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Early View

Original article

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DELIVERED DOSE WITH JET AND MESH NEBULIZERS DURING SPONTANEOUS BREATHING, NONINVASIVE VENTILATION, AND MECHANICAL VENTILATION USING ADULT LUNG MODELS

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Summary of "Take Home" Message: Delivered dose distal to the trachea of an adult lung model is similar or greater with mechanical ventilation than noninvasive ventilation and spontaneous breathing, suggesting that artificial airway may provide a similar or better pathway for medical aerosols to the lung. While the delivery efficiency of the mesh nebulizer mesh nebulizers was greater than the jet nebulizer, It differed between mechanical ventilation, noninvasive ventilation, and spontaneous breathing. Aerosol deposition was low with JN and similar between the modes of ventilation tested in this study. Further clinical studies are warranted.

DELIVERED DOSE WITH JET AND MESH NEBULIZERS DURING SPONTANEOUS BREATHING, NONINVASIVE VENTILATION, AND MECHANICAL VENTILATION USING ADULT LUNG MODELS

ABSTRACT

What is the delivered dose with jet (JN) and mesh nebulizers (MN) during spontaneous breathing (SB), noninvasive ventilation (NIV), and mechanical ventilation (MV) using an adult lung model with exhaled humidity (EH)?

Albuterol sulfate (2.5mg/3mL) delivery with JN (Mistymax10) and MN (AerogenSolo) was compared during SB, NIV, and MV using breathing parameters (Vt=450 mL, RR=20 bpm, I:E=1:3) with three lung models simulating EH. A manikin was attached to a sinusoidal pump via a filter at the bronchi to simulate an adult with SB. A ventilator (V60) was attached via a facemask to a manikin with a filter at the bronchi connected to a test lung to simulate an adult receiving NIV. A ventilator-dependent adult was simulated through a ventilator (Servo i) operated with a heated humidifier (Fisher&Paykel) attached to an ETT with a heated-wire circuit. The ETT was inserted into a filter (RespirgardII). A heated humidifier was placed between the filter and test lung to simulate EH (35±2˚C, 100% RH). Nebulizers were placed at the Y-piece of the inspiratory limb during MV and positioned between the facemask and the leak-port during NIV. A mouthpiece was used during SB. The delivered dose was collected in an absolute filter that was attached to the bronchi of the mannequin during each aerosol treatment and measured with spectrohoptometry.

Drug delivery during MV was significantly greater than NIV and SB with MN (p=0.0001) but not with JN (p=0.384). Delivery efficiency of MN was greater than JN during MV (p=0.0001), NIV (p=0.0001), and SB (p=0.0001).

Drug delivery with MN was greater and differed between MV, NIV, and SB, while deposition was low with JN and similar between the modes of ventilation tested.

Keywords: Drug delivery, aerosols, nebulizers, mechanical ventilation, noninvasive ventilation, spontaneous breathing, and adults.

INTRODUCTION

Aerosolized medications are commonly used in the treatment of patients with pulmonary diseases. For many decades, researchers have attempted to understand variables impacting aerosol drug delivery with different nebulizers and levels of ventilatory support.[1-21] However, little has been done to identify the best methods of delivering aerosolized medications to different patient populations such as ventilator-dependent patients, spontaneously breathing adults, and patients receiving noninvasive ventilation. Assumptions are commonly made that patients with spontaneous breathing inherently receive more drugs than patients receiving ventilatory support. One rationale has been that there is a greater aerosol loss in artificial airways or breathing through the mask than through the mouthpiece. Also, the clinical decision to optimize aerosol delivery is often arbitrary, and the exact drug dosages are used with different nebulizers and patient populations. With increasing recognition of inefficient aerosol therapy and its consequences in healthcare, identifying strategies to optimize aerosol delivery with various nebulizers in different patient populations remains a high priority.

McIntyre[22] reported radiolabeled aerosol deposition with jet nebulizers (JN) of 12% via mouthpiece with spontaneous breathing subjects compared to 3% via endotracheal tube during mechanical ventilation with heated humidifier. Since this seminal paper in 1985, the

assumption has been that inhaled dose is greater with spontaneous breathing than mechanical ventilation, especially with jet nebulizers. The lower dose with MV was due to aerosol passing through the endotracheal tube.

Since that time, there have been no reports of direct comparison of aerosol delivery efficiency with mechanical ventilation, noninvasive ventilation, and spontaneous breathing under similar breathing parameters. Although previous research has found many factors that affect aerosol delivery to patients, no single approach has been determined as the best one. Also, many patients transition between spontaneous breathing, noninvasive ventilation, and mechanical ventilation. Although aerosol therapy is done based on the clinician's judgment and experience, it is not individualized based on the patient's needs and the aerosol device used for therapy. If patients receiving aerosol therapy, there is a tendency to apply the same dose across interfaces. While the same drug dosages are used for all patient populations and nebulizers, there are no reports that compared the delivery efficiency of jet and mesh nebulizers between various modes of ventilation. Also, previous in vitro studies reported up to a 40% reduction in aerosol drug delivery with heated humidified ventilator circuits.[23-26] However, the lung models with dry or heated/humified circuits that were used in these studies do not simulate active heating and humidity of exhaled gases. Whether the patient is ventilator dependent or spontaneously breathing, they exhale heated and humidified gas close to body temperature. Our previous work showed that in vitro lung models without exhaled humidity overestimate aerosol drug delivery compared to models using exhaled humidity in simulated spontaneously breathing tracheotomized patients as well as simulated ventilator-dependent patients using heat moisture exchangers (HMEs).[2-4, 27] However, to date, there is no study that evaluates

the impact of exhaled humidity on aerosol drug delivery across different types of ventilation. Therefore, the purpose of this study is to quantify and compare aerosol deposition with jet (JN) and mesh (MN) nebulizers during spontaneous breathing (SB), noninvasive ventilation (NIV), and mechanical ventilation MV using an adult lung model with exhaled humidity. Understanding differences in delivery efficiency between MV, NIV, and SB could provide guidance as to how to adjust doses between types of ventilation to improve consistent targeted drug delivery to the lungs of patients.

MATERIAL AND METHODS

Study Design: As shown in Figure 1, drug delivery with JN (Mistymax10, Carefusion, Yorba Linda, CA, USA) and MN (Aerogen Solo, Aerogen Ltd., Galway, Ireland) was compared during SB, NIV, and MV using three different lung models with exhaled humidity.

Figure 1. Scheme of the study design, including each nebulizer and modes of ventilation.

Lung Models: To simulate a mechanically ventilated adult, a ventilator (Servoi, Getinge, Wayne, NJ, USA) was operated with a heated humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) attached to an 8 mm ID ETT via a heated-wire circuit (Figure 2A). The ETT cuff was inflated in a 15 mm ID/22 mm OD adapter, which was then inserted into the housing of an absolute filter (Respirgard II, Vital Signs, Totowa, NJ, USA), fixing the tip of the ETT approximately 1 cm from the filter media. A heated humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) was placed between the collecting filter and test lung to simulate exhaled humidity (35±2˚C, 100% relative humidity) as with all lung models used in this study, with exhaled temperature and humidity measured with Digital hygrometer/thermometer (Model 485, Dwyer, Michigan City, Indiana) between the humidifier and collecting filter.

Breathing parameters were set at Vt:450 mL, RR:20 bpm, I:E ratio 1:3. Figure 2 shows the lung models used in this study.

As shown in Figure 2B, an adult receiving noninvasive ventilation was simulated using a turbine ventilator (V60 Phillips Healthcare, New Jersey, USA) with an unheated single-limb circuit incorporating a fixed leak that was attached via a nonvented oronasal face mask (AF541, Respironics Inc, Murrysville, PA). The mask was securely attached to the face of an adult teaching manikin, with a collecting filter placed at the level of the bronchi distal to the trachea and connected to a passive test lung via a heated humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand).

To simulate a spontaneously breathing adult, a teaching manikin with a collecting filter was placed at the level of the bronchi and connected via a heated humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) to a breathing simulator (Figure 2C).

Figure 2. Lung models used in this study (A. Mechanical Ventilation Lung Model, B. Noninvasive Ventilation Lung Model, and C. Spontaneous Breathing Lung Model)

Data Collection and Analysis: During MV, aerosol devices were placed in the inspiratory limb proximal to the Y piece with a T-piece provided by the manufacturers, while all aerosol devices were positioned at the patient end of the single-limb circuit between the fixed leak port and face mask during NIV. In SB, a mouthpiece was sealed to the mouth of the mannequin, and the nares were sealed during aerosol therapy. The JN was used with a simple T-piece provided by the manufacturer, with a 6-inch length of 22 mm ID corrugated tubing attached to the other end of the T-piece, serving as a reservoir. The MN was attached to a valved chamber (Aerogen Ultra, Aerogen Ltd, Galway, Ireland) with supplementary oxygen of 6 L/min. The JN was also

operated at 6 L/min with oxygen continuously until sputter, while the MN was run until the end of nebulization. The condensation in the circuits was cleared before each run, and the lung model was stabilized for a few minutes before the start of each experiment.

Albuterol sulfate (2.5 mg/3 mL) was placed into the reservoir with both JN and MN, and each experiment was run five times (n=5). The delivered dose was collected in an absolute filter that was attached to the bronchi of the mannequin during each aerosol treatment and measured with spectrohoptometry. On completion of each experiment, the collecting filters were capped and labeled for analysis. The drug deposited on an absolute filter was eluted with 10 mL solution (20% ethanol with 0.1 N HCl). The amount of albuterol depositing in the collecting filter was analyzed via spectrophotometry (276 nm) and expressed as the total fraction of the nominal dose placed in each nebulizer. Descriptive statistics were used to calculate the means and standard deviations for each component of the total inhaled drug mass obtained with JN and MN during SB, NIV, and MV. Differences in means between the inhaled mass for the two nebulizers and three modes of ventilation were compared with a two-way factorial analysis of variance. Paired t-test was used to compare JN and MN at each mode of ventilation. When the p-value was less than 0.05, differences were considered statistically significant.

RESULTS

Effect of Modes of Ventilation on Aerosol Deposition: Table 1 shows the percent of albuterol dose (mean ±SD) delivered distal to the trachea airway of the models with JN and MN during MV, NIV, and SB in adults.

Regardless of the type of nebulizer used, aerosol drug delivery during MV trended higher than NIV and SB. Aerosol delivery with MN was greater with MV than NIV or SB

(p=0.0001); however, there was no significant difference in aerosol delivery with MN between NIV and SB (p=0.411). In contrast, no difference between the three modes of ventilation was found when the JN was used in this study (p=0.384).

Effect of Nebulizers on Aerosol Deposition: As shown in Table 1, the delivery efficiency of MN was greater than JN during MN (p=0.0001), NIV (p=0.0001), and SB (p=0.0001). Regardless of modes of ventilation tested in this study, using MN for aerosol therapy increased drug delivery > 3-fold compared to JN.

Table 1. Mean (±SD) percent dose delivered with jet and mesh nebulizers during mechanical ventilation, noninvasive ventilation, and spontaneous breathing in adults.

	Mechanical Ventilation	**Noninvasive Ventilation**	**Spontaneous Breathing**	***p-value***
Jet Nebulizer	6.80 ± 1.55	6.10 ± 0.34	6.12 ± 0.26	*0.384*
Mesh Nebulizer	23.16 ± 0.67	18.36 ± 1.06	17.29 ± 1.69	*0.0001*
p-value	*0.0001*	*0.0001*	*0.0001*	

DISCUSSION

In this study, we simulated identical adult breathing parameters during aerosol administration with MV, NIV, and SB to compare inhaled dose distal to the trachea with both jet and mesh nebulizers. This is the first study to show that aerosol delivery via MV with adult breathing parameters was greater than or equal to NIV and SB with both jet and mesh nebulizers, with similar delivery efficiency between NIV and SB.

Our results are consistent with prior reports with delivery efficiency of mesh nebulizers up to 3-fold greater than JN during MV, NIV, and SB. In our previous in vitro research on the

influence of nebulizer type in a simulated adult lung model during mechanical ventilation[28], the inhaled dose obtained with the jet nebulizer was 4.7% as opposed to 5.2% in this study. Aerosol delivery with the mesh nebulizer was 13.4% in our previous research in contrast to 23%. The discrepancy in our findings can be explained by the differences in our models and peak inspiratory flow rates (PIF) we used in both studies. In the current study, we used two heated humidifiers with the lung model. While one utilized to simulate exhaled humidity, the other one provided heated humidity during mechanical ventilation. The PIF was set at 60 L/min in our previous research, compared to the lower 45 L/min in this study.

Using a similar ventilator-dependent adult lung model with exhaled humidity, our previous research evaluated the effect of HMEs on aerosol deposition during MV.[2] The findings of this study showed that aerosol delivery with MN was 10.6% as opposed to 5.4% with JN in the control group, where no heated humidifier was used in the circuit. Also, the placement of HME between the patient and the nebulizer reduced aerosol deposition by 5.91% and 2.80% with MN and JN, respectively. In our current study, we used a heated humidifier in the ventilator circuit that explains at least part of the differences in our results.

Alquaimi et al. determined the efficiency of jet and mesh nebulizers during noninvasive ventilation.[5] Using an in vitro lung model without exhaled humidity, they reported an aerosol deposition of 13% and 29% with jet and mesh nebulizers, respectively. In contrast, our results showed lower delivery efficiency with JN(6%) and MN (18%). The difference again may reside in the exhaled humidity simulated with our current model. Regardless of the type of nebulizers used, aerosol delivery during noninvasive ventilation was higher than with the exhaled humidity model was used in this research. In each iteration of the model, exhaled gas was heated to

simulate gas conditions leaving the lungs. This has been shown to reduce some of the higher inhaled doses previously reported with models that use unconditioned exhaled gas.[12, 23, 24, 26, 29]

McIntyre et al.[22] radiolabeled aerosol JN reporting 12% lung deposition via mouthpiece with SB compared to 3% with intubated subjects receiving MV with heated humidifier. Since this seminal paper in 1985, the assumption has been that inhaled dose is greater with SB than MV, especially with JN. The lead author (personal communication) posited the lower dose with MV to aerosol passing through the endotracheal tube. In our study, the ETT may provide a similar to or better pathway for aerosol than the upper airway model. In his study, McIntyre placed the nebulizer in the inspiratory limb of the ventilator circuit. A previous study with similar adult parameters and placement of nebulizer in the inspiratory limb of a heated humidified circuit reported the delivered dose of 3.61 +/- 0.2% with the jet nebulizer.[12] Based on the lower PIF in our current study, we would expect a higher inhaled dose with the jet nebulizer consistent with in vitro model reported by Dugernier et al.[30]

Galindo-Filho et al. evaluated aerosol drug delivery during noninvasive ventilation in patients with asthma exacerbations.[31] They reported no improvement in a radio-aerosol pulmonary deposition during noninvasive ventilation compared to the control group that had nebulization alone. This is consistent with our findings of no significant difference in aerosol deposition between noninvasive ventilation and spontaneous breathing.

More recently, Galindo-Filho et al.[32] comparing the delivery of radiolabeled aerosol during NIV with jet and mesh nebulizers in moderate to severe COPD patient-reported lung

dose of 3.14% with JN vs. 12.05% with MN. Their lower reported lung dose than our in vitro reports is likely due to our use of collecting filters which are known to overestimate inhaled dose, and filters do not allow for exhalation of aerosol that occurs in vivo. However, during NIV, aerosol deposition with MN was > 3-fold greater than jet nebulizer with both in vivo and in vitro reports.

In a radio-aerosol scintigraphy study, Franca et al.[33] compared pulmonary deposition with a jet nebulizer in 13 healthy subjects. They reported lower lung deposition during noninvasive ventilation compared to spontaneous breathing. However, their measures of respiratory rate, tidal volume, minute ventilation, and inspiratory flow during spontaneous breathing were substantially lower compared to parameters with noninvasive ventilation. Differences in breathing parameters may explain lower aerosol delivery in spontaneous breathing. In contrast, we used the same breathing parameters for all conditions of this study.

In an in vitro study of spontaneously breathing tracheotomized adults with active exhalation, we found a substantial difference in aerosol deposition obtained with JN (6.61%) and MN (17.67%) in room air.[4] Although there is a discrepancy between the results of this study and our current research, it is important to note that we used an adult lung model with tracheostomy in the previous study. Also, the breathing parameters that were used in our previous research (Vt: 400 mL, RR 20 bpm, and I:E ratio 1:2) may account for the differences in our results.

Dugernier et al.[34] with SPECT-CT comparison of lung deposition in 6 healthy subjects reported lung dose of 5.2 % with JN vs. 34.1 % with MN and chamber. Both studies report similar deposition with both nebulizers. Previously, we compared JN and MN in simulated

spontaneously breathing adults and found that the delivery efficiency of the jet nebulizer was 7% while the mesh nebulizer was 35%.[7] In contrast, the aerosol deposition obtained in our current study was 6% and 18% with JN and MN, respectively. Although we used the same type of nebulizers in both projects, different flow rates were used to operate the nebulizers. For instance, the jet nebulizer was operated at 10 L/min in our previous research as opposed to 6 L/min in this study. Similarly, the MN (Aerogen Ultra) was run at 6 L/min in the current project as opposed to no oxygen flowrate in the Alcoforado et al. study. We previously reported that the inhaled dose was 2-fold higher with the MN and chamber without oxygen flow than with oxygen flow of 6 L/min. The simulated exhaled humidity in our model combined with differences in breathing parameters used in both projects likely contributed to the discrepancy in our results. Consequently, our findings appear to be consistent with these two in vivo studies of spontaneous breathing.

Limitations and Future Research

First, we used only one set of adult breathing parameters in this study that does not represent the array of ventilator settings, patterns, and modes in clinical practice. Second, only one type of JN and MN was used in this research, and their performance on different modes of ventilation should not be generalized to other nebulizers within each type. Similar studies with other aerosol devices such as pMDIs are needed. Also, it is well known that small particles are exhaled by patients while they are captured on the collecting filter used in bench studies that overestimate aerosol drug delivery. Therefore, in vivo, clinical studies are needed to better quantify delivered dose with various aerosol devices during MV, NIV, and SB.

In conclusion, the delivered dose distal to the trachea of an adult lung model is similar or greater with MV than NIV and SB, suggesting that artificial airway may provide a similar or better pathway for medical aerosols to the lung. Delivered dose to the adult lung model with MN was greater and differed between MV, NIV, and SB, while deposition was low with JN and similar between the modes of ventilation tested. Further clinical studies are warranted.

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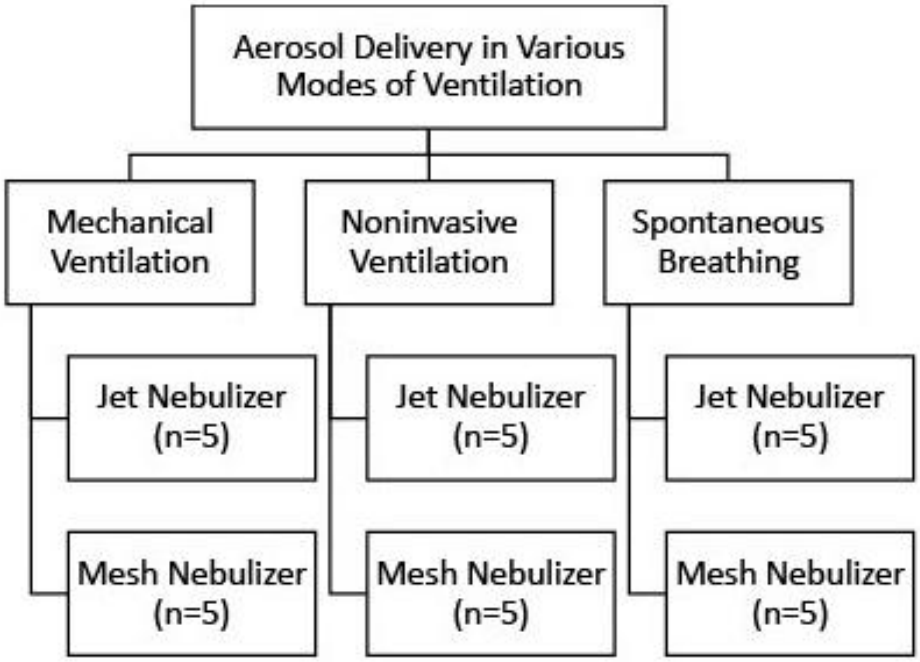
Aerosol Delivery in Various Modes of Ventilation
Mechanical Ventilation
Noninvasive Ventilation
Spontaneous Breathing
Jet Nebulizer (n=5)
Jet Nebulizer (n=5)
Jet Nebulizer (n=5)
Mesh Nebulizer (n=5)
Mesh Nebulizer (n=5)
Mesh Nebulizer (n=5)

Figure 1

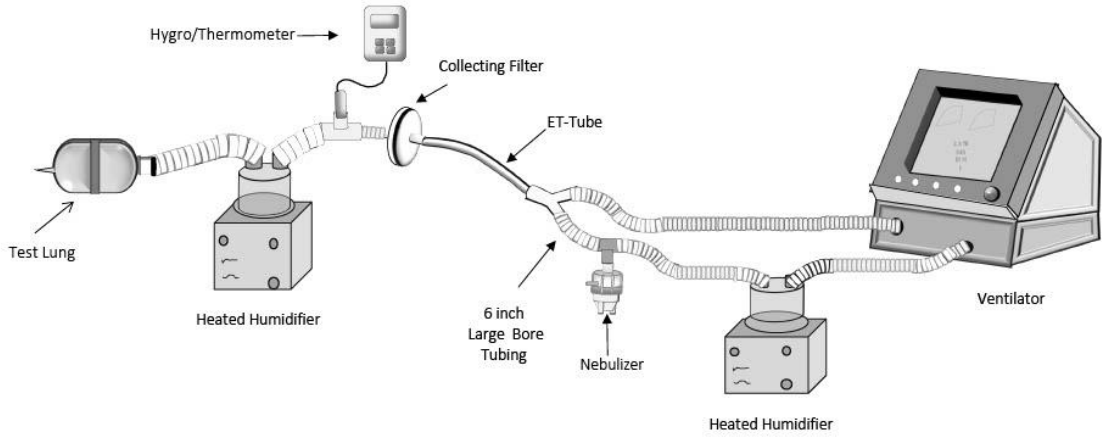
Hygro/Thermometer
Collecting Filter
ET-Tube
Test Lung
Heated Humidifier
6 inch
Large Bore
Tubing
Nebulizer
Heated Humidifier
Ventilator

Figure 2A

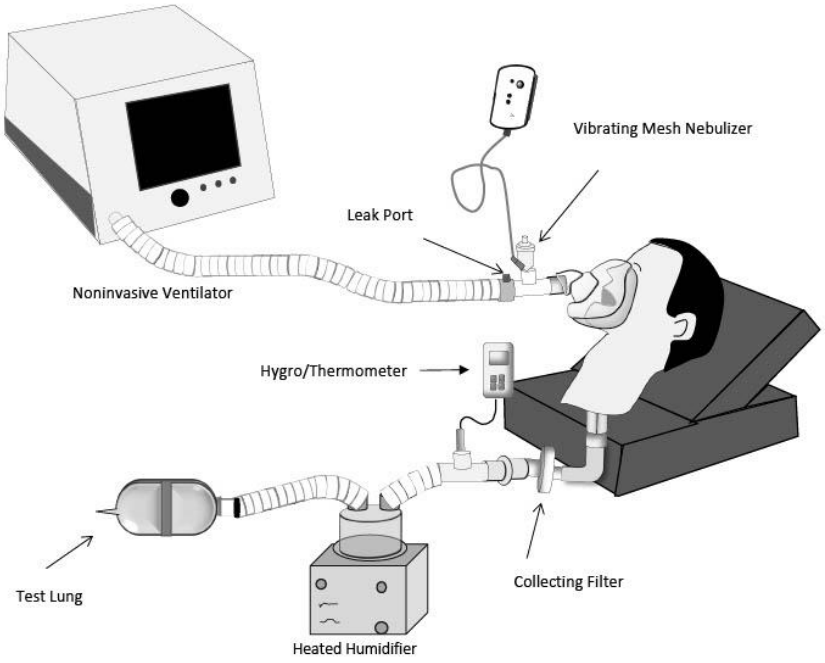
Vibrating Mesh Nebulizer
Leak Port
Noninvasive Ventilator
Hygro/Thermometer
Test Lung
Collecting Filter
Heated Humidifier

Figure 2B

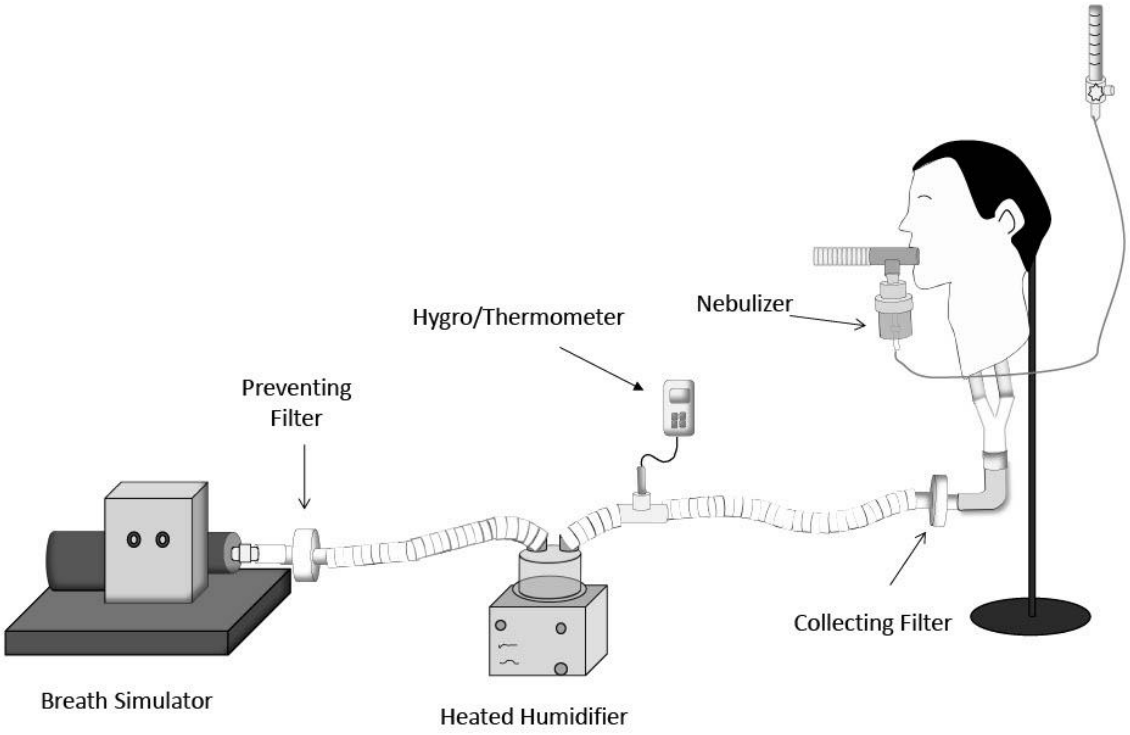
Hygro/Thermometer
Nebulizer
Preventing
Filter
Collecting Filter
Breath Simulator
Heated Humidifier

Figure 2C