aerosol deposition at a compliance level of 40 ml/cm H_2O was 35.08%. The HFOV group deposition results were extremely higher, and this was not expected. The initial expectation was that there would be minimal deposition, especially when compared to the CMV group, because

HFOV has a continuous bias flow and active exhalation. The continuous and high bias flow causes the development of more turbulent flow in the HFOV circuit, which should cause aerosol deposition to be lower (Niederer, Leuthold, Bush, Spahn, & Schmid, 1994). The active exhalation in HFOV also might contribute to a decrease in aerosol deposition (Herridge & Slutsky, 1996), because it might prevent albuterol particles from reaching the collecting filter placed proximal to the lung simulator, which could enhance the loss in the expiratory limb of the circuit. For these reasons, the expectation was that the deposition of aerosol in the HFOV group would be lower than that of the CMV group.

However, the test results showed the opposite. The deposition of aerosol in the HFOV group was much higher than in the CMV group. The high deposition of aerosol in the HFOV group may be explained by the distinctive flow profiles and gas exchange mechanisms of HFOV. The oscillations generated by the extreme frequencies and the high flow rates in HFOV produce unique flow velocity profiles that cause gas to mix in the airways. These unique flow velocity profiles are responsible for gas exchange and transport in HFOV(Chang, 1984). The flow velocity profiles of HFOV include bulk convection, Taylor dispersion, asymmetric velocity profiles (coaxial flow velocities), pendelluft phenomena, cardiogenic mixing, molecular diffusion, and collateral ventilation (Chang, 1984). The following sections explain these profiles in detail.

***Direct bulk flow*.** This movement has a major role in ventilating the proximal airways. Some alveoli located in the proximal tracheobronchial tree receive a direct flow of inspired air. This results in gas exchange by traditional mechanisms of convective or bulk flow (Krishnan & Brower, 2000).

Longitudinal/Taylor dispersion. Taylor dispersion can result in a mixing of fresh and residual gases along the front of a flow of gas through a tube. According to Pillow (2005) "the longitudinal dispersion of tracer molecules in a diffusive process is augmented by radial transport mechanisms when laminar flow is applied in both the absence or presence of turbulent eddies and secondary swirling motions. Some fresh gas may mix with gas from alveoli, increasing the amount of gas exchange that would occur from simple bulk flow".

Asymmetric velocity profiles. In this profile, air in the center of the airway lumen moves into the lung while air that is close to the outer airway wall moves out toward the mouth. This movement occurs because air closest to the tracheobronchial wall has a lower velocity than air in the center of the airway lumen. This phenomenon is apparent at the airway bifurcations where gas is transported to the alveoli through the center of the airway, while exhaled gas is expired via the outer airway wall. This mechanism promotes axial gas exchange with expired alveolar gas, thus playing an important role in the longitudinal convective transport mechanisms during HFOV (Pillow, 2005).

Pendelluft phenomena. In this profile, gas mixing occurs between adjacent alveoli with incongruent time constants. This means that air swings between lung regions. The varying Raw and compliance in different lung regions cause some regions of the lungs to fill and empty more rapidly than others. This happens especially in regions that are close to each other(Chan, et al., 2007).

Cardiogenic mixing. In this profile, researchers presume that heart contractions contribute to gas mixing, especially in lung regions that are close to the heart. The cardiogenic mechanism is caused by the strong contractions of the heart, which, in turn, cause the lung

regions near the heart to generate air flow (Pillow, 2005). However, the role of cardiogenic mixing during HFOV still needs more investigation (Slutsky & Brown, 1982).

***Molecular diffusion*.** This mechanism occurs in the smallest bronchioles and alveoli, near the alveolocapillary membranes. Molecular diffusion can occur at the alveolar level secondary to the added kinetic energy from the oscillations. This mechanism has an important role in explaining how gas exchange occurs at the alveolar level. In the alveolar regions, gas velocities approximate zero as a result of the total cross-sectional area in this zone. The dominant mechanism for gas mixing in this zone is molecular diffusion, with net transport of gas best described by Fick's law (Chang, 1984; Pillow, 2005).

***Collateral ventilation*.** Collateral ventilation occurs between neighboring alveoli, and it allows air movement between air sacs in the lungs. Researchers presume that this mechanism improves gas exchange during HFOV because of air flowing between asynchronous adjoining airways (Armengol, Jones, & King, 1985; Chan, et al., 2007).

Figure 4 shows the gas transport mechanisms and pressure damping that occur during HFOV. The mechanisms include the direct bulk flow, the longitudinal/Taylor dispersion, the asymmetric velocity profiles, the pendelluft phenomena, cardiogenic mixing, molecular diffusion, and collateral ventilation.

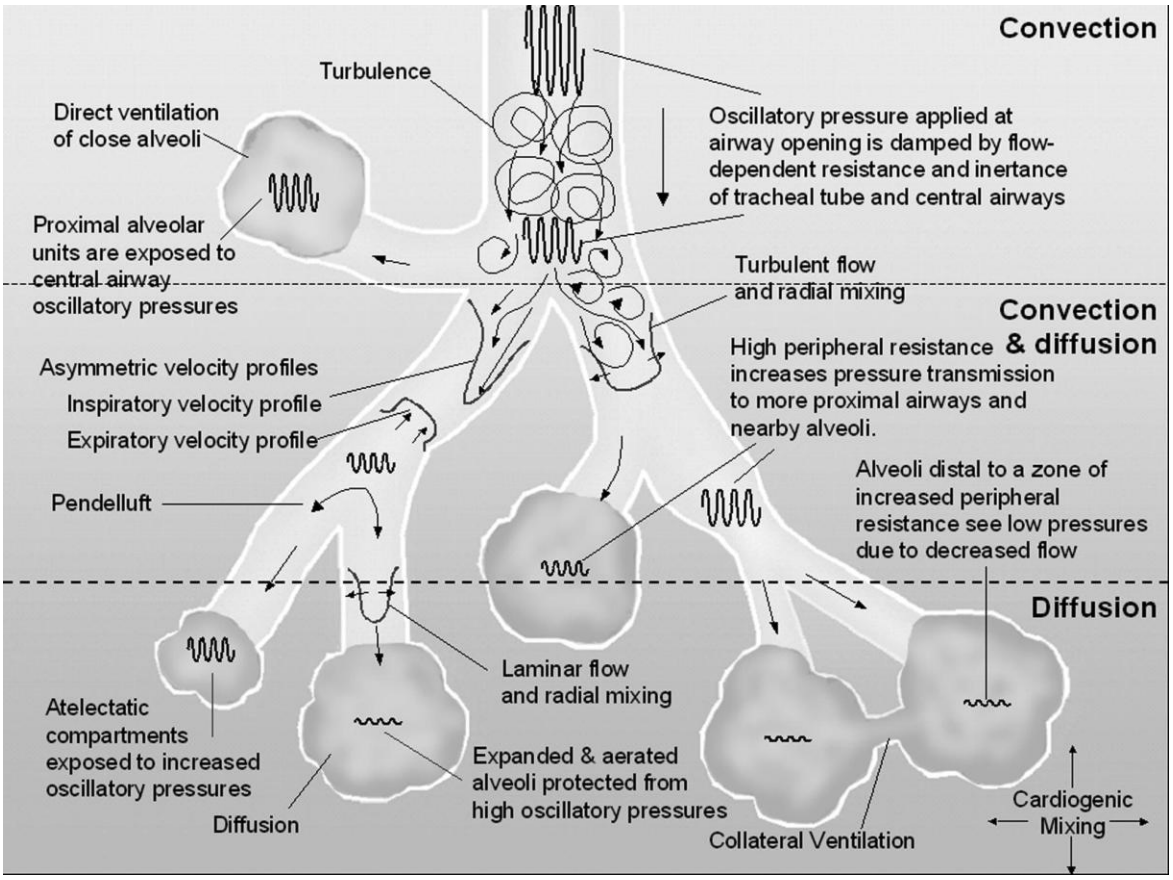

Figure 4. Gas transport mechanisms and pressure damping during HFOV. (Modified with permission from Wolters Kluwer Health).

These distinctive flow profiles and gas exchange mechanisms in HFOV can help us understand how air is transported to and from the lungs and thus help to understand how aerosol particles are carried when administered in HFOV. An additional factor that might contribute to the increase in aerosol deposition found in this study during the HFOV group is the usage of the HFA pMDI and the usage of the dual spray pMDI actuator. The HFA pMDI particle size produced and the geometry of the actuator orifice allow for the formation of a cloud containing particles of the drug that is easier to inspire and thus increase the chances of more drug delivery. Also, the use of the patented dual-spray nozzle delivery system in the pMDI spacer resulted in a bidirectional aerosol plume, thus improving delivery of the pMDI medication. Due to the dual-

spray nozzle, upon actuation of the pMDI canister, the drug plume sprays in both directions, minimizing the amount of drug impinging on the walls of the tubing; thus the evaporation of pMDI propellant is enhanced.

The repeated measure ANOVA comparison of the HFOV, the synchronized CMV, and the unsynchronized CMV groups at the compliance level of 20 ml/cm H_2O and 40 ml/cm H_2O showed statistically significant results. Post-hoc multiple comparisons showed that in compliance level 20 ml/cm H_2O and 40 ml/cm H_2O, there was significant statistical difference among all groups in each correspondent level of compliance. At the level of 20 ml/cm H_2O compliance, significant statistical difference between the unsynchronized CMV group and the synchronized CMV group was found. This can be explained because of the synchronization of pMDI puffs with the inspiratory phase allowed more aerosol to travel to the patient as compared to when the pMDI is not synchronized with the inspiratory phase. Comparing the unsynchronized CMV group with the HFOV group showed a significant statistical difference. Furthermore, comparing the synchronized CMV group with the HFOV group showed a significant statistical difference as well. Again, this can be explained by the distinctive flow profiles and gas exchange mechanisms of the HFOV as explained earlier.

Comparing the compliance level of 40 ml/cm H_2O with the HFOV, the synchronized CMV, and the unsynchronized groups showed a statistical significance. Post-hoc multiple comparisons showed that at a compliance level of 40 ml/cm H_2O, there was a significant statistical difference between the unsynchronized CMV group and the synchronized CMV group. This can be explained because of the synchronization of pMDI puffs with the inspiratory phase allowed more aerosol to travel to the patient as compared to when the pMDI is not synchronized with the inspiratory phase. Also, another reason that contributes to this is the level of compliance

of the lungs. At a compliance level of 40 ml/cm H_2O, the lungs are more flexible and compliant. This allows a higher volume of air to be delivered to the lungs with less pressure compared to the compliance level of 20 ml/cm H_2O. The increased amount of compliance creates less resistance and therefore less turbulent flow and more aerosol deposition. Comparing the unsynchronized CMV group with the HFOV group and the synchronized CMV group with the HFOV group showed a significant statistical difference as well and can be explained by the same reasons illustrated previously in the level 20 ml/cm H_2O compliance.

In the literature, there are no studies published about using aerosol pMDI in adult patients receiving HFOV. Also, there is no study available comparing HFOV and CMV in the delivery of aerosolized medications using pMDI in the adult population. This study was the first to compare albuterol delivery between HFOV and CMV in a simulated adult lung model using different compliance levels.

However, A single study in the literature published by Garner, Wiest, & Bradley (2000) investigated albuterol delivery using pMDI in a pediatric lung model. Their results were different from this study's results. Garner et al. found that the aerosol delivery with HFOV in a pediatric lung model is negligible. The contrasting results between the two studies may be due to lung size: we used an adult lung model in which higher volumes are delivered and they used a pediatric lung model in which lower volumes are delivered. Also, this study used a f of 5 Hz, which is actually lower than the 10 Hz used by Garner et al.

Another factor that might account for the differences in results was our use of a patented dual-spray nozzle delivery system. Garner et al. did not specify if they used a dual-spray nozzle delivery system. Additionally, each study used a different type of pMDI. In this study, an HFA

pMDI was used, while Garner et al. used a CFC pMDI. A final difference between the studies centers on the measurement of aerosol deposition. Garner et al. used a high performance liquid chromatography to measure the amount of aerosol deposition. In this study, a spectrophotometer was used to acquire the amount of aerosol deposition. These differences in study design could account for the incongruent results between this study and that of Garner et al.

Clinical Implications of the Study

The clinical implications of this study include:

1. The delivery of albuterol via pMDI and a spacer is possible with HFOV.
2. Albuterol deposition with pMDI was more than twofold greater with HFOV than with CMV.
3. Synchronizing pMDI actuations during CMV improved aerosol delivery up to fourfold.
4. The level of lung compliance is a factor affecting the deposition of aerosol therapy (Albuterol deposition is increased with better levels of lung compliance).

Limitations

Limitations that might prevent this study from being applied in a clinical situation include the fact that this was an in vitro study. This study does not address the clinical efficacy of albuterol delivery during CMV and HFOV. Also, in this study, a homogenous test lung was used. Human test subjects would show heterogeneous lungs with various lung conditions. Furthermore, this study did not explore the effect of different ventilator settings on albuterol delivery to adults with low lung compliance. Other limitations of this study are the factors that were not studied, such as the use of different pMDI spacers, the use of dry air, the use of different levels of resistance, and the use of different positions of the pMDI delivery within the patient-ventilator circuit.

Avenues for Future Research

The effect of Raw on the delivered aerosol using pMDI should be explored in future studies to determine how aerosol particles from a pMDI are affected by changes in Raw. Also, future studies are needed to explore the effects of changing the ventilator setting on the delivered aerosol particles. Furthermore, future studies should explore the effect of different spacers and different aerosol generators on aerosol delivery during HFOV.

Conclusion

Albuterol deposition with pMDI was more than twofold greater with HFOV than with CMV in this in vitro lung model. Changing lung compliance has an almost twofold impact on aerosol delivery during both modes of ventilation. Synchronizing pMDI actuations during CMV improved aerosol delivery up to fourfold.

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