INVESTIGATION INTO THE EFFECTS OF VALVE PRESSURE ON TOTAL DELIVERED DOSE (TTD) FROM VHCs

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Summary

Total delivered dose and valve pressure differential tests have been conducted and compared for several valved holding chambers (VHCs). The results of total delivered dose were compared to the corresponding valve pressure results to identify whether or not there is a correlation between valve pressure and the total delivered dose (TDD).

Both total delivered dose and valve pressure differential (VPD) measurements of several valve holding chambers have been conducted to test the hypothesis that the pressures generated by valves have an impact on the VHCs delivered dose. Results show that there is variance in the pressure differentials created by different valve designs, with the cross-valve producing the lowest pressure differentials on inhalation at tidal breathing simulations for both adult and paediatric rates (0.447 and 0.167 cm/H_2O) followed by the disc valve (0.661 and 0.291 cm/H_2O) then the single slit valves (0.702 – 0.727 and 0.284 – 0.413 cm/H_2O). VHCs exhibiting a lower tidal pressure differential deliver a higher dose (82.41 – 74.69 ug, adult; 71.75 – 69.60 ug, paediatric) when compared to VHCs with higher pressure generation (61.28 – 65.90 ug, adult; 60.10 – 66.45 ug, paediatric). In most cases the cross valve and disc valve generated less pressure than the 2 single slit valves; which correlates with the TDD results where the cross valve and disc valve gave a higher dose than the single slit valves in both adult and paediatric breathing rates.

Introduction

Valved holding chambers are designed to hold the active ingredients in the chamber, ready for inhalation. This mechanism ensures that it is less critical to time actuation with inhalation, making VHCs beneficial for the very young or old, or an individual suffering an asthmatic episode [1]. VHCs have the added advantage of allowing multiple inhalations without removing the device from the patient's mouth.

There are a wide variety of VHCs on the market today, many with different valve designs. There is little known about the importance of VHC valve design and the impacts of superior or inferior valve design on the TDD. It is hypothesised that increased valve resistance may prevent the valve from fully opening, which may impact how drug inside the chamber deposits onto the surface of the chamber, resulting in a lower delivered dose. This would be particularly relevant in paediatric cases, where the patient is less capable of producing enough force to open higher resistance valves. Other factors including high back pressure during exhalation though the VHC may discourage the patient from keeping the device in their mouth, which in turn may increase the delay time between successive breaths.

In this study, we compare 4 available VHCs to identify whether or not the differing valve designs have an effect on the pressures generated by normal breathing through the device, as well as identifying any correlation between valve pressure differentials and VHC TDD.

Experimental Methods

TDD and VPD testing was conducted on four unique VHCs as outlined in Table 1.

Table 1: List of VHC's tested, VHC abbreviation, and sample distribution/testing matrix

VHC	Abbrev.	Static Vol. (ml)	No. of samples	VPD testing (ALL)	TDD Adult	TDD Paed.
Anti-static Compact Space Chamber Plus	AS-CSCP	160	9	3	3	3
AeroChamber Plus Flow-Vu Anti-static VHC	ACFV+	149	9	3	3	3
OptiChamber Diamond Anti-static Chamber	OCD-AS	140	9	3	3	3
VORTEX Non Electrostatic Holding Chamber	VOR-NE	194	9	3	3	3

Salbutamol sulfate was primed according to manufacturer's recommendations before use in testing. All VHCs were used either straight from the original packaging without priming (AS-CSCP, ACFV+ & OCD-AS) or washed before use (VOR-NE) as per manufacturer's instructions. VPD testing was conducted by simulating a consistent tidal breathing rate which was maintained using a waveform generator. As outlined in the Canadian standards for testing the performance of VHCs, measurements of performance made under static flow conditions may not fully describe device behaviour under the continuous varying flow and pressure changes that are associated with the respiratory cycle [2].

The waveform generator was calibrated to take 14 x 500mL breaths per minute when testing adult lung volumes and 18 x 200mL breaths per minute when testing paediatric lung volumes. The simulation continued for 5 minutes per VHC. The pressure differential was captured and tabulated, then the average of the triplicate VHCs was graphed.
The same 4 brands of VHC were then tested for TDD at both paediatric and adult tidal breathing rates using salbutamol sulfate. TDD tests were run in triplicate using 1 pMDI which was actuated 3 times into each VHC. Each VHC was connected directly to the Dosage Unit Sampling Apparatus (*DUSA*) which in turn was connected to the waveform generator. Once the waveform generator was set to the appropriate parameter (adult or paediatric), the pMDI was shaken well and prepared for actuation by inserting the pMDI into the device to be tested. The actuation was timed so that the medication was injected at the beginning of inhalation (to mimic 0s delay testing). Once the first actuation had taken place, 2 full breaths were allowed to pass before repeating for a second actuation at the beginning of the third inhalation [3]. This process was completed a total of 3 times for each VHC at each breathing rate. The VHCs and DUSA-filters were washed/extracted using 50:50 MeOH:H_2O and analysed by HPLC.

References

1. Jolyon P Mitchella , Mark W Nagelb, *Valved holding chambers (VHCs) for use with pressurised metered-dose inhalers (pMDIs): a review of causes of inconsistent medication delivery*, Primary Care Respiratory Journal (2007); 16(4).
2. *Spacer and holding chambers for use with metered-dose inhalers*, CSA Standards, Update No.2, CAN/CSA-Z264.1-02, January 2008.
3. André Schultz, Timothy J. Le Souëf, André Venter, Guicheng Zhang, Sunalene G. Devadason, Peter N. Le Souëf, *Aerosol Inhalation From Spacers and Valved Holding Chambers Requires Few Tidal Breaths for Children.* Pediatrics, December 2010, VOLUME 126 / ISSUE 6

Results

Experimental TDD results, displayed in units of µg of salbutamol as sulfate, for each VHC tested at both adult and paediatric breathing rates are summarised in Table 2 below. Graphs 1 – 8 display the difference in average pressures produced by the VHCs when monitored over 5 minutes at both tidal breathing rates and static flow rates.

Table 2: Experimental results for Total Delivered Dose

VHC	Total Delivered Dose Adult breathing rate (µg)	Total Delivered Dose Paediatric breathing rate (µg)
AS-CSCP	82.41	69.60
ACFV+	74.69	71.75
OCD-AS	65.90	60.10
VOR-NE	61.28	66.45

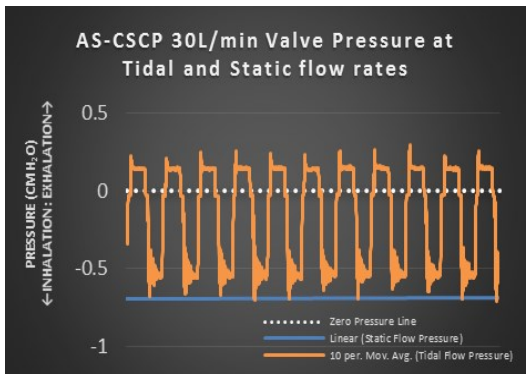
When testing using adult flow rates, the VHCs returned TDD results in the following order from largest to smallest AS-CSCP > ACFV+ > OCD-AS > VOR-NE. The correlating average tidal inhalation pressure from lowest to highest was as follows AS-CSCP > ACFV+ > OCD-AS > VOR-NE. The order of performance when testing the pressures produced at a static 30L/min flow rate was ACFV+ > AS-CSCP > VOR-NE > OCD-AS.

When testing using paediatric flow rates, the VHCs returned TDD results in the following order from largest to smallest ACFV+ > AS-CSCP > VOR-NE > OCD-AS. The correlating average tidal inhalation pressure from lowest to highest was as follows AS-CSCP > VOR-NE > ACFV+ > OCD-AS. The order of performance when testing the pressures produced at a static 15L/min flow rate was AS-CSCP > ACFV+ > VOR-NE > OCD-AS.

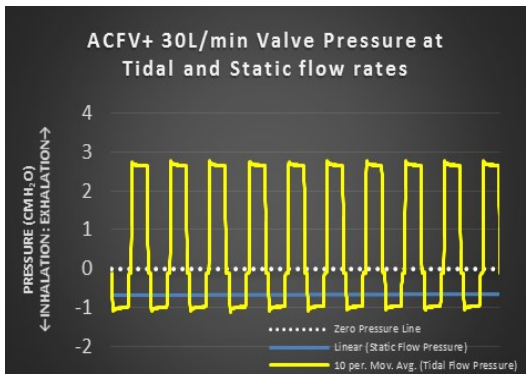
Table 3 summarises the data represented in graphs 1 to 8. The initial 4 columns show the overall averages of inhalation and exhalation pressure over the entire 5 minute periods of tidal breathing simulation. The final 2 columns display the average pressures produced after 5 minutes of constant static flowrates of 30 and 15L/min.

Table 3 : Average inhalation data for adults and paediatric at both static and tidal breathing

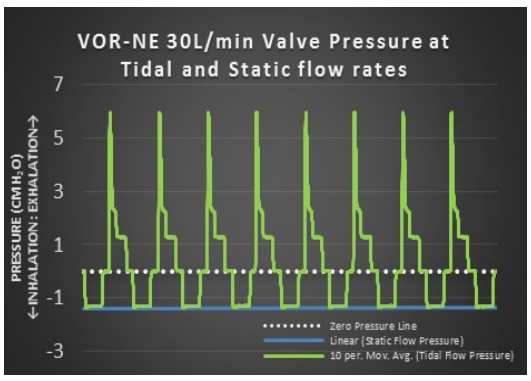
VHC	Adult TIDAL breathing pressure differential (cm/H_2O)		Paed. TIDAL breathing pressure differential (cm/H_2O)		Adult STATIC pressure differential (cm/H_2O)	Paed. STATIC pressure differential (cm/H_2O)
	Inhalation	Exhalation	Inhalation	Exhalation	Inhalation Only	Inhalation Only
AS-CSCP	-0.447	0.359	-0.167	0.134	-0.682	-0.706
ACFV+	-0.661	2.568	-0.291	0.785	-0.574	-0.794
OCD-AS	-0.702	1.033	-0.413	0.093	-2.390	-1.459
VOR-NE	-0.727	1.497	-0.284	0.380	-1.386	-1.112



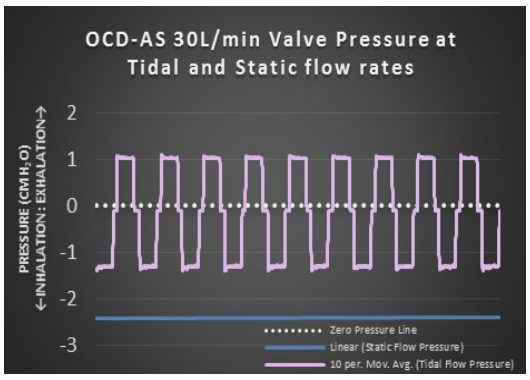
Graph 1: AS-CSCP average pressure using adult static vs tidal flow rates



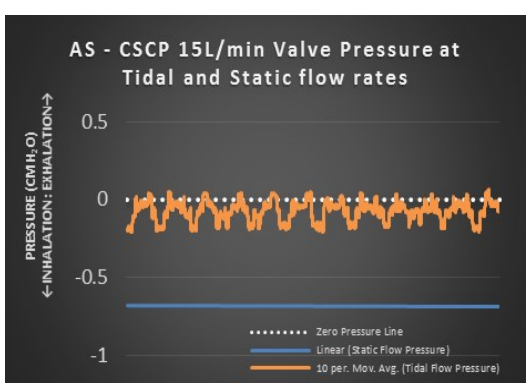
Graph 2: ACFV+ average pressure using adult static vs tidal flow rates



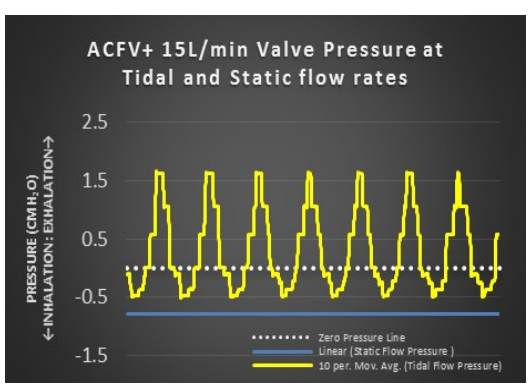
Graph 3: VORTEX average pressure using adult static vs tidal flow rates



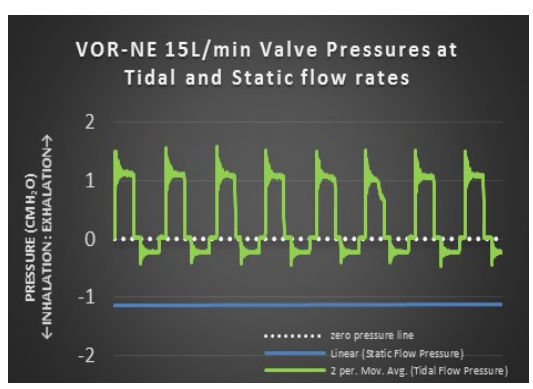
Graph 4: Respironics average pressure using adult static vs tidal flow rates



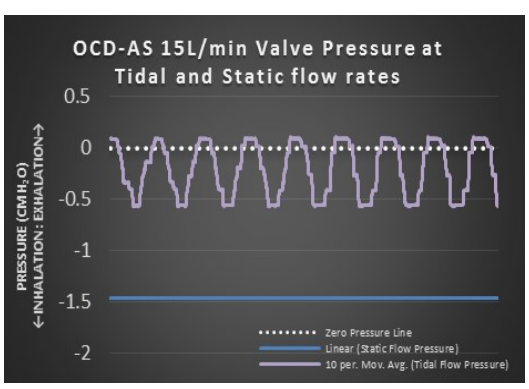
Graph 5: AS-CSCP average pressure using paediatric static vs tidal flow rates.



Graph 6: ACFV+ average pressure using paediatric static vs tidal flow rates.



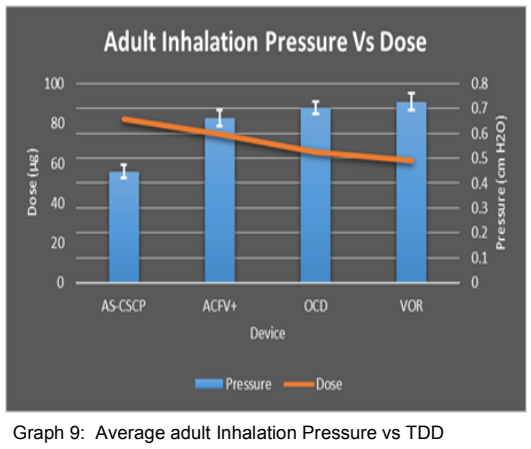
Graph 7: VORTEX average pressure using paediatric static vs tidal flow rates



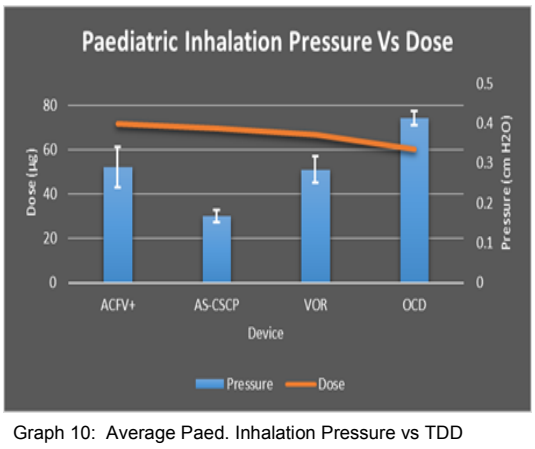
Graph 8: Respironics average pressure using paediatric static vs tidal flow rates.

Discussion

At adult flow rates the AS-CSCP displays the lowest valve pressure on inhalation. This is also true for paediatric tidal breathing rates and paediatric static rates. The order of the TDD from highest to lowest for adult tidal flow rates was AS-CSCP > ACFV+ > OCD-AS > VOR-NE and ACFV+ > AS-CSCP > VOR-NE > OCD-AS for paediatric flow rates. The AS-CSCP delivers the highest TDD compared with the other 3 devices at adult flow rates while producing the lowest valve pressure. The results also show that even though the AS-CSCP delivers slightly less than the ACFV+ at paediatric flow rate (2.15%), these 2 devices provide the lowest pressure differentials in 3 of the 4 flow rate categories, particularly in the static flow rate categories where the AS-CSCP and ACFV+ produce approximately half the pressures on both inhalation and exhalation. The lower inhalation pressure correlates with the higher TDD with the AS-CSCP and ACFV+ comparing favourably with the OCD-AS and VOR-NE when tested using either adult or paediatric tidal breathing waveforms.



Graph 9: Average adult Inhalation Pressure vs TDD



Graph 10: Average Paed. Inhalation Pressure vs TDD

Conclusions

Total delivered dose and valve pressure differential tests have been conducted and compared for several valved holding chambers under simulated tidal breathing conditions. The results confirm a correlation between lower valve pressure generation and improved delivered dose. Valves which produce lower pressure differentials tend to return the better total delivered dose results. This improved TDD is more pronounced at adult breathing rates.

A future, larger study will use a post-actuation delay to alter drug residence time and aim to better determine the factor(s) that cause valve resistance to influence drug dosage.