Effect of the heated humidification on the *in vitro* aerosol delivery with a pressurized-metered dose inhaler and with a vibrating mesh nebulizer in mechanical ventilation.

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Summary

Aim of this study was to evaluate the *in vitro* aerosol delivery with a pressurized-metered dose inhaler and a vibrating mesh nebulizer (VMN) in heated and humidified mechanical ventilation circuits in comparison to dry circuits. Effect on drug delivery of turning off the heater and humidifier (HH) prior to the experiments was investigated as the influence of the position of the spacer in the circuit. **Methods**: A ventilator was used in volume-controlled mode with adult settings. The active HH was set at a temperature of 37°C± 2°C and a relative humidity (RH) of 100%. A filter connected to the endotracheal tube was used to collect the drug. The CombiHaler® spacer located just before the Y piece was used with both a pMDI and a VMN in heated and humidified circuits in comparison to dry circuits. Measurements were performed with both the HH turned on and off during drug administration. Aerosol delivery with the spacer located just before the HH was also evaluated in the heated and humidified circuit. **Results:** A decrease of aerosol delivery was observed of about 25% and 50% with respectively the VMN and the pMDI when the circuit was heated and humidified in comparison to the dry circuit. Turning off the HH prior to the experiments increased by 20% the aerosol delivery with the VMN and did not increase aerosol delivery with the pMDI. Locating the spacer just before the Y piece increased aerosol delivery.

Key Message

In a model of a mechanically ventilated patient, delivered dose from a VMN increased if the HH is turned off prior drug administration. This effect was not observed when drug was delivered by a pMDI. The location of the VMN and pMDI relative to the HH significantly affected dose delivered.

Introduction

Effectiveness of aerosol therapy during mechanical ventilation is influenced by many factors depending on patient, ventilatory parameters or inhalation devices used. Heat and humidity in the mechanical ventilation circuit have a great influence on drug delivery. Indeed, aerosol drug delivery may be reduced by up to 40% when heated/humidified breathing circuits are used in comparison with non-humidified circuits [1; 2]. However, heating and humidifying air in the mechanical ventilation circuit is essential to prevent drying patient's airway mucosa [3].

Active heated humidifiers (HH) inserted into the inspiratory limb are often used during mechanical ventilation. Even though heating and humidifying the mechanical ventilation circuit has unwanted effect on the aerosol delivery, removing the HH is not recommended because it implies stopping breathing assistance, breaking the circuit and changing it or waiting for it to dry [4]. Some clinicians suggested to turn off the HH prior to drug administration to avoid this decrease in aerosol delivery [5].

The aim of this present study is to investigate the effect of heat and humidity on aerosol drug delivery when using the CombiHaler® spacer with a pMDI and with a VMN in an adult mechanical ventilation model. *In vitro* aerosol delivery was evaluated in a heated and humidified ventilation circuit (with the humidifier turned on, 37°C, 100 % relative humidity (RH)) compared to a non-heated and non-humidified ventilation circuit. Aerosol delivery was also evaluated in a heated and humidified circuit (37°C, 100% RH) when the HH was turned off just prior to drug administration. Effect of the position of the spacer in the heated and humidified ventilation circuit was also evaluated, the spacer was inserted in the inspiratory limb: 1) just before the Y piece, 2) just before the HH.

Materials and Methods

A ventilator (Evita 2 Dura, Dräger) was used in volume-controlled mode with the following respiratory parameters: Tidal volume 450 mL, frequency 15 breaths/min, Positive End Expiratory Pressure (PEEP) 5 cm H_2O, ratio between inspiratory and expiratory time ½ and a flow rate of 21 L/min. The ventilator was connected to the test lung model (SmartLung Adult, IMT medical sets with a resistance of 5 mbar/L/s and a compliance of 30 mL/mbar) as described in figure 1.

A 7.5 mm inside diameter endotracheal tube (ETT) and a right-angle elbow adapter were inserted between the Y piece and the test lung model. The active heated humidifier (MR730, Fisher&Paykel) was located in the inspiratory limb and was set to deliver humidified gas at approximately 37°C at the airway. The delivered dose was collected on a filter inserted between the ETT and the test lung model.

Measurements were performed:

- With a pMDI: 10 doses containing 100 µg of salbutamol (Ventolin® 100µg, GlaxoSmithKline) were actuated in the prototypes during the beginning of inspiration.
- With a vibrating mesh nebulizer (VMN): A solution containing 5 mg of salbutamol (Salbutamol MYLAN, 2.5 mg/2.5mL) was nebulized with the vibrating mesh nebulizer Aeroneb Solo® (Aerogen).

The filter was recovered with a NaCl solution (0.1M) and quantified by UV spectrophotometry. Each measurement was performed five times. Results are expressed as means ± standard deviation (SD).

CombiHaler® was tested in different conditions (figure 1):

- In heated and humidified conditions (heater and humidifier MR730, 37 ± 2°C, 100% RH). When temperature was stable at 37± 2°C, the ventilator circuit was heated and humidified for approximately 10 minutes before drug administration. CombiHaler® was inserted at two different positions: just before the Y (position 1) piece and just before the heated humidifier (position 2.
- In heated and humidified conditions (heated and humidifier MR730 37± 2°C, 100% RH). When temperature was stable at 37 ± 2°C, the ventilator circuit was heated and humidified for approximately 10 minutes before drug administration. During drug administration, the humidifier was turned off. CombiHaler® was inserted just before the Y piece (position 1).
- In non-heated and non-humidified conditions with CombiHaler® inserted just before the Y piece.

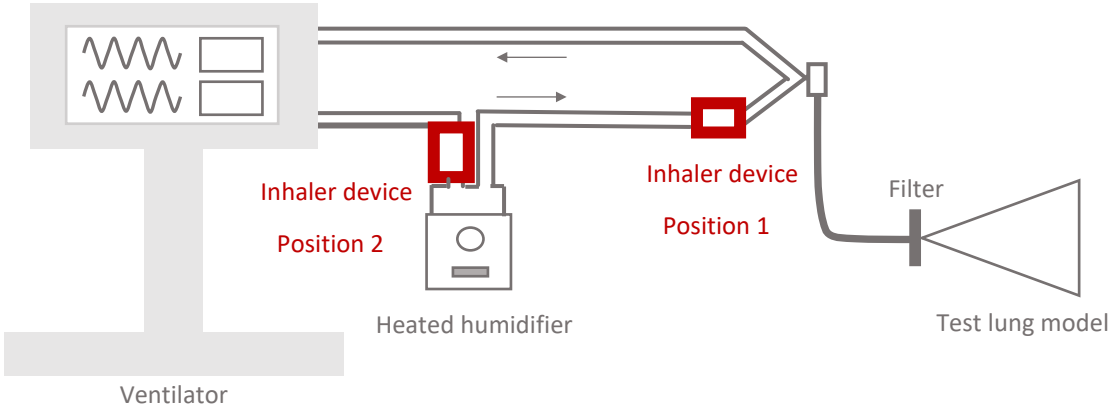

Figure 1: Schematic drawing of the bench models. *heated and humidified ventilation circuit with CombiHaler® inserted just before the Y piece (position 1) and just before the heated humidifier (position 2). Measurement were performed with pMDI and VMN in both positions. In dry conditions, CombiHaler was inserted just before the Y piece (position 1) and the HH was omitted entirely.*

Statistical analyses were performed using GraphPad Prism 6.01 (GraphPad Software, CA) and consisted of multiple t-tests. A p-value < 0,05 was considered significant. Results are expressed as percentage of the nominal dose.

Results and discussion

Effect of the heat and humidity on the aerosol delivery

Figure 2 shows the results obtained with the VMN and the pMDI, in percent of the nominal dose, with CombiHaler® inserted just before the Y piece in the three following conditions: 1) in heated and humidified conditions with the HH turned on during the drug administration, 2) in heated and humidified conditions with the HH turned off during the drug administration and 3) in dry conditions.

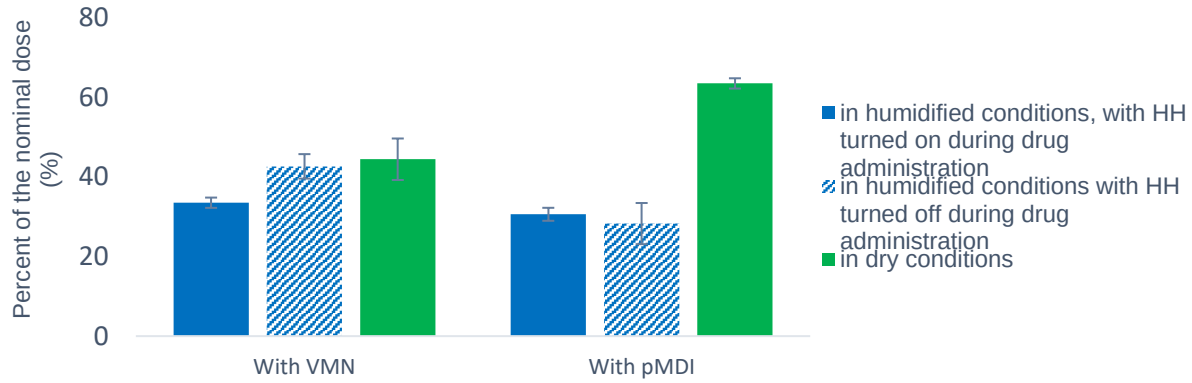

Figure 2: Effect of heat and humidity on drug delivery with CombiHaler®. *Aerosol delivery was obtained: in humidified conditions, with the heated humidifier turned on or off during drug administration and in ambient conditions. CombiHaler® with the VMN and with the pMDI was used. Results are expressed as means ± SD.*

With the VMN, results obtained show a decrease in drug delivery of about 20% between dry conditions and heated and humidified conditions with the HH turned on during drug administration (44.43 ± 5.21% vs 33.51 ± 1.29%) ($p < 0.05$). Drug delivery is similar between dry conditions and heated and humidified conditions with the HH turned off during drug administration (44.43 ± 5.21% vs 42.64 ± 3.07%) ($p = 0.50$).

With the pMDI, results obtained show a decrease of about 50% between dry conditions and heated and humidified conditions with the HH turned on during drug administration (63.47 ± 1.29% vs 30.6 ± 1.63%) ($p < 0.05$). When the HH was turned off during drug administration, aerosol delivery did not increase (28.27 ± 5.17%). These results are consistent with results obtained in a previous study where authors didn't observe an increase of the drug delivery when the HH was turned off. They attributed these results to the accumulation of water and thermal mass of the circuit. However, they heated and humidified the mechanical circuit for a longer time before conducting the experiments than us [5].

Decrease in aerosol delivery between dry conditions and heated and humidified conditions with both nebulizers and pMDI are consistent with previous studies and may be due to the hygroscopic growth of the particles [1;2].

Effect of the position of the spacer on the aerosol delivery in heated and humidified conditions.

Figure 3 presents results obtained with the VMN and the pMDI, in percent of the nominal dose, in a heated and humidified mechanical ventilation circuit, with the HH turned on during drug administration. CombiHaler® was inserted in two different locations on the breathing circuit: 1) just before the Y piece (figure 1a), 2) just before the HH (figure 1b).

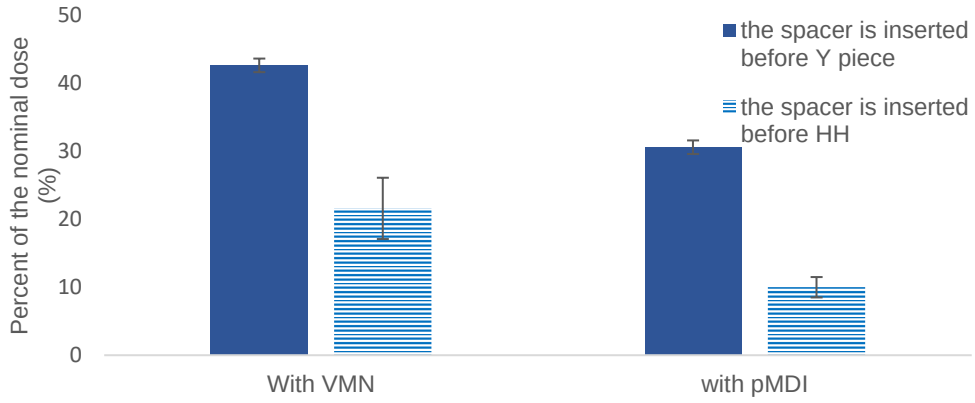

Figure 3: Effect of position of CombiHaler® in breathing circuit on drug delivery. *Results with VMN and pMDI were obtained in heated and humidified conditions with CombiHaler® inserted just before the Y piece in comparison with CombiHaler inserted just before the HH. Results are expressed as means ± SD.*

The results obtained show a higher aerosol delivery when the spacer is inserted just before the Y piece with both the VMN and the pMDI (with VMN: 42.64 ± 3.07 % vs 21.6 ± 1.51 %; with pMDI: 30.60 ± 1.63 % vs 10.10 ± 1.56 %) ($p<0.05$).

These results could be explained by the loss of drug into the humidification chamber and the inspiratory limb when the device is located just before the HH.

Conclusion

This study confirmed the lower efficiency of the drug administration by pMDI and VMN in a heated and humidified circuit compared to a dry circuit. When a pMDI was used, turning off the HH before drug administration did not increase aerosol delivery. When the VMN was used, turning off the humidifier before drug administration did increase aerosol delivery. However, turning off the humidifier can cause bronchospasm, atelectasis, airway obstruction and other problems [6]. Based on these findings we would recommend not interrupting heated humidity before drug administration, especially when using a pMDI.

The type of inhaler device has also a great influence on aerosol delivery which is higher when using a VMN instead of a pMDI. However, pMDIs are cheaper and more easily accessible. Using both pMDI and VMN with the same device has considerable clinical benefits.

Position of the spacer into the heated and humidified mechanical ventilation circuit had also a great influence on drug delivery which is higher when the device is located just before the Y piece.

The internal diameter (ID) of the endotracheal tube could also have an influence on drug delivery. It could be interesting to perform measurements in a heated humidified circuit with a larger ID endotracheal tube to evaluate the influence of the ID of the endotracheal tube on the aerosol delivery.

References

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