Inhalation chambers and neonates : Development and *in vitro* evaluation of a new prototype without dead space and effect of breathing cycles number on the delivered dose.

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Introduction

Maintaining an inhalation mask on a neonate face is difficult, because it is not well tolerated and could result to the neonate's crying. For these reasons, it could be interesting to know how many breathing cycles after a dose of drug administration is necessary to deliver an optimal drug delivery with a pressurized metered dose inhaler (pMDI) and with an inhalation chamber. The aim of this study is to evaluate the effect of breathing cycles number after each pMDI dose administered on the *in vitro* delivered dose, and so to know how much time it is necessary to apply the inhalation mask on the face of the baby after drug administration. This study permitted also to evaluate the *in vitro* performance of a new inhalation chamber prototype without dead space in comparison to commercially inhalation chambers.

Materials and Methods

Three inhalation chambers were evaluated (Figure 1 - 4) :

Figure 1 :
TipsHaler® with its infant facemask (Laboratoire OptimHal-ProtecSom).

Figure 2 : Aerochamber Flow Vu® with its infant facemask (Trudell Medical).

Figure 3 : NeonatHal® prototype inhalation chamber (Laboratoire OptimHal-ProtecSom) with its prototype facemask (created with CAO software (SolidWorks, Dassault System) and 3D printed).

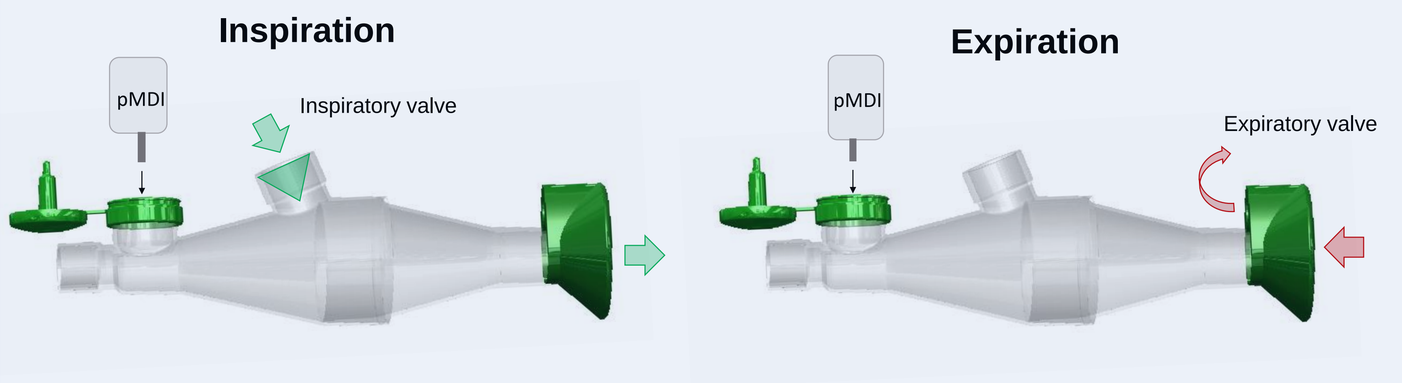


Figure 4 : Schematic view of the NeonatHal® prototype. Principle of functioning during patient's breathing cycle. The patients inspires directly air containing drug particles and expires via the expiratory valve on the facemask.

Measurements mimicking fully coordinated and fully uncoordinated use with tidal breathing to establish emitted mass were made with a breathing simulator. Breathing parameters used were the representative tidal breathing pattern of a neonate patient according to the US Pharmacopeia 1602 (Tidal volume 25 mL, frequency 40 cycles/min, I/E ratio 1/3). The inhalation chamber with facemask were applied to a face model representing an infant (Copley Scientific) with a 0.8 kg force. A filter was positioned between the face model and the breathing simulator to collect the drug. Five pMDI doses (Salbutamol, 100 µg/dose) were administered in the inhalation chamber with 1 minute interval. All components were tested for drug deposition. Deposited doses were quantified by UV spectrophotometry at 225 nm. Measurements were performed with 2 (3 seconds), 4 (6 seconds), 6 (9 seconds), 8 (12 seconds) and 40 (1 minute) cycles after each pMDI dose administration.
Statistical analysis were performed using two ways ANOVA. A value of $p < 0.05$ was considered significative.

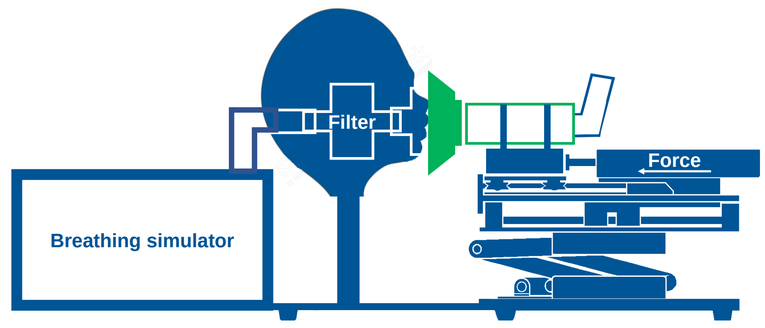
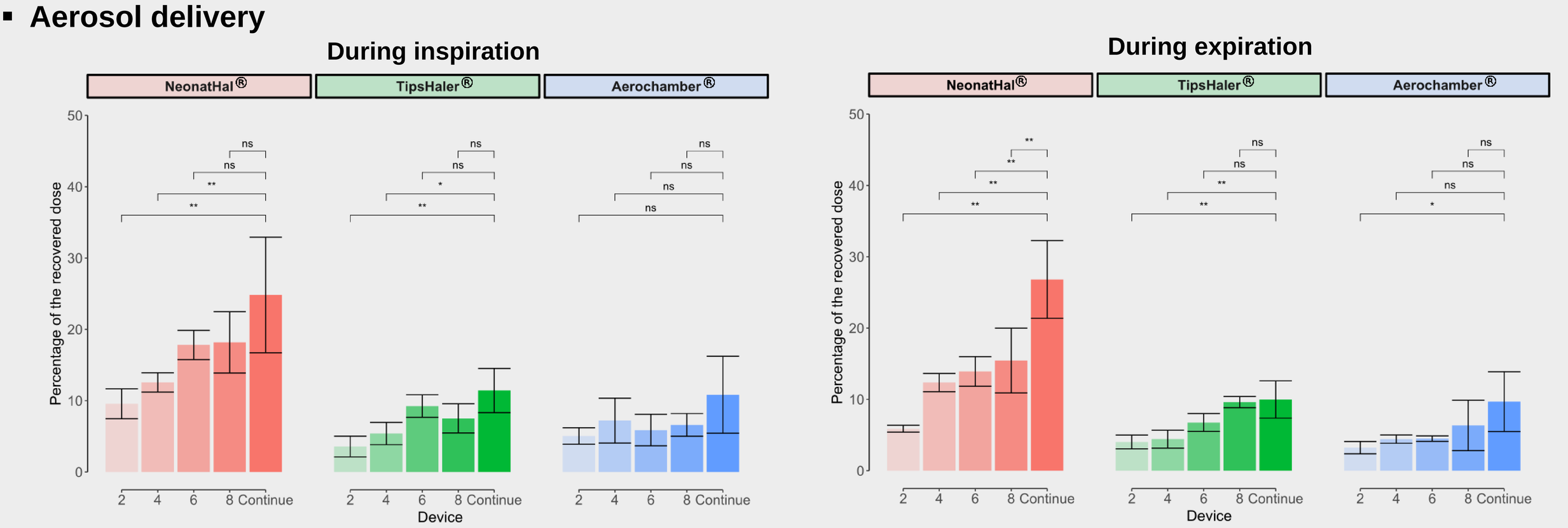


Figure 5 : Schematic drawing of the bench model used.

Aerosol delivery



- **Effect of the number of breathing cycles after each pMDI actuation on drug delivery**

Except for Aerochamber Flow Vu®, the delivered dose increases progressively with the number of respiratory cycles regardless of the synchronization with inspiratory or expiratory phase.

- **Effect of the inhalation chamber on drug delivery**

The drug delivery obtained with the prototype inhalation chamber NeonatHal® is significantly higher than the drug delivery obtained with TipsHaler® and Aerochamber Flow Vu®, regardless of the number of breathing cycles after each pMDI dose.

- **Effect of the timing of actuation on drug delivery**

Overall, the effect of synchronization to inspiratory or expiratory phase of the respiratory cycle is marginal in front of the type of device used to deliver the drug.

Conclusion

The results obtained in this *in vitro* study show that the number of cycles after each pMDI actuation and so the duration of maintaining the facemask on the baby's face has an impact on the drug delivery. The dead space volume seem also to have an effect on drug delivery. The NeonatHal® prototype is the most performant device tested in this study and allows to deliver the maximal dose of salbutamol in less than 9 s when the pMDI actuation is synchronized with inspiration.