Clinical Communications

Salbutamol delivery in small children: Effect of valved holding chamber and breathing patterns

Laura Ojanperä, MD[a], Lauri Lehtimäki, MD, PhD[b,c], Balázs Kelemen, MD[a], and Péter Csonka, MD, PhD[a,d]

Clinical Implications

Inhaled salbutamol's effective delivery is significantly influenced by the breathing patterns of small children and type of valved holding chamber (VHC) used. Regulatory authorities should carefully evaluate and, if necessary, restrict the approval and availability of VHCs that exhibit poor drug delivery characteristics.

Delivering inhaled medication in preschool children is challenging due to lack of co-operation, variable respiratory rate (RR), and low tidal volume (V_t). The breathing parameters are influenced by factors such as age, development, and the severity of bronchial obstruction, which, in turn, affect the delivery and response to medication.[1]

Valved holding chambers (VHCs) offer additional space for aerosol plume development, and they ease the need for coordination between actuation and inhalation from a pressurized metered-dose inhaler (pMDI). They also reduce oropharyngeal deposition while increasing the delivery of fine particles to the lungs.[2] Furthermore, pMDI+VHC is preferred over nebulizers and is strongly recommended in international guidelines.[2]

VHCs differ in various aspects, such as volume, material, aerodynamic characteristics, valve properties, shape, and electrostatic characteristics. The drug output can vary manyfold depending on the combination of pMDI+VHC,[3-5] which can have implications for safety and clinical outcomes. The optimal size of a VHC and whether smaller (<350 mL) VHCs with similar sizes are equally efficient in drug delivery remain unclear.

The *in vitro* drug delivery of inhaled medication should ideally be studied with cascade impactors. These devices provide valuable information not only about the total delivered dose but also the aerodynamic particle size distribution (APSD). To reach the small airways, the optimal particle size for inhaled medication lies between 1 and 5 μm, known as the respirable range. Some studies have suggested that particles measuring 1 to 3 μm may achieve the greatest lung dose in small children.[6]

For preschool children, tidal breathing remains the only feasible inhalation technique. Children exhibit variable V_t, RR, and inspiration/expiration (I/E) ratio, which undergo changes with growth and development.[1,7] Previous studies on the drug output of the pMDI+VHC combination have primarily focused on the total delivered dose without considering the fine particle dose or have used continuous steady flow not well representing inhalation in children. Only a limited number of studies have evaluated the impact of pediatric breathing patterns,[8,9] and even fewer have simulated "obstructive breathing."[3,4,8] Surprisingly, there are no publications available that have evaluated APSD while taking account for patient-specific variables such as breathing patterns, tidal volume, and lung function.

This is the first publication that meets international standards for testing inhaled medication *in vitro* using clinically relevant breathing patterns for small children. We used an *in vitro* setup to assess the impact of 3 pediatric breathing patters using 3 different VHC models on the total delivered dose, throat deposition, and APSD of inhaled salbutamol. The breathing profiles were as follows: calm breathing in 6-years-old (RR 24/min, V_t 220 mL, I/E 1.0 s/1.5 s) and 4-years-old (RR 24/min, V_t 150 mL, I/E 1.0 s/1.5 s), and obstructive breathing (RR 50/min, V_t 50 mL, I/E 0.5 s/0.7 s). Details of the methods are available in this article's Online Repository at www.jaci-inpractice.org.

The delivered dose varied significantly among different VHCs across all breathing profiles, and the median delivered dose was the highest with OptiChamber Diamond (OD) and lowest with Babyhaler (BH). AeroChamber (AC) fell in between the two (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The delivered dose decreased across all 3 VHCs as the V_t decreased. Notably, the delivered dose was substantially low during obstructive breathing, especially with BH. There was a statistically significant difference when comparing the calm breathing patterns with the obstructive breathing pattern for each VHCs.

For calm breathing, OD demonstrated the most optimal APSD for both 3 to 5 μm and 1 to 3 μm particle sizes (Figure 1). The delivered dose was significantly lower for the 4-year-old breathing pattern compared with the 6-year-old setup, especially in the 1 to 3 μm particle size range.

In obstructive breathing scenarios using a loading dose (600 μg of salbutamol), OD consistently exhibited the highest delivered dose for 1 to 5 μm particles. However, during obstructive breathing, the delivery of respirable range particles (1 to 5 μm) was significantly low, particularly with BH (Figure 2).

Salbutamol more significantly was trapped in the throat during bronchial obstruction, but less so when using OD. During obstructive breathing, throat deposition significantly increased in comparison with calm breathing, with a noticeable difference between VHCs (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org).

Our results align with previous research that used simple filter collectors and breathing simulator systems.[3,4] When comparing OD with BH, the delivered dose was better with OD in each breathing pattern. Moreover, there was a statistically significant difference in the 1 to 5 μm range.

The obstructive pattern posed challenging circumstances for all tested devices. The delivered dose markedly reduced, and the proportion of throat deposition increased. In real-life situations, the delivery of salbutamol is particularly crucial for wheezing children compared with periods of remission. Therefore, the findings emphasize OD's capability to provide significantly higher doses of salbutamol in optimal particle sizes than BH during bronchial obstruction. Even with high doses (600 μg), OD might be the only VHC among the tested devices capable of delivering enough salbutamol.

The throat deposition during obstructive breathing was substantial for all VHCs, in some cases reaching close to 100%. This

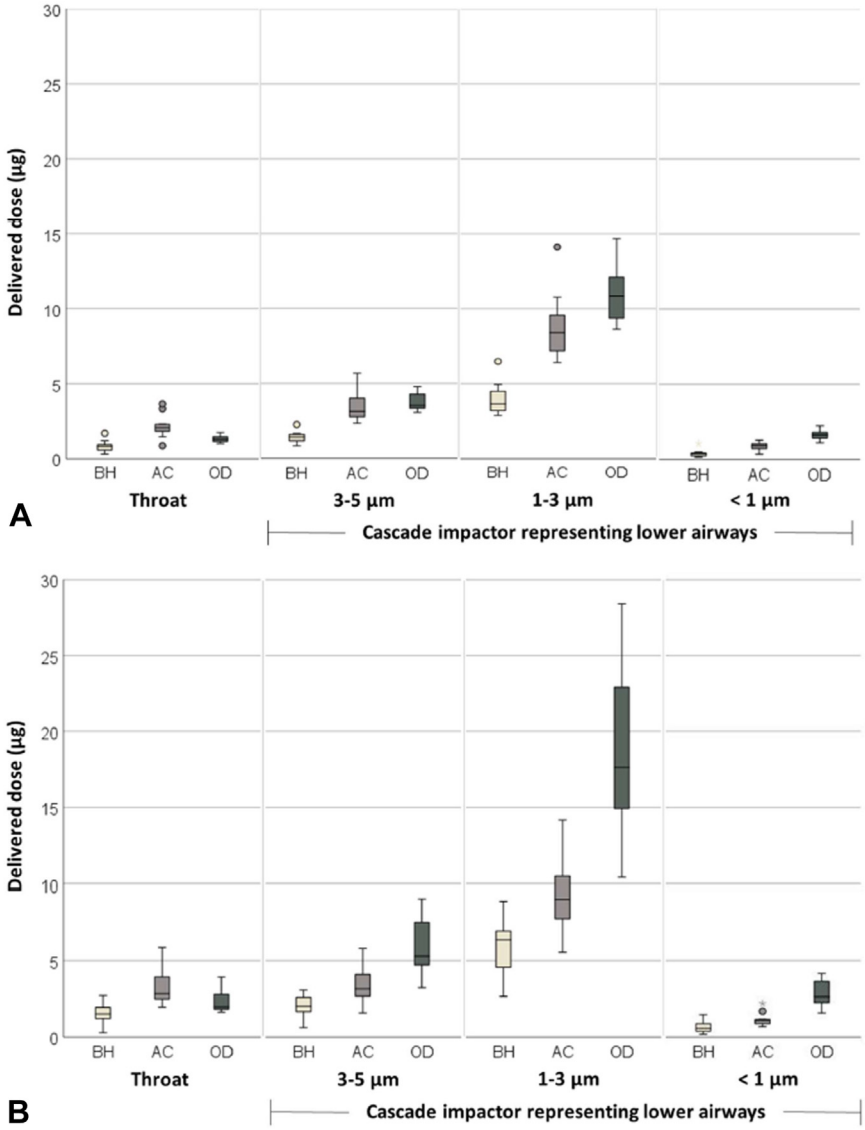

FIGURE 1. Throat and lower airway deposition with the aerodynamic particle size distribution of 100 µg of salbutamol with (**A**) the calm 4-year-old breathing pattern (tidal volume 150 mL) and (**B**) the calm 6-year-old breathing pattern (tidal volume 220 mL) with 3 different valved holding chambers: Babyhaler (BH), AeroChamber Plus (AC), and OptiChamber Diamond (OD). Respiratory rate 24/min and inspiration/expiration ratio 1.0 s/1.5 s.

observation is noteworthy as the overall delivered dose is small and the majority of it might end up deposited in the throat. In line with previous studies,[3,4,8] it appears that the volume of the VHC is not the sole factor influencing drug delivery.

Our results are limited to the *in vitro* model used and may not fully reflect the true therapeutic effect of salbutamol administered to a child in a clinical setting.[9] However, the highly standardized *in vitro* model allowed us to control for important confounding factors present in real-life setting, such as poor co-operation, crying, incomplete lip seal, and variable breathing.

This study represents an incremental advance over previous inhaler studies by looking at APSD using breathing patterns and volumes expected in preschool aged children. Our findings underscore the importance of not assuming interchangeability between different types of VHCs, even if they resemble each other or share similar volumes. Furthermore, the breathing patterns in small children probably have a substantial impact on successful drug delivery of inhaled salbutamol. Clinicians should be mindful of these potential pitfalls when selecting VHCs and while evaluating clinical responses during inhaled drug therapy. All VHCs on the market should be tested using internationally accepted standardized methods for the delivered dose and APSD in various pediatric populations and clinically meaningful breathing patterns. Regulatory authorities should restrict the approval and availability of VHCs with poor drug delivery characteristics.

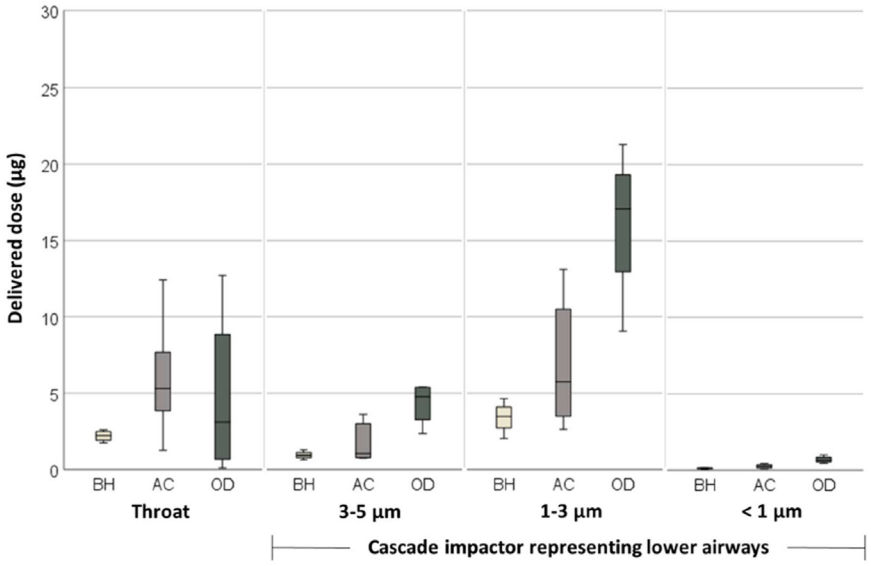

FIGURE 2. Throat and lower airway deposition with the aerodynamic particle size distribution of 600 µg of salbutamol with the obstructive breathing pattern (tidal volume 50 mL, respiratory rate 50/min, and inspiration/expiration ratio 0.5 s/0.7 s) with 3 different valved holding chambers: Babyhaler (BH), AeroChamber Plus (AC), and Optichamber Diamond (OD).

[a]Centre for Child Health Research, Tampere University and Tampere University Hospital, Tampere, Finland
[b]Allergy Centre, Tampere University Hospital, Tampere, Finland
[c]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[d]Department of Pediatrics, Terveystalo Healthcare, Tampere, Finland

This study was supported by the Foundation of the Finnish Anti-Tuberculosis Association, Tampere Tuberculosis Foundation, and Väinö and Laina Kivi Foundation.
Conflicts of interest: P. Csonka has received fees for lectures, advisory board meetings, or clinical trials from ALK, GSK, Orion Pharma, Sanofi, and Thermo Fisher Scientific. L. Lehtimäki has received fees for lectures, advisory board meetings, or clinical trials from ALK, AstraZeneca, Chiesi, GSK, Novartis, Orion Pharma, and Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication August 11, 2023; revised November 6, 2023; accepted for publication November 9, 2023.
Available online ■■

Corresponding author: Laura Ojanperä, MD, Tampere University, Arvo Ylpön katu 34, 33520 Tampere, Finland. E-mail: laura.ojanpera@tuni.fi. Or peter.csonka@tuni.fi.

2213-2198

https://doi.org/10.1016/j.jaip.2023.11.013

REFERENCES

1. Rubin BK, Fink JB. Optimizing aerosol delivery by pressurized metered-dose inhalers. Respir Care 2005;50:1191-7.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2022 Update) Accessed August 1, 2023. https://ginasthma.org/gina-reports/
3. Csonka P, Lehtimäki L. Valved holding chamber drug delivery is dependent on breathing pattern and device design. ERJ Open Res 2019;5:00158-2018.
4. Csonka P, Lehtimäki L. In vitro drug delivery performance of five valved holding chambers with and without facemasks. Pediatr Pulmonol 2019;54:1457-65.
5. Janssens HM, Heijnen EM, De Jong VM, Hop WC, Holland WP, De Jongste JC, et al. Aerosol delivery from spacers in wheezy infants: a daily life study. Eur Respir J 2000;16:850-6.
6. Cole CH. Special problems in aerosol delivery: neonatal and pediatric considerations. Respir Care 2000;45:646-51.
7. Motamedi-Fakhr S, Iles R, Barker N, Alexander J, Cooper BG. Reference equations for tidal breathing parameters using structured light plethysmography. ERJ Open Res 2021;7:00050-2021.
8. Mitchell JP, Nagel MW. In vitro performance testing of three small volume-holding chambers under conditions that correspond with use by infants and small children. J Aerosol Med 1997;10:341-9.
9. Berg E, Madsen J, Bisgaard H. In vitro performance of three combinations of spacers and pressurized metered dose inhalers for treatment in children. Eur Respir J 1998;12:472-6.

ONLINE REPOSITORY

MATERIALS AND METHODS IN DETAIL

We used an *in vitro* setup where the pressurized metered-dose inhaler (pMDI) and valved holding chamber (VHC) were connected to a child throat model (Child Alberta Idealised Throat; Copley Scientific Limited, Nottingham, UK) using a silicone adapter. The throat model was followed by a preseparator and Next Generator Cascade Impactor (NGI; Copley Scientific Limited). Drug delivery was measured from the throat model (upper airway deposition) and the NGI (lower airway deposition). For the purpose of this study, facemasks were excluded, and thus, the breathing profiles examined were formulated to be relevant to the patient population that does not use facemasks in real life, specifically children over 4 years old.

Three different breathing profiles were used simulating calm breathing in 6-years-old (RR 24/min, V_t 220 mL, I/E 1.0 s/1.5 s) and 4-years-old (RR 24/min, V_t 150 mL, I/E 1.0 s/1.5 s), and obstructive breathing (RR 50/min, V_t 50 mL, I/E 0.5 s/0.7 s).

The delivery of salbutamol was generated by a pMDI (Ventolin Evohaler 100 μg/dos; GlaxoSmithKline Inc, Evreux, France). Three types of VHCs were studied without masks: OptiChamber Diamond (OD), AeroChamber plus Flow-Vu (AC), and Babyhaler (BH). Three separate VHCs from different manufacturing lots were used for each brand. Before the experiments the components of the VCHs were washed and dried according to the manufacturers' instructions.

The Breathing simulator BRS 3100 (Copley Scientific Limited, Nottingham, UK) was used to generate the sinusoid wave pattern and administer the dose to the cascade impactor. The fine particle dose was assessed using a next-generation impactor. To synchronize with the actuation, the initiation of the breathing profile was manually timed.

Two different doses of salbutamol were used for the measurements. Initially, one dose of salbutamol (100 μg/dos) was administered. After 5 breathing cycles, samples were collected from the throat model and the 8 stages of the NGI. For the obstructive breathing pattern, 6 doses (600 μg) of salbutamol were used, equivalent to the so-called loading dose administered in the emergency room to treat acute obstruction. To achieve this, 1 dose was actuated at a time to the VHC, and after each actuation, 5 breathing cycles were conducted before collecting the samples. This process was repeated 6 times before the samples were collected. Each study setting was repeated 4 times with each separate VHC.

Before conducting the actual test measurements, a series of test samples were collected to validate the method's operability and reliability. Before each test, the device setting was checked for leaks and appropriate flow. In total, 1188 samples were analyzed.

Before conducting the measurements, the cups representing the stages of the NGI were coated with a fixation solution to minimize bounce-off. After the breathing simulation was completed, the throat model and cups were filled with either 10 mL or 15 mL of suitable solvent and stirred using the Gentle Rocker (Copley Scientific Limited). The NGI samples were analyzed by high-performance liquid chromatography carried out by Emmace Consulting AB (Lund, Sweden) with the following setup: mobile phase: methanol/50 mM phosphate buffer pH 3.0 20/80 (vol/vol); pump flow rate: 1 mL/min; injection volume: 10 μL; detection wavelength: 224 nm; column: Symmetry (Waters), C18, 5 μm, 50 mm × 3.9 mm (internal diameter). The method is linear between 0.1 and 31 μg/mL. The limit of quantitation is 0.2 μg/mL.

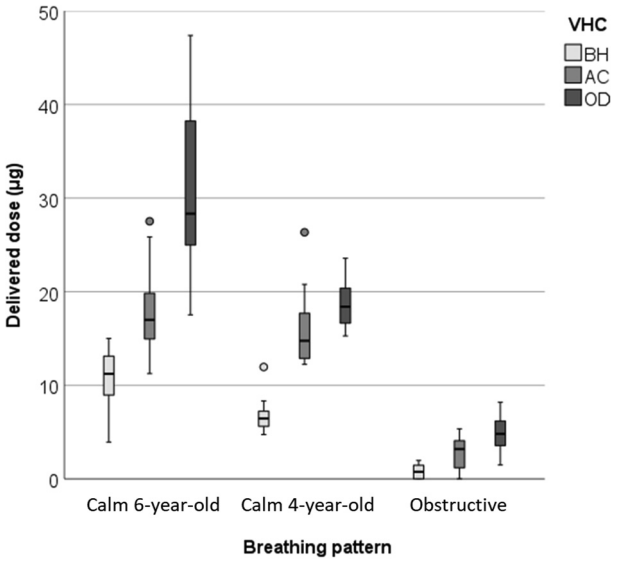

FIGURE E1. Total delivered dose, including the throat model and cascade impactor, of 100 µg of salbutamol with 3 different breathing patterns and 3 different valved holding chambers (VHCs). Calm 6-year-old (V_t 200 mL, RR 24/min, I/E 1.0 s/1.5 s). Calm 4-year-old (V_t 150 mL, RR 24/min, I/E 1.0 s/1.5 s). Obstructive (V_t 50 mL, RR 50/min, I/E 0.5 s/0.7 s). *AC*, AeroChamber Plus; *BH*, Babyhaler; *I/E*, inspiration/expiration; *OD*, OptiChamber Diamond; *RR*, respiratory rate; V_t, tidal volume.

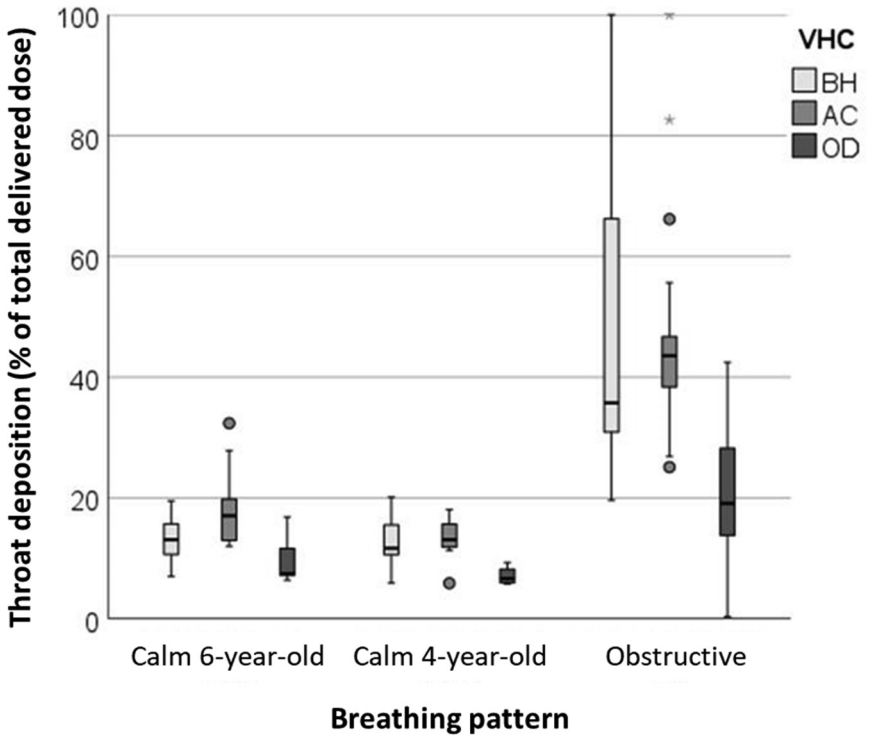

FIGURE E2. Throat deposition of salbutamol with 3 different breathing patterns and 3 different valved holding chambers (VHCs). Calm 6-year-old (V_t 200 mL, RR 24/min, I/E 1.0 s/1.5 s). Calm 4-year-old (V_t 150 mL, RR 24/min, I/E 1.0 s/1.5 s). Obstructive (V_t 50 mL, RR 50/min, I/E 0.5 s/0.7 s). *AC*, Aerochamber Plus; *BH*, Babyhaler; *I/E*, inspiration/expiration; *OD*, Optichamber Diamond; *RR*, respiratory rate; V_t, tidal volume.