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The Effects of Aerosol Drug Delivery on Airway Resistance through Heat-Moisutre Exchangers

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ACCEPTANCE

This thesis, THE EFFECT OF AEROSOL DRUG DELIVERY ON AIRWAY RESISTANCE THROUGH HEAT-MOISTURE EXCHANGERS (HMEs), by Matthew Hart 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, certify that this thesis has met all standards of excellence and scholarship as determined by the faculty.

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ABSTRACT

THE EFFECT OF AEROSOL DRUG DELIVERY ON AIRWAY RESISTANCE THROUGH HEAT-MOISTURE EXCHANGERS (HMEs)

By

Matthew Hart

Introduction: The use of heat moisture exchangers (HMEs) is becoming more popular with many institutions delivering aerosolized medications between the HME and the endotracheal tube of patients being mechanically ventilated. When HMEs become saturated resistance can increase which can cause changes that can lead to patient-ventilator dysnchrony, development of intrinsic PEEP, and weaning difficulty. The purpose of this study was to determine the effects of aerosol drug delivery on resistance through heat-moisture exchangers.

Method: An in-vitro model to simulate exhaled heat and humidity from a patient's lungs was developed by connecting the test lung to a cascade humidifier that was placed between the endotracheal tube and the test lung. Temperature (37 ºC) and relative humidity (100%) were held constant through all test runs. Ventilator settings used for the study were as follows: Tidal volume 500 mL, frequency 15/min, PEF 60 L/min, PEEP 5 cmH_2O, bias flow 2 L/min and I:E ratio 1:3.The pressurized metered-dose inhaler (pMDI; ProAir HFA) with a minispacer (Thayer Medical), hand-held nebulizer (HHN; Salter Labs) and placebo (No aerosol generator or medication) were compared. Albuterol sulfate (2.5 mg/3 ml) was administered through continuous HHN and six puffs of albuterol were given from a pMDI equaling one treatment. Neither medication nor aerosol device was used with the placebo group in order to determine the effect of HME on airway resistance during mechanical ventilation. Six aerosolized treatments were given to simulate a patient receiving albuterol every four hours over a twenty-four hour period. While five minutes was allowed between treatments, airway resistance was measured via the ventilator before and after the administration of the placebo, pMDI and HHN, which equaled five-minute intervals.

Data Analysis: Descriptive statistics, dependent t-tests, one-way analysis of variance (ANOVA), repeated measures ANOVA and post-hoc multiple comparisons were utilized for the data analysis of this study, using SPSS version 16.0. A p-value<0.05 was considered significant.

Results: There is a linear time effect with means of airway resistance increasing overtime not only with the placebo but also with the pMDI and nebulizer. At the end of all treatments, the means of resistance with the placebo, pMDI and nebulizer were 9.31 $cmH_2O/L/sec$, 9.37 $cmH_2O/L/sec$ and 11.20 $cmH_2O/L/sec$, respectively. While no significant difference was found between the placebo and the pMDI ($p=0.452$), the nebulizer significantly increased airway resistance when compared to placebo ($p=0.004$) and the pMDI ($p=0.02$).

Conclusion: Airway resistance increases with use of the placebo, pMDI, and JN groups. Aerosol generators showed a greater increase in resistance when compared to placebo with the greater increase in resistance by HHN.

THE EFFECT OF AEROSOL DRUG DELIVERY ON AIRWAY RESISTANCE THROUGH HEAT-MOISTURE EXCHANGERS (HMEs)

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ABBREVIATIONS

HME	Heat-moisture exchanger
pMDI	Pressurized metered-dose inhaler
PEEPi	Intrinsic PEEP
COPD	Chronic obstructive pulmonary disease
FRC	Functional residual capacity
VAP	Ventilator associated pneumonia
ANOVA	Analysis of variance

CHAPTER I

INTRODUCTION

Providing heat and humidity to mechanically ventilated patients is important. The upper airway usually serves this purpose but since this is bypassed in intubated patients receiving mechanical ventilation, other methods to heat and humidify the airway must be used. Historically institutions have used heated humidifiers for intubated patients. But over the past years many hospitals have switched to using heat moisture exchangers (HME). They provide adequate heat and humidity without having to monitor the temperature or water levels of a conventional heated-humidifier. But removing the heated humidifier and replacing it with an HME can cause some ventilatory changes such as an increase in dead space from the HME device and changes in resistance occurring during both inspiration and expiration.

The HME is placed between the endotracheal tube and the wye-adapter of the patient-ventilator circuit. It acts by using the natural heat and moisture that occurs during exhalation. This heat and moisture is trapped in this device so when inspiration occurs, the air passes through the device and becomes humidified. By its very placement within the patient-ventilator circuit one would expect that any added moisture, lung secretions or aerosol administration, would contribute to airway resistance. Research shows that over time, as the HME becomes more saturated, the airway resistance does increase. Previous research has assessed the amount of time an HME should be used. The researchers compared changing them everyday vs. once a week. The results showed that once a week was sufficient and did not put the patient at risk for nosocomial infections (Thomachot et al, 2002). Other research shows that as airway resistance increases, insufficient humidity is produced leading to reduced internal diameter of the endotracheal tube from viscous secretions especially during extended mechanical ventilation (Villafane MC, Canella G, Lofaso F, et al. 1996). This research then begs the question, would inline aerosol delivery affect airway resistance through the HME?

Patients who require mechanical ventilation receive breathing treatments, especially those who have preexisting lung disease. Bronchodilators can be given by either nebulizer or metered dose inhaler. These patients usually receive bronchodilators every 4 to 6 hours. Is there any difference seen in resistance through an HME when aerosol treatments are given inline through the patient-ventilator circuit? Although research in the past has focused on efficiency of humidification and filtration more research is now being conducted to ascertain results of mechanical affects such as those created from aerosol administration through the patient-ventilator circuit.

With several different ways of delivering aerosols, it is best to see which is most efficient between nebulizers and metered-dose inhalers because if airway resistance is affected by aerosol administration then deposition will be affected as well. There is no clear-cut winner in the nebulizer versus pMDI debate. O' Riordan et al. (1994) reported a lung deposition of 15.3% when using a nebulizer while Harvey et al. reported a lung deposition of 30% when using a nebulizer with a spacer. Rau, Harwood, and Groff (1992) reported a 32.1% drug deposition from a pMDI in a test lung while Fuller and colleagues showed only a 6.33% lung deposition in mechanically ventilated patients. When comparing nebulizers to pMDIs directly in a study, the results still vary. Some research shows a difference of approximately 4% greater deposition with pMDIs than with nebulizers (Fuller, Dolovich, Posmituck, Pack, & Newhouse, 1990). Other research suggested that nebulizers could provide close to 15% more deposition than pMDIs (Diot, Morra, & Smaldone, 1995). As one can see, the research varies.

It is important to study HMEs because they may be kept within the patient-ventilator circuit for days even though this is not recommended (White, 2005). However, with hospitals trying to cut costs, this is one small area that may be overlooked resulting in the extended use of HMEs. During this timeframe, the patient may receive dozens of aerosol treatments inline with the patient-ventilator circuit. If these do saturate the HME, resistance through the ventilator

circuit could increase. It is expected that resistance will increase both during inspiration and expiration potentially causing patient-ventilator dysnchrony. An increase in resistance is not as big a concern during inspiration since the ventilator can compensate for this. If a patient is receiving volume control ventilation, the ventilator will guarantee that the patient will receive that set volume by increasing the delivery pressure (Manthous and Schmidt, 1994). Dual control modes such as pressure regulated volume control ventilation will also respond by increasing driving pressure to maintain set tidal volume. In either case since the HME is a low resistance device a slight increase in pressure will result. Nevertheless, an increase in inspiratory resistance has shown to extend weaning from the ventilator as well as causing respiratory muscle fatigue (Shapiro, Wilson, Casar, Bloom, and Teague, 1986).

On the other hand as resistance increases during expiration, this could possibly lead to dynamic pulmonary hyperinflation of the patient's lungs as intrinsic positive end-expiratory pressure (PEEPi) increases. This occurs by air leaving the lungs during expiration being slowed by the airway resistance since expiration is a passive process. With this decrease in the speed of expiration, the patient will not have time to exhale completely before another breath is delivered (Iotti, Olivei, and Braschi, 1999). This may be more of a problem for non-COPD patients than it is for COPD patients. COPD patients can show PEEPi due to bronchial collapse during expiration during mechanical ventilation. The collapse does not allow all the air to flow out of their lungs thus resulting in hyperinflation (Conti et al., 1990). In the COPD patient PEEPi may help to stint the airways open helping to reduce collapsed airways an d allowing some of the trapped air to be removed. An increase in expiratory resistance could prove beneficial to COPD patients, as it is a simulated version of pursed lip breathing or an expiratory retard. Other problems associated with increased expiratory airway resistance can arise such as the patient experiencing difficulty triggering the ventilator leading to an increase work of breathing.

The findings of this bench study will suggest which aerosol generator is the best to use in mechanically ventilated patients with HMEs to reduce resistance during mechanical ventilation. Thus, quantifying resistance through HMEs from a pMDI or a nebulizer for patients using HMEs will give a better understanding for clinicians caring for critically ill patients. Therefore, the purpose of this study is to measure the impact of pMDI and nebulizer administration on resistance in mechanically ventilated patients using an HME.

The questions that were asked in this study are:

1. What is the effect of HME on airway resistance?
2. What is the effect of each aerosol generator (pMDI or jet nebulizer) on airway resistance during mechanical ventilation when an HME is being used?
3. To what extent does the weight of HMEs change after the administration of placebo, pMDI, and jet nebulizer?

This is significant in today's healthcare climate where patient outcomes and resources to achieve these outcomes are under intense scrutiny.

CHAPTER II

REVIEW OF THE LITERATURE

A literature review was performed using terms relevant to resistance through HMEs. Aerosol delivery using nebulizers and pMDIs was also researched. The databases used were Medline, Science Direct, Proquest, Ebsco Host, Web of Science, and PubMed. From an exhaustive search, the research questions were formulated to investigate how resistance changes through HMEs when aerosolized medication is introduced in the patient-ventilator circuit.

Heat-Moisture Exchangers

In a study performed by Cohen, Weinberg, Fein, & Rowinski (1988) the risk of occlusion of endotracheal tubes with the use of HMEs was examined. The study investigated the use of HMEs in 170 patients over an 8-month period. Over this time period, the researchers found that HMEs became occluded 15 times. This was compared to just one occlusion in patients who received humidity by a cascade humidifier. Also, the patients who had occlusions required minute volumes greater than 10 L/min and a FiO2 greater than 0.40. It was concluded at that time that the use of HMEs should not be used outside the operating room. More recent research does not agree with this research. Today, improvements in HMEs have occurred and their use is more widely accepted.

Conti et al. (1990) looked at the effects of HMEs on COPD patients. The purpose of the study was to find if PEEPi could occur with COPD patients if a HME was used inline during mechanical ventilation. Resistive properties were taken into consideration. These resistive properties were thought to decrease expiratory flow, which would create a PEEPi effect. It was also believed the duration of HME use would effect PEEPi. A group of COPD patients were tested for PEEPi levels and functional residual capacity levels before the use of a HME. These levels were then recorded after the insertion of an HME to the patient-ventilator circuit as well as

twelve hours after insertion. There was no significant increase of PEEPi or FRC after twelve hours of use.

Chiaranda and colleagues published a similar article in 1993. They explored flow-resistance through HMEs after 24 hours of use. It was noted that an increase in resistance through the HMEs was seen in 83% of the 96 patients tested. However, the increase was insignificant. A greater increase in resistance was seen in four patients who had heavier secretions. The researchers suggested that the use of HMEs should be used with caution especially in those patients with heavy secretions (Chiaranda et al., 1993).

Researchers looked at how HMEs could change the work of breathing of spontaneously breathing patients who had no history of obstructive lung disease. Two different HMEs were used to show the difference. Work of breathing was greater with the larger HME. There was no significant difference between the two when respiratory rate, PEEPi, rapid shallow breathing index, and arterial CO2 and O2 partial pressures were measured. The patient had to make a greater inspiratory effort, however with the larger HME although no evidence of discomfort was noted. The smaller HME did not increase the patient's effort and was concluded to be the preferable choice between the two HMEs (Catalina, Bardini, Latronico, & Candiani, 1994).

Pelosi et al. (1996) performed a study that showed the effects of HMEs on minute ventilation, ventilatory drive, and work of breathing in respiratory failure patients. They compared two different HMEs. The researchers found that the use of HMEs should be carefully used in such patients. An increase in minute ventilation of 2.6 L/min was seen in group one and a 1.4 L/min increase in the other group. PEEPi increased by 3.2 cm H_2O in one group and a 2.6 cm H_2O increase in the other. An increase in work of breathing was also noted. This was recorded as a 5.7 joule/min increase in one group and a 6.1 joule/min increase in the other group. A decrease

in gas exchange was not noted however as minute ventilation increased to balance the added deadspace caused by the HME.

The mechanical effects of HMEs were also tested by Iotti et al. (1997). The study used ten mechanically ventilated patients. Three different conditions were tested: a heated humidifier, an HME without a filtering function, and an HME with a filtering function. The patient's ventilatory drive, $P_{0.1}$, work of breathing, and arterial blood gases were all recorded. It was noted that an increase in inspiratory resistance, ventilation requirements, and PEEPi were seen. Minute ventilation also increased as a result of the increased dead space. Alveolar ventilation remained the same. A mild increase in PEEPi was noted. This increase in PEEPi was compared to a previous study that was done with COPD patients. The authors suggest that the HME acts as an expiratory resistor. The suggestion was made that this resistor actually helps COPD patients by preventing bronchial collapse. However, this is not a beneficial effect for patients with normal lungs.

Morgan-Hughes, Mills, & Northwood (2001) tested the resistance through three HMEs after they became wet. The three types of HMEs tested were a composite felt filter and cellulose exchanger (Dar Hygrobac-S), a composite pleated ceramic membrane and cellulose exchanger (Dar Hygroster), and a pleated ceramic membrane (Pall BB22-15). The study was performed by distributing 5 mL of normal saline into the patient side of the device. The researchers then tested to see if any of the saline spilled out. This process was continued until the maximum volume of saline was found that did not spill out. This was known as the "retention volume." The cellulose exchangers retained the most volume with 25 mL of saline. The Pall BB22-15 did not retain any saline. Airflow resistance was then tested using a BiPAP machine. Changes in inspiratory pressures were measured as changes in airflow resistance. The Dar Hygrobac-S displayed a pressure drop of 5.7 cm H_2O when 15 mL of saline was added to it. The Dar Hygroster showed a drop of 5.1 cm H_2O when 15 mL of saline was added. The Pall BB22-15 showed the least change

in pressure with only a 3.7 cm H_2O drop after 15 mL was added. These results provide information about how much resistance changes from HMEs that become saturated.

Thomachot et al (2002) compared the use of HMEs over 7 days versus 1 day. Subjects were 155 patients receiving mechanical ventilation for longer than two days. The patients were divided into two groups: one group had their HME changed everyday and the other group was changed every week. During the study, no HMEs became occluded and nobody had to be switched to a heated humidifier. Peak inspiratory pressures and mean airway pressures were no different between the two groups which shows that airway resistance did not change over a week's time. The average peak inspiratory pressure of the 1-day group was 35.3 mmHg at the beginning of the study and 29.2 mmHg at the end. The 7 days group's peak inspiratory pressures were 34.7 mmHg at the beginning and 28.3 mmHg at the end. The incidence of ventilator-associated pneumonia between the two groups was also explored. The group that had their HMEs changed everyday had a higher rate of VAP with 26% developing VAP. The seven-day group had a 14% VAP rate. It was also found that it was less expensive changing the HMEs every week instead of everyday, which would be expected.

A study published in 2004 by Jaber and colleagues compared the use of heated humidifiers and HMEs. Over a 10-month period all patients that needed mechanical ventilation for more than 48 hours were included in this study. The researchers divided the 10 months into two 5-month periods. The first group used a heated humidifier. During the second 5 months, an HME was used. During both periods, the inner volume of the endotracheal tube was measured as well as the resistance. This was done three times a week. Thirty-six patients were watched over the first period and twenty-six during the second. At the midway point of the study, there was no difference in inner volume reduction between the two groups. However, at the end of the study, the HME group had a greater reduction in the inner volume in the endotracheal tube. The change in resistance was then measured and no difference was found between the two groups. At the end

of the study, there was a greater resistance seen in the HME group than the heated humidifier group. It was suggested that the reason for the increased resistance was due to the reduction of inner volume of the endotracheal tube because of accumulation of bronchial secretions and biofilm.

A study by Turnbull et al (2005) tested 14 different types of HMEs. Each HME was tested under wet conditions to assess which design contributed to airway obstruction. The wet condition was achieved by adding saline to the HME. The change in pressure required to deliver the same volume was measured. The test was stopped when saline was ejected from the HME back into the endotracheal tube. The ceramic pleated-membrane filters performed the best because it did not retain any saline. The maximum inspiratory pressures ranged from 1.9 cmH_2O to 4.5 cmH_2O. The cellulose-paper-based filters performed the worst. This type retained the most amounts of saline and required higher pressures to deliver tidal volume. The pressures ranged from 6.7 cmH_2O to 13.4 cmH_2O. This study concluded that the type of HME used makes a difference in how much moisture is absorbed therefore affecting the airway resistance.

Drug Deposition Using Aerosol Generators

Nebulizers

A study performed by MacIntyre et al (1985) explored the differences in drug deposition between intubated and nonintubated patients. They looked at seven patients who were receiving mechanical ventilation because of respiratory failure. Aerosolized medication was delivered in-line with the endotracheal tube. The medication was radiolabelled so deposition could be measured. The researchers had a total of eleven scans (four of the seven patients were studied twice). The control group included three non-intubated patients. The control group received the same aerosolized medication delivered by mouthpiece. The intubated group showed a more “heterogeneous” distribution of the aerosol. Also, tracheal deposition was greater in the intubated

group than the non-intubated group. The amount of drug deposited in the trachea of the intubated group was 1.6% compared to 0.3% in the nonintubated group. Aerosol deposited in the lung parenchyma was 2.9% in the intubated group as compared to 11.9% deposition in the lung parenchyma of the nonintubated group. The intubated group had no deposition in the stomach while the nonintubated group had 7.3%. Other findings showed no significant changes in heart rate between the two groups. The authors suggest that the reason less drug was deposited in the intubated patients was because some of the drug is deposited inside the endotracheal tube. According to this study, the intubated patients required higher inspiratory pressures and could not effectively give a breath hold due to their abnormal lung condition. The nonintubated group had normal lungs. They stated that the intubated patients had less distribution to the parenchyma because of their airway disease not allowing the aerosol to reach these areas. It was also shown that the intubated patients had more aerosol deposition in the central airways.

Another study performed by O'Riordan, Palmer, and Northwood (1994) looked at factors that would affect aerosol delivery such as nebulizer type, volume fill, ventilator settings, and humidity. They tested nebulizer delivery to mechanically ventilated patients under optimal conditions. They chose seven patients who had a tracheostomy. A radiolabelled aerosol was used filling the nebulizer with 2 mL of saline to dissolve the radiolabelled substance. It was then placed in the inspiratory limb, twelve inches from the wye-adaptor. The ventilator nebulizer function was used to deliver aerosol during inspiration only. Several variables were investigated. First, the percent inhaled was found to be 30.6%. The deposition in the tracheostomy tube during inspiration ranged from 1.8% to 3.0%. Lung deposition was 15.3% while 12.6% was exhaled from the lungs. The suggestion was made that drug deposition was optimal because of the findings of their bench study. A 2 mL volume fill was found to be the best volume to use. Also, no humidity was used. This is a good form of research because it tests the validity of in-vitro

studies. It would be interesting to see the researchers reverse these optimal parameters to see how this affects deposition in living subjects.

Harvey et al (1995) described an in-vivo study that was performed as a comparison with the in-vitro studies that have already been done to see if the use of a spacer in the patient-ventilator circuit improves aerosol delivery when using a nebulizer. The in-vitro model showed that aerosol delivery to a test lung was 30% greater with a spacer. For the in-vivo model, ten patients were given aerosolized treatments that had been radiolabelled. A gamma camera was used to measure the amount of drug that was deposited in each patient's lungs. Their results showed that drug deposition was less in the left lung of all patients. The research also showed that the ventilation to the left lung was reduced. The use of a spacer increased lung deposition by 36%. This correlates well with the in-vitro model. However, in this study the author never stated how far away the spacer was placed from the endotracheal tube.

Metered-Dose Inhalers

Kroger and Bishop (1989) tested the efficiency of pMDIs given through endotracheal tubes. This particular study found that a portion of drug exits back out of the endotracheal tube before it could deposit in the lungs. The amount that exits depends on the size of the endotracheal tube. The results showed that 3.0% exited out of a 6.0 mm ETT while 6.5% exited out of a 9.0 mm ETT. The researchers also discussed how timing of dose actuation effects deposition, which is consistent with other research. Coordination of actuation with inhalation is the optimal for lung deposition. The conclusion was made that pMDIs deliver a great deal of drug to the trachea, which is also consistent with other research.

In 1992, a study done by Rau, Harwood, and Groff tested the efficiency of a reservoir device for pMDIs during mechanical ventilation. In this in-vitro study, three different models were tested. The first model used a pMDI directly on the endotracheal tube using an actuator

adaptor. The second used an inline chamber (Monaghan AeroVent) placed on the inspiratory limb just before the wye-adaptor. The third used the AeroVent placed between the endotracheal tube and the wye adaptor. Five pMDIs were used with each method and the same researcher made each actuation to reduce variability. A total of ten actuations were made each one 30 seconds apart. A spectrophotometer was used to determine drug delivery. The results showed significant differences among the three methods. The pMDI directly on the endotracheal tube delivered 7.3% of the medicine. The method with the reservoir on the inspiratory limb showed a 32.1% deposition while the reservoir placed between the endotracheal tube and the wye-adaptor showed 29% deposition. The use of a reservoir showed a significant increase in the amount of drug delivered yet the positioning of the reservoir did not show a significant increase statistically ($p>0.05$) although the reservoir on the inspiratory limb did show greater deposition.

Fuller, Dolovich, Turpie, & Newhouse (1994) compared drug deposition from a pMDI in mechanically ventilated patients. The main purpose of the study was to compare four different ways of delivering the medicine with four different spacers/chambers. Device (A) was a 167 mL holding chamber, device (B) a 700 mL holding chamber, device (C) a nonchamber device, and device (D) a nonchamber device on the end of the endotracheal tube. The study was done in-vivo using a radiolabelled aerosol. Setups A, B, and C were placed on the inspiratory limb of the patient-ventilator circuit, 22 cm away from the endotracheal tube. Forty-eight patients were selected with 18 patients using device A, 11 using device B, 8 device C, and 11 device D. They found that a chamber device significantly increases deposition. Device A provided 5.53% deposition, device B 6.33% deposition, device C had 1.67% deposition, and device D had 3.89% deposition. The larger chamber device, B, had greater deposition than the smaller chamber device A. It is interesting that the device directly on the endotracheal tube delivered more drug than the inline device on the inspiratory limb.

Comparing pMDIs and Nebulizers

In 1990, Fuller et al tested the differences in aerosol distribution between nebulizers and pMDIs in mechanically ventilated patients. The study involved twenty-one participants that were receiving mechanical ventilation. The patients were divided into two groups with one receiving 4 puffs of radiolabelled fenoterol by pMDI while the other group received 1.75 mL of radiolabelled fenoterol by nebulizer. Only twenty patients finished the study with 9 receiving the pMDI and 11 the nebulizer. However, two from each group were excluded due to past pneumonectomy or lobectomy. The pMDI group received 4 puffs at 5-minute intervals between each actuation. An inline chamber was used that was placed 15 cm from the endotracheal tube. The nebulizer was breath actuated and lasted for 15 minutes. The pMDI showed to have a greater deposition with 5.65% being deposited compared to 1.22% from the nebulizer. Peak inspiratory pressures were noted and there was not a significant change seen in either group that may have affected the outcome of the study.

In 1991, Gay and colleagues compared the efficacy of albuterol using a pMDI and a nebulizer. The study included twenty stable patients who required mechanical ventilation and who were ordered bronchodilator therapy. Albuterol 2.5 mg was delivered using a nebulizer while three puffs from a pMDI were used. The three puffs totaled 270 μg. Each pMDI actuation was done one minute apart with a breath hold of "several seconds." The study showed that patient response to a delivery modality depended on the patient. Three patients responded only to the nebulizer treatment while one only responded to the pMDI treatment. Response was defined as a change in airway pressure and change in expiratory flow. The study showed no significant increase in post-bronchodilator therapy flow compared to baseline flow between the two delivery methods. One limitation of the study was that the pMDI was actuated between the wye adaptor and the endotracheal tube. This would possibly cause a lot of the drug to be deposited on the inside of the endotracheal tube. Furthermore, the study explored the cardiovascular effects

between the two methods and cost. There was no difference in cardiovascular side effects and they found it was less expensive to use pMDIs instead of nebulizers.

Diot, Morra, & Smaldone (1995) did another comparison study using an in-vitro model. The design was structured to look at the affects of humidification, the type of device used to actuate the pMDI, and the synchronization of the pMDI with inspiration. The nebulizer was filled with 3 mL of normal saline and 2.5 mg of albuterol. It was allowed to run until empty, which lasted 40 minutes. The deposited percentage was 45, 41, and 40% respectively for the three different types of nebulizers used. The pMDI delivering a 90 μg/puff with the Aerovent spacer and humidity showed 15.4% deposition as compared to 25.1% deposition with no humidity. The Marques adaptor was then used and was less efficient showing only 7.2% deposition with no humidity. This holds true that humidification reduces deposition because it caused aerosolized particles to become larger and thus rainout. Diot et al stated synchronizing actuation with inspiration was important. If actuation was not synchronized with inspiration, a decrease of 35% in deposition was seen.

Another in-vitro study evaluated the effect of ventilator mode on aerosol bronchodilator delivery with nebulizers and pMDIs during mechanical ventilation (Hess, Dillman, & Kacmarek, 2003). Aerosol was collected on a filter placed between the wye adaptor and the test lung and measured using spectrophotometry. The ventilator was set in either VCV (volume control ventilation) or PCV (pressure control ventilation). A tidal volume of 600 mL, a respiratory rate of 15/min., and a PEEP of 5 cmH20 were all set. Several ventilator parameters varied. Inspiratory times of 1 and 2 seconds were examined, constant flow and descending flow were compared in VCV, and no humidity was provided to the circuit. The nebulizers were filled with 1 mL of 0.5% albuterol, which was dissolved in 3 mL of normal saline. Four puffs of albuterol were given through a spacer with 15 seconds occurring between each actuation. The test lung was also set at two variables. One was set at high compliance and high resistance while the other was low

compliance and low resistance. The nebulizer showed a significant difference between the two inspiratory times. Deposition by nebulizer was greater during PCV with high compliance and high resistance. Also the longer inspiratory time allowed for greater deposition with the nebulizer. Unlike the delivery of medication by nebulization, the researchers found that pMDI delivery does not depend on inspiratory time. Deposition by pMDI was also the same regardless of which mechanical ventilation mode was used.

After reviewing the literature, the use of inline-aerosolized treatments may have an effect on resistance through a HME. The HME will become saturated with drug as well as humidity from the patient. This may cause an increase in resistance on inspiration and expiration. Any increase during inspiration should not cause a detrimental effect, as the ventilator will compensate for resistance increases during inspiration. However, the increase in resistance across the HME during expiration may cause a more significant problem. As the literature has shown, expiratory resistance can lead to dynamic pulmonary hyperinflation causing the lungs to develop PEEPi. Again this may not be as much of a problem for COPD patients but can be for those without COPD.

CHAPTER III

METHODS

Instruments

An in-vitro lung model was constructed using a rubber test lung to simulate mechanically ventilated patients. An 8.0 mm ID endotracheal tube was connected to a standard ventilator circuit (Allegiance Healthcare Corporation, McGraw Park, IL) while using the Respironics Esprit Ventilator (Philips/Respironics, Murrysville, PA).

The rubber test lung was connected to a cascade humidifier (Covidian-Puritan Bennett, Boulder, CO). The humidifier was used to simulate the heat and humidity from the lungs of a patient. A digital hygrometer/thermometer (Control Company, Friendswood, TX) was used to measure the heat and relative humidity. It was held constant at 37° C with 100% relative humidity. The ventilator was checked prior to experimentation. All test measurements passed successfully. The test lung was checked routinely prior to each experiment to ensure all connections were tight and that the lung compartments were moving properly. The heat-moisture exchanger (Hygrobac S Filter/HME; Nellore, Boulder, CO) was positioned between the wye-adapter and the endotracheal tube. The HME was positioned in a vertical position above the endotracheal tube to prevent condensation from entering the HME. The endotracheal tube was connected to the other opening of the cascade humidifier. Standard ventilator settings were used with a tidal volume of 500 ml, respiratory rate of 15/min, peak inspiratory flow of 60 L/min, PEEP of 5 cmH_2O, a bias flow of 2 L/min, and an I:E ratio of 1:3.

Data Collection

Airway Resistance: Three placebo runs were performed first. First, the weight of the HME was measured before placement in the patient-ventilator circuit. It was then placed between

the wye-adapter and the endotracheal tube. Resistance was recorded right after placing the HME in the patient-ventilator circuit. After every five minutes the resistance was recorded. Resistance values began to plateau after fifteen minutes. This was used during further experimentations to determine that the HME had become adequately saturated. After the test run, the HME was measured for comparison.

The pMDI was placed between the endotracheal tube and the HME (See Figure 1). Six puffs of the Proventil HFA pMDI (Schering-Plough, Kenilworth, NJ) were actuated with each test. A MiniSpacer (Thayer Medical Group, Tucson, AZ) was used to connect the pMDI to the ventilator circuit.

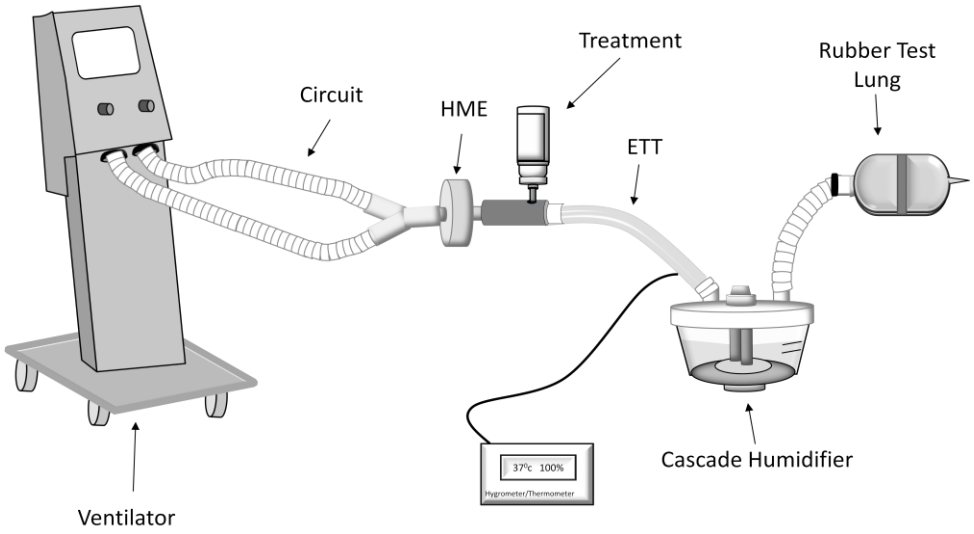

Figure 1. Placement of pMDI within patient-ventilator circuit.

The pMDIs were primed before experimentation by shaking and actuating three times per the company's instructions. The canisters were removed from the actuators and positioned in the spacer. They were not disconnected from the spacer between treatments. Actuation was synchronized at the beginning of inspiration, per manufacturer's instructions. A total of one minute was allowed between pMDI actuations. This was done to allow the valve to refill. The same operator actuated each pMDI dose to prevent operator error. Six puffs of albuterol were

actuated through each pMDI to be evaluated. This was then repeated six times to simulate a patient receiving a treatment every four hours over a 24-hour time span. This was considered one run. A total of three runs were conducted.

The nebulizer was filled with albuterol sulfate (2.5 mg/3 ml). The nebulizer was placed in the patient-ventilator circuit between the endotracheal tube and the HME using a T-piece (See Figure 2).

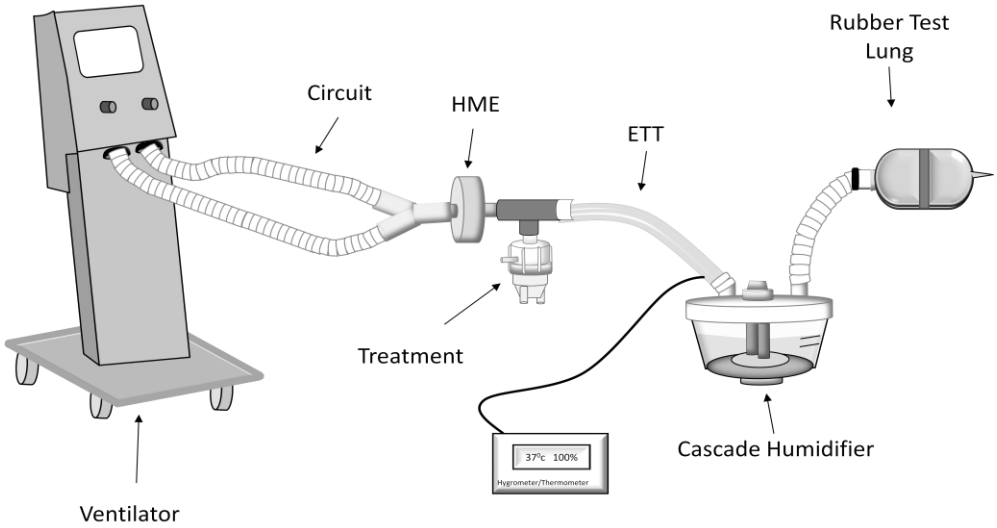

Figure 2-Placement of nebulizer within patient-ventilator circuit.

The nebulizer was allowed to run continuously using 8 L/min of flow. The flow was turned off one minute after the first sputter was heard. Five minutes were allowed between each treatment. A total of six treatments were given to simulate a patient receiving a treatment every four hours over a 24-hour time span. This was considered one run. A total of three runs were performed.

Using the resistance value that appears in the patient data section of the ventilator monitor, the resistance data was collected. The initial resistance was recorded after placement of a new HME. Fifteen minutes were allowed to pass before the first treatment was given to allow the

resistance through the HME to plateau. The treatments were given and the resistance value was recorded after each treatment. Each method of drug delivery was tested a total of 18 times. The exact same protocol was followed for each test. The entire system was checked for correct positioning, ventilator settings, temperature, relative humidity, and order prior to testing.

Weight of HME: Before each experiment was conducted, the weight of the HME was weighed and recorded. At the end of each experiment, it was weighed again. The change in weight was compared. This also gave an indication of just how saturated the HME became and how weight is correlated to airway resistance.

Data Analysis

Data analysis was performed using SPSS (version 16.0). Several different types of data analyzes were used. First, descriptive statistics were utilized. The mean airway resistance was computed after each aerosol generator. The standard deviation of each was calculated as well as the minimum value, the maximum value, and the number (n) of each experiment was reported. Second, repeated measures ANOVA were used to show trending among the placebo, pMDI, and nebulizer groups. Third, to compare the resistance measurement among the placebo, pMDI, and nebulizer, one-way ANOVA was performed. Fourth, a dependent t-test was used to compare the before and after weights of the HMEs. Dependent t-test was also used to compare the first resistance recording with the last, using placebo, pMDI, and nebulizer.

All experiments were run over a two-day period. The data collection went smoothly with no problems. The data was analyzed and compared. The data will be reported in the next chapter.

CHAPTER IV

RESULTS

A series of tests were performed to show how aerosol delivery to a patient receiving mechanical ventilation with a HME placed in-line of a patient-ventilator circuit would affect airway resistance through that HME. In this chapter, the changes in airway resistance will first be analyzed followed by weight analysis.

Airway Resistance Analysis

As stated earlier, HMEs are known to increase resistance through the patient-ventilator circuit when they become saturated. The first step was to quantify this using repeated measure ANOVA (See Table 1).

Table 1. Mean airway resistance ($cmH_2O/L/sec$) after fifteen minutes and thirty minutes among the three testing groups with standard deviations.

	Initial	15 min	30 min
Placebo	9.02 ±0.17	9.21 ±0.26	9.23 ±0.09
pMDI	9.14 ±0.00	9.14±0.03	9.23±0.10
Neb	9.10±0.08	9.48±0.04	9.91±0.26

When a new HME was placed in-line, the mean airway resistance was 8.99 $cmH_2O/L/sec$. A linear increase was noted after each five-minute interval. The initial airway resistance was 9.02 cm $H_2O/L/sec$ with the final airway resistance value being measured at 9.23 cm $H_2O/L/sec$.

The pMDI resistance values were also analyzed using repeated measures ANOVA. After 15 minutes of saturation was allowed, the first treatment was given. The mean resistance after the

first treatment was 9.14 $cmH_2O/L/sec$. A linear increase was also seen after each treatment with the final mean resistance being 9.37 $cmH_2O/L/sec$.

Using repeated measures ANOVA, analysis of the resistance values with the nebulizer was done. The same protocol was followed as with the pMDI. The initial mean resistance following the first treatment was 9.10 $cmH_2O/L/sec$. A linear increase was again seen with the resistance making a greater increase. The final resistance value was 10.50 $cmH_2O/L/sec$.

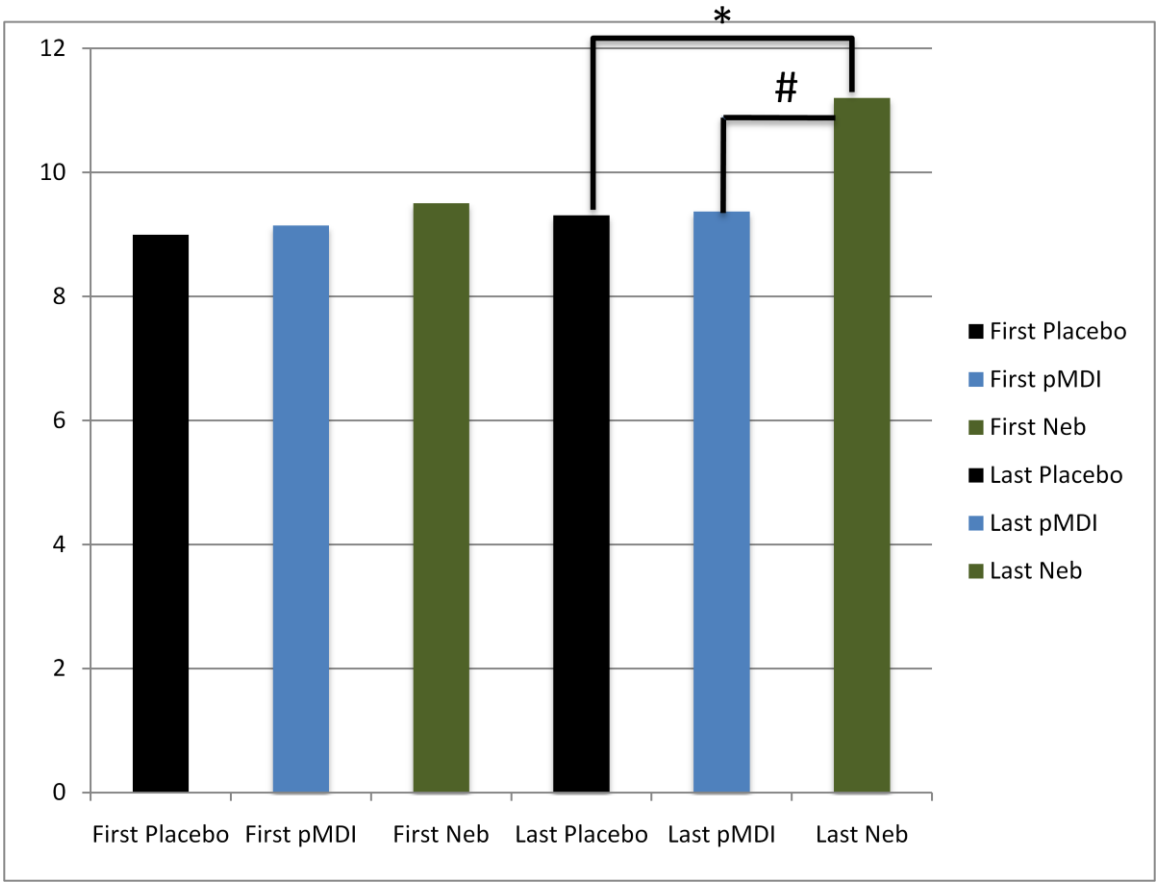

Figure 3-Mean resistance among the three groups at the time of placement in-line with the patient-ventilator circuit and after treatments had been given. *=$p<0.05$ between the placebo and nebulizer. #=$p<0.05$ between the pMDI and nebulizer.

One-way analysis of variance (ANOVA) was used to compare the resistance values among the three groups. When aerosol generators were compared to placebo, a significant increase in resistance was observed only with nebulizers. pMDI did not show a significant increase in resistance with a p-value=0.452. The nebulizer however showed significance in the increase of resistance with a p-value=0.004. Nebulizers showed a significant increase in resistance compared to pMDI with a p-value=0.020.

Weight Analysis

The weight of the HME was also taken into consideration. The HME was weighed before being placed in-line and after the treatments were given. The mean placebo weight before experimentation was 27.92 g. with a weight of 28.68 g. following experimentation. Dependent t-test results showed an insignificant increase in weight with a p-value=0.976. The mean weight of the HMEs used before pMDI experimentation was 27.85 g. This was compared to 28.69 g. after the treatments were given. A significant increase in the weight with a p-value=0.001 was found. The mean weight of new HMEs placed before the nebulizer treatments were 27.71 g. This was compared to a weight of 32.23 g. following the treatment. This was a significant increase with a p-value=0.001.

ANOVA analysis was done to compare the weights among the three groups. No significance was seen on initial airway resistance when comparing placebo with the pMDI, and nebulizer groups with a p-value=0.541. This showed uniformity in the HMEs prior to experimentation. However, when comparing placebo weight after giving treatments with pMDI and nebulizers, a significant increase was seen only with nebulizers. pMDI did not show a significant increase with a p-value > 0.05. Nebulizers showed a significant increase when compared to placebo and pMDI with p-values both being 0.001.

The data, as stated earlier in this chapter, suggests that an increase in airway resistance is noted through HMEs when aerosolized medication is used inline with the patient-ventilator circuit. The next chapter will discuss the finding and observations further.

CHAPTER V

DISCUSSION

After the running of tests and analysis of the data, it is noted that airway resistance does increase through HMEs with the delivery of aerosolized medication. The following discussion will look closer at observations during the study, how this study compares with the literature, and limitations of this study.

Observations

After analyzing the data, several observations were noted. The first observation made was that the continuous nebulization increased the resistance through the HME the greatest. This was expected. In this study, aerosol is continuously being introduced into the patient-ventilator circuit. Having this occur allows the aerosol to be exhaled back into the HME during expiration. This caused the HMEs used with the continuous nebulizer to become heavier than the HMEs used with pMDIs. This is because the HMEs became more saturated with albuterol from the continuous nebulizers than from the pMDIs. This does not mean that airway resistance did not increase with the pMDIs; the change was just not as great. It was also noted that the resistance during continuous nebulization increased from 11 cm H_2O/L/sec to 13 cm H_2O/L/sec. This may cause a problem for a patient while receiving the treatment. A continuous treatment lasts about ten minutes with much of the aerosolized drug being exhaled into the HME especially in those patients with longer expiratory times. As more drug saturates the HME, the patient could experience an increase in inspiratory demand (measured in terms of joules/liter, pressure-time product, etc.) as well as greater resistance to expiration as seen in the development of PEEPi and dysnchrony with the ventilator. This may not be as much of a problem with HMEs that are changed every 24 hours (as recommended by the manufacturer). In those patients that have HMEs in place for longer than 24 hours, greater resistance changes may be seen with the delivery

of in-line medications. Patients undergoing T-piece trials for weaning and are receiving aerosol administration may fail the trial because of the added resistance load of the HME. These patients may be categorized as difficult or failure to wean. Additionally, those patients being weaned by pressure support ventilation may require higher levels of pressure support due to a significantly higher inspiratory effort required because of PEEPi. In patients that are difficult or potentially difficult to wean such as COPD patients, it may be best to change the HME every 24 hours or remove the HME and use a heated humidifier.

Another observation was that the heavier the HME, the greater the resistance. The HMEs that became the heaviest have more drug that is being deposited on them. This would cause resistance through the HME to increase. The heaviest HME was the one used with continuous nebulization.

An increase in delivered tidal volume was also observed during continuous nebulization. This was due to the added flow from the nebulizer through the patient-ventilator circuit. It was a significant increase almost doubling the exhaled tidal volume. A slight increase in resistance was seen with each actuation of the pMDI as well. It was not as great an increase as the nebulizer and the duration of the increase was very brief. Resistance increased more when actuations were timed perfectly with inspiration. This could be a problem especially in those patients with ARDS receiving low volume, lung protection therapy. It is recommended that when delivering medication by jet nebulizer to use the ventilator nebulizer function. The ventilator that was used did not have this option available. This was not a concern during this experiment however. The main objective was to see if aerosol drug delivery would affect resistance through an HME. It does. The question of whether breath actuated nebulization using the ventilator nebulized function would affect the resistance as well is for another study.

Comparisons With Literature

The findings of this study correlated with the literature. Chiaranda and colleagues in 1993 showed that an increase in resistance was seen in 83% of the 96 patients they tested. However they found the increase insignificant. This agrees with the data from this study. No significant change in resistance was seen with just heat and humidity being delivered. However, with nebulization, a significant increase was seen. This factor was not introduced in Chiaranda's study. Conti et al, in 1990 stated that a significant increase in PEEPi was not seen after twelve hours of use with HMEs in COPD patients. Again, this study did not take into account any aerosolized medications or twenty-four hours of administration. With the greater increase after nebulized drug delivery and keeping the HME in for greater than twelve hours, PEEPi could possibly become a factor. Iotti et al, stated in 1997 that an increase in PEEPi was seen with regular use of HMEs. In that study, the suggestion was made that COPD patients might benefit from the expiratory resistance created by HMEs. The findings of this study show that the greater resistance seen after aerosolized drug delivery could be more detrimental to patients who do not have COPD.

Limitations

There were several limitations to this study. One limitation was that it was an in-vitro study. Different patient lung changes may be seen in-vivo. In this study, a test lung was used which represents a homogenous lung. Human test subjects would show heterogeneous lungs with various lung conditions. Another limitation was time. Treatments were given on a Q4 hour basis and only five minutes was allowed between treatments. Greater resistance changes may be seen if four hours were allowed to pass between treatments. The fact that only continuous nebulization was used is also a limitation of the study. The ventilator that was used did not have a nebulizer function. The effects of drug delivery were the only focus, not which mode of nebulization would

affect resistance the greatest. The last limitation is that only one type of HME was used. This was due to cost.

With these limitations come questions that can be answered at a later time. Does an in-vivo model affect the resistance any differently than an in-vitro model? Does a study that is done over a 24-hour time span make a difference in the resistance? What change, if any, will be seen in resistance with breath-actuated nebulization as opposed to continuous nebulization? Do different types of HMEs affect resistance in similar ways?

Conclusions

Clinicians should be cautious when using HMEs and delivering aerosolized medication. Aerosol drug delivery is very helpful to the patient as are HMEs. Clinicians need to be conscious of the resistive effects that the aerosolized medication may have on the HME. Whenever a patient is being administered medications in-line, close monitoring of airway resistance, PEEPi, and work of breathing changes should be a priority especially in patients with HMEs in place longer than twenty-four hours.

The purpose of this study was to measure the impact of the pMDI and nebulizer administration on airway resistance in mechanically ventilated patients using an HME. Heat-moisture exchangers increase airway resistance during mechanical ventilation. The natural humidity from a patient's lungs saturates the HME making it more resistive to flow. Aerosolized medications placed in-line within the patient-ventilator circuit increases resistance across the HME greater than humidity alone. When pMDIs are compared to nebulizers, nebulization increases the resistance greater than pMDI.

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