

In Vitro Performance Testing of Three Small Volume-Holding Chambers under Conditions That Correspond with Use by Infants and Small Children

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ABSTRACT

The *in vitro* behavior of three types of small volume-holding chambers intended for use by infants and small children (child AeroChamber®, Vent-170 and Space Chamber™) has been compared with two pMDI-delivered aerosol formulations (salbutamol: 100 µg unit dose and beclomethasone di-propionate (BDP): 50 µg unit dose) widely prescribed for this age group of patients. All devices were evaluated using a pediatric breathing simulator that created respiratory conditions likely to be encountered with infants and small children. The filter that collected aerosol delivered from the holding chamber on test was located at approximately the position that the patient's lips would be in the mask, by means of an annular support plate glued into the mask itself. At the lowest tidal volume (50 ml), no salbutamol or BDP was delivered by either the Vent-170 or Space Chamber™, whereas the unit doses from the child AeroChamber® were 39.7 ± 1.6 µg and 11.8 ± 1.2 µg, respectively. The Vent-170 and Space Chamber™ delivered measurable doses of both drugs when the tidal volume was increased to 100 ml and again to 200 ml, however, the corresponding doses available from the AeroChamber® were always significantly greater. These findings emphasize the importance of designing *in vitro* tests that mimic use by the patient group for which the device is intended. *In vitro* measurements made at constant high flow rates in excess of 20 l/min do not reveal these differences in performance that are clinically significant, and may lead the physician to prescribe a device that under certain conditions may not deliver any drug to infants or small children.

Key words: PMDI holding chamber, pediatric, low flow rates

INTRODUCTION

It is well known that the efficacy of delivery of inhaled drugs in aerosol form from pressurized metered dose inhalers (pMDIs) to receptor sites in the lung is dependent on factors such as patient coordination and inhalation behavior.⁽¹⁾ During the last 15 years, various designs of spacer and holding chamber have been developed to condition the aerosol cloud formed following pMDI actuation, so that the mass percentage of so-called "respirable" particles (often defined as being finer than $4.7\ \mu\text{m}$ aerodynamic diameter), that penetrate beyond the oropharyngeal region is optimized and, at the same time, becomes less dependent on patient use. *In vitro* testing is normally undertaken as a first step to characterize the performance of these devices in view of the high cost of obtaining reliable *in vivo* data. However, it is important that the conditions in such bench-top testing resemble the circumstances of patient use as closely as possible. For instance, data obtained at inhalation flow rates more typical of adults may not be applicable if the spacer or holding chamber is being used by a child, especially one who is severely symptomatic.

The AeroChamber® valved holding chamber (145 ml volume; Fig. 1a) was developed

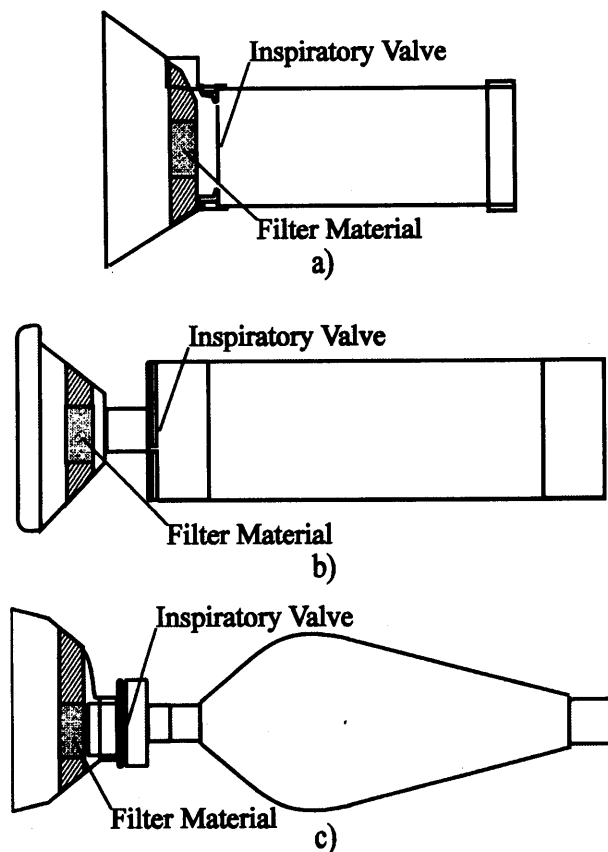


FIG. 1. Schematics of each holding chamber, showing location of filter for aerosol collection.

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from the work of Corr *et al.*,⁽²⁾ and is available in several forms suited to different patient ages, included child AeroChamber® (Trudell Medical Group, Canada) that is intended for use with infants and small children. The design of this device has been optimized to deliver a highly respirable dose of aerosol from almost all pMDI formulations to this group of patients whose tidal volumes are typically less than 200 ml.

The Space Chamber™ (Medical Developments Australia; Fig. 1b), a small volume-holding chamber (250 ml) significantly larger than the child AeroChamber®, is being marketed in some countries with a mask for use by infants and small children. Finlay *et al.*⁽³⁾ recently reported in testing of the product intended for adult use that the capability of this holding chamber to deliver respirable doses of pMDI-delivered salbutamol and BDP is comparable with that of the AeroChamber®. These tests were undertaken at a continuous flow rate of 28.3 l/min, and it is well known that more drug will be delivered to the patient from a larger volume chamber under these conditions.⁽⁴⁾ The Vent-170 (Nordac Design, Canada; Fig. 1c) is another small volume holding chamber (170 ml), also being marketed in some countries for use by infants and small children.

The present study is the result of a comparison between these three devices using a system that simulates breathing by infants or small children. Emphasis has, therefore, been placed on the attainment of total unit dose values at tidal volumes in the range from 50 to 200 ml, representing breathing conditions that more accurately reflect those likely to be achieved in use by these groups of patients than with adults.

METHODS

A purpose-built system was developed to compare the performance of three examples of each of the three types of holding chamber under realistic breathing conditions (Fig. 2). Each device was connected in turn to the slave section of a training test lung (Vent Aid®, Michigan Instruments, Grand Rapids, MI) with 22-mm diameter flexible tubing. The aerosol emitted from the device on test was collected using an electret filter collector (Filtrete™ Media, 3M Corp., St. Paul, MN) located at the approximate position of the lips of a typical user by means of an annular support plate glued to the mask itself. Validation tests confirmed that the amount of drug particle penetration beyond this filter was below the limit of detection. A pediatric ventilator (Infant Star® 200, Infrasonics Inc., San Diego, CA) was connected to the drive side of the test lung to operate the system. The ventilator was set to provide the following three representative breathing conditions for infants and small children, in accordance with recommendations of Barry and O'Callaghan⁽⁵⁾:

1. Tidal volumes (V_t) of 50, 100, and 200 ml
2. Inspiratory/expiratory (I/E) ratio of 40:60 at all tidal volumes
3. Breathing rates of 30/min ($V_t = 50$ ml), 26/min ($V_t = 100$ ml), and 18/min ($V_t = 200$ ml)

A VenTrak™ respiratory monitoring system (Novamatrix Medical System, Wallingford, CT) was used to monitor the breathing pattern during each test via a calibrated pneumotachometer sensor that was located immediately behind the filter.

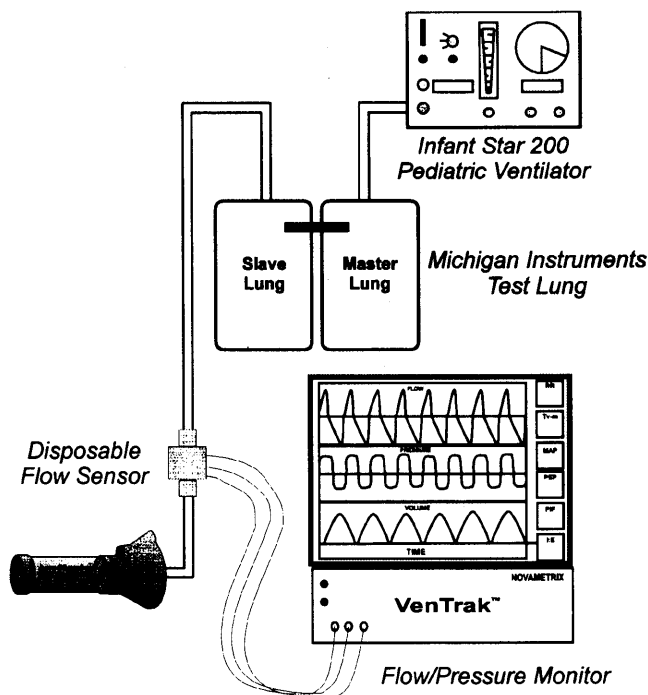


FIG. 2. Purpose-built ventilator-test lung facility for performance testing of spacers and holding chambers under conditions of use by infants or small children.

Prior to the measurements, each holding chamber was washed in warm water containing a mild household detergent, rinsed, and allowed to dry naturally, thereby minimizing any influence of electrostatic charge build-up on the chamber body.⁽⁶⁾ The holding chamber was then connected to the system with the filter located correctly and the breathing parameters adjusted to the desired values. When breathing conditions had stabilized, a pre-primed pMDI (Ventolin®: 100 µg/unit dose or Beclovent®: 50 µg/unit dose (Glaxo-Wellcome Canada Inc.) was actuated into the chamber once to coincide with the start of an inhalation. Aerosol sampling took place for a further 5 inhalations before the filter was removed from the mask plate and transferred to a 40-ml glass container. The container was agitated by hand for 30 seconds, and a sample was subsequently withdrawn and filtered into a 2 ml HPLC glass vial. Assay of either salbutamol or BDP was undertaken by HPLC (Varian Canada, Inc.) using a 150 mm long × 4.6 mm diameter Spherisorb® ODS-2, 5 µm diameter silica-microsphere-based separation column (Alltech Associates, Deerfield, IL) with 60% v/v methanol/40% v/v aqueous sodium dodecyl sulfate-acetic acid (salbutamol) and 70% v/v methanol/30% v/v water (BDP) as eluent.

All measurements were made at room temperature ($22^{\circ} \pm 2^{\circ}\text{C}$) at a relative humidity close to 50%.

Statistical interpretation of the data at each of the three representative tidal volumes was undertaken using a one-way analysis of variance (ANOVA; SigmaStat™, Jandel Scientific, San Rafael, CA). Differences were deemed significant when $p < 0.05$.

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RESULTS

The mass (mean $\pm$ 1 SD) of Ventolin® or Beclovent® delivered by each of the three types of holding chamber (total unit dose) at each breathing condition are given in Table 1 and Table 2, respectively. Each result is based on 5 replicate measurements with each of 3 holding chambers of the same type. Because tidal volume is the breathing parameter that is most closely related to the magnitude of the peak inspiratory flow rate, the variation of total unit dose available as a function of tidal volume is illustrated in Fig. 3 and Fig. 4 for Ventolin® and Beclovent®, respectively.

The child AeroChamber® provided significantly more of either drug than the other holding chambers at all three tidal volumes (Kruskal-Wallis one-way ANOVA on ranks, $p < 0.001$), and it is notable that the unit doses delivered at the smallest tidal volume (50 ml) were 76% and 80% of the dose obtained at 200 ml tidal volume for Ventolin® and Beclovent®, respectively. The mass of either drug obtainable from this holding chamber was, therefore, relatively insensitive to tidal volume within the range studied. In contrast, although the unit dose of both drugs delivered by the Space Chamber™ approached 70% that of the child AeroChamber® at the highest tidal volume, a negligible mass of Beclovent® was obtainable at 50 or 100 ml tidal volume, and no Ventolin® was collected at 50 ml tidal volume. Similarly, the Vent-170 provided no Ventolin® at 50 ml tidal volume or Beclovent® at either 50 or 100 ml tidal volumes. The unit doses of Ventolin® and Beclovent® at 200 ml were only 46% and 10% of the equivalent unit doses obtained with the child AeroChamber®.

DISCUSSION

The unit doses of both Ventolin® and Beclovent® delivered via the child AeroChamber® were comparatively insensitive to variations in tidal volume, and the inhalation valve was observed to open normally even at the lowest tidal volume, equivalent to a peak inspiratory flow rate of about 5 l/min. The slight decrease in unit dose observed at smaller tidal volumes can be explained in terms of increased particle loss to the interior chamber walls. Such losses are primarily due to the effect of gravitational sedimentation during the period

TABLE 1. THE MASS OF VENTOLIN®: 100 μ G UNIT DOSE (MEAN $\pm$ 1 SD μ G)
RECOVERED FROM THE SPACE CHAMBER,™ VENT-170, AND CHILD AEROCHAMBER®
(5 REPLICATE MEASUREMENTS WITH EACH OF 3 DEVICES AT EACH CONDITION)

<i>Breathing conditions</i>	<i>Space Chamber™</i>	<i>Vent-170</i>	<i>Child AeroChamber®</i>
Tidal volume: 50 ml I/E ratio: 40/60 rate: 30/min	0.0	0.0	36.9 $\pm$ 2.7
Tidal volume: 100 ml I/E ratio: 40/60 rate: 26/min	29.0 $\pm$ 3.3	13.5 $\pm$ 3.4	38.4 $\pm$ 3.4
Tidal volume: 200 ml I/E ratio: 40/60 rate: 18/min	37.8 $\pm$ 6.3	22.4 $\pm$ 3.8	48.8 $\pm$ 3.0

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TABLE 2. THE MASS OF BECLOVENT®: 50 µg UNIT DOSE (MEAN ± 1 SD µg)
RECOVERED FROM THE SPACE CHAMBER,™ VENT-170, AND CHILD AEROCHAMBER®
(5 REPLICATE MEASUREMENTS WITH EACH OF 3 DEVICES AT EACH CONDITION)

Breathing conditions	Space Chamber™	Vent-170	Child AeroChamber®
Tidal volume: 50 ml I/E ratio: 40/60 rate: 30/min	0.0	0.0	11.8 ± 1.2
Tidal volume: 100 ml I/E ratio: 40/60 rate: 26/min	0.0	0.9 ± 1.8	12.5 ± 2.1
Tidal volume: 200 ml I/E ratio: 40/60 rate: 18/min	9.0 ± 2.6	1.5 ± 2.6	14.7 ± 1.8

required to empty the 145 ml chamber of aerosol by the repeated inhalation maneuvers. This is primarily a function of the ratio of tidal volume to chamber volume, particularly when the tidal volume is smaller than the volume of the chamber. The exhalation valve located in the mask of this product prevented exhaled air from mixing with residual aerosol within the chamber, which might otherwise have further reduced the concentration available at the next inhalation.

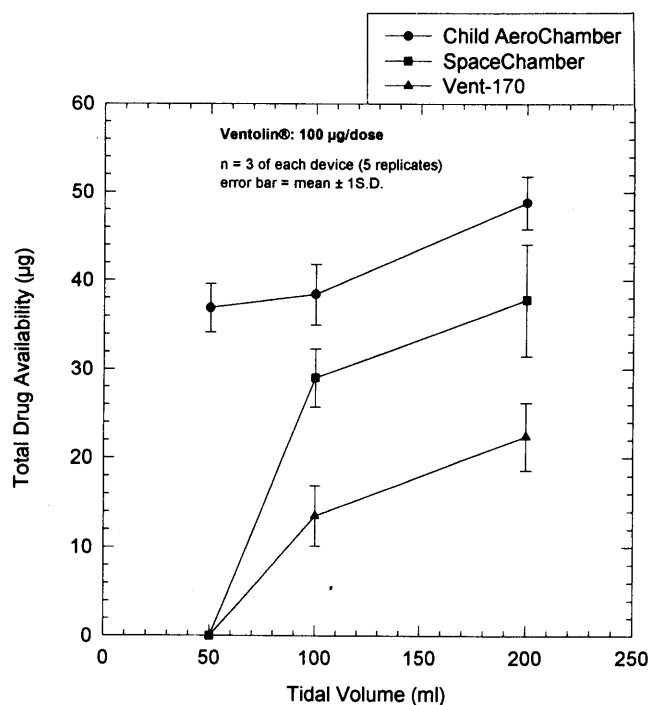


FIG. 3. Performance of three valved holding chambers at low-tidal volumes—Ventolin® (100 µg/dose).

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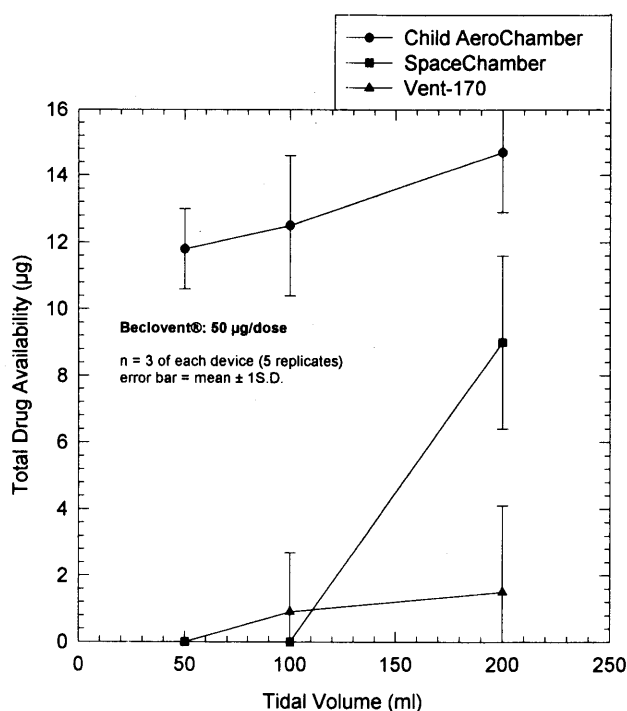


FIG. 4. Performance of three valved holding chambers at low-tidal volumes—Beclovent® (50 µg/dose).

In contrast, both the Space Chamber™ and the Vent-170 provided negligible amounts of either Ventolin® or Beclovent® at the lowest tidal volume, and the delivery capabilities of either device at 100 ml tidal volume (peak inspiratory flow rate of 10 l/min) were marginal, especially with Beclovent®. It was noticeable during testing under these conditions, that the inhalation valves of both these holding chambers were barely opening during the inhalation portions of the breathing cycle. Under this circumstance, the aerosol contained within either holding chamber could not become available to be collected by the filter. At the highest tidal volume (equivalent to a peak inspiratory flow rate of 14.5 l/min), the vacuum developed during inhalation was just sufficient to allow the inhalation valve of both holding chambers to open, so that some drug could be collected. It was unclear, however, whether these valves were open to their fullest extent at this condition.

Note that all the holding chambers were pre-washed in mild household detergent and allowed to dry naturally, as it is known that surface electrostatic charging can cause increased aerosol deposition within these devices, which may have an adverse effect on the mass of drug delivered to the patient.^(6,7) Wildhaber *et al.*⁽⁸⁾ have recently shown that *in vitro* performance of holding chambers is significantly improved when a detergent followed by air drying is used to reduce electrostatic charging, and the advice given to users by the manufacturer of the AeroChamber® reflects this practice. Although washing prior to use may not be done in the clinical environment, and may not be clinically relevant, the nonreproducible nature of electrostatic charging from device to device made it essential to pre-wash each device to obtain reproducible results in this *in vitro* study.

CONCLUSION

The efficient operation of holding chambers at small tidal volumes (equivalent to low peak inspiratory flow rates) typical of infants and small children involves both consideration of the patient interface as well as design of holding chamber geometry. In particular, care has to be taken that the amount of dead volume between patient and inhalation valve as well as the movement of the inhalation valve are optimized so that aerosol generated following pMDI actuation is transported to the patient as efficiently as possible, whilst at the same time eliminating larger nonrespirable particles.

In vitro assessments of spacer or holding chamber performance made under continuous flow conditions, such as those required for cascade impactor measurements, do not necessarily reveal weaknesses that only become evident in a breathing cycle where the inhalation flow rate is continuously varying between zero and the peak inspiratory flow rate. This is especially true of tests that aim to compare the performance of devices intended for use by infants and small children, or even severely symptomatic adults. The peak inspiratory flow rate achievable by these groups of patients may be less than 50% of that achieved during a cascade impactor test undertaken at a constant flow rate close to 30 l/min, equivalent to a peak inspiratory flow rate that is more representative of normal adults. Thus, a physician interpreting data from continuous flow rate testing may be led to prescribe a device that is partly effective or noneffective with this group of patients.

In the short term, the measurement of total unit dose using a breathing simulator, such as that described here, provides part of the solution to the problem of providing the most realistic simulation of *in vivo* use of spacers or holding chambers. However, ultimately, there is a need to develop cascade impactors that operate at low flow rates more typical of those achieved by this patient population to provide the necessary information concerning the portion of the dose that is respirable.

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