Functional analysis of several valved holding chamber inspiratory valves.

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Introduction

Inhalation of bronchodilators and corticosteroids is the cornerstone for the therapeutic management of asthma or chronic obstructive pulmonary disease (COPD), however a good intake of inhaled drug requires good hand-lung coordination [1]. To improve inhaled drug delivery, valved holding chambers (VHC) are often used to briefly contain aerosolized drug from pressurized metered dose inhalers (pMDI), removing the necessity of hand-lung coordination and strongly reducing oropharyngeal impaction [2,3]. VHC inspiratory valves have therefore a critical role in drug output from VHCs [4]. The following study aimed at characterizing valve's essential proprieties and how they impact drug delivery by measuring its resistance and its ability to close.

Material and method

Because different valve configurations required different mouthpiece shapes and volumes (ranging from 10,5 to 21,5 mL), six custom-built VHCs were developed differing only by their inspiratory valves and mouthpieces. The six inspiratory valves have different weights, materials and shapes (2 conical, 3 flat and 1 butterfly, show in figure 1).

Valve resistance (cmH20/L/s) was measured by differential pressure analysis at different flow rates (5, 15, 30 or 60 L/min). The ability of the inspiratory valve to close was determined by measuring flow rates with flowmeters placed on both mouthpiece and backpiece of the VHC during USP child breathing patterns simulation, with or without inclination (30°) of the VHC. Delivery of fluticasone propionate (Flixotide 50 µg, GSK) to a filter (emitted dose, ED) was assessed for each custom-built chamber using a breathing simulator (Copley Scientific) simulating coordinated and uncoordinated pediatric use (Child USP pattern).

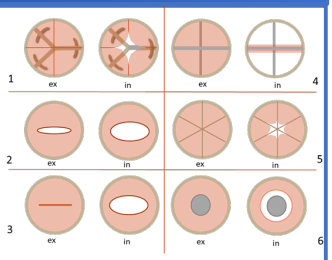

Figure 1: Schematic representation of inspiratory valves during inhalation (in) and exhalation (ex).

Results

1- Resistance

Valve resistance generated at low inspiratory flow rate (5 L/min) varies greatly between the different valves ranging from 9,5 (for valve 3) to 0,27 cmH2O/L/s (for valve 6), however as the flow rate increases, variations are reduced (3,98 to 0,43 cmH2O/L/s at 60 L/min).

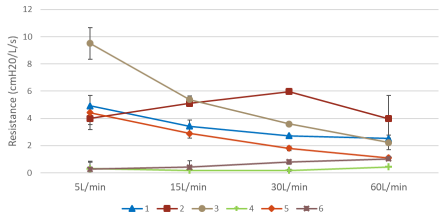

Figure 2. Valve resistance (cmH20/L/s) for the six custom-built VHCs at different flow rate (L/min).

2-Flow rate analysis

The ability to close varies strongly from one valve to another: for some valves, during child breathing pattern, only a low flow rate is detected during exhalation (0.2 L/min) while for others only partial closing can be achieved (Figure 3) and an important flow rate is detected inside the VHC (7.78 L/min).

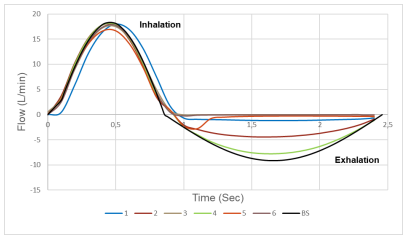

Figure 3. Flow rate analysis for the six custom-built VHCs during child breath simulation (BS).

3- Mass distribution of salbutamol

Similar conclusions are observed with adult breathing pattern and the chamber tilting does not affect these results (Table 1). These results are confirmed by measuring the flow through the expiratory valve, maximum (100% of the initial flow rate) when inspiratory valves are completely closed.

Table 1: Closing capacity of the 6 inspiratory valves depending on breath pattern and VHC tilting.

		Flow passing through the inspiratory valve (L/min)					
Breath Pattern	VHC tilting	Valve 1	Valve 2	Valve 3	Valve 4	Valve 5	Valve 6
Child	0°	-1,20	-6,05	-0,51	-7,78	-0,22	-2,82
	30°	-3,69	-5,56	-0,48	-7,98	-0,66	-2,75
Adult	0°	-1,41	-6,63	-1,55	-16,54	-1,67	-3,50
	30°	-1,26	-6,56	-1,64	-16,15	-0,92	-3,39

4- Emitted dose

As show in figure 4, ED measured with pediatric breathing parameters in coordinated use, is similar for four of the custom VHCs (approximately 31±0.66 µg/puff) while with the other two VHCs ED is lower (approximately 27.6±0.69 µg/puff for valves 3 and 4). When simulating uncoordinated use, ED remains similar for the first four VHCs (30.5±1.49 µg/puff), while the other two VHCs shows an even lower ED (18±1.4µg/puff).

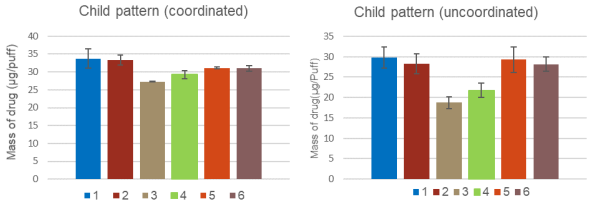

Figure 4. Effect of inspiratory valves on the emitted dose of fluticasone propionate during coordinated and uncoordinated VHC use. (values are means ± SD, n = 3)

Conclusion

Four of the six custom VHCs showed high ED even when simulating uncoordinated use. Among them, all block properly exhaled air excepted one that could only partially block exhaled air. Three showed average resistance and one little resistance to low flow inhalation flow rate. Concerning the two lowers ED VHCs, one showed little resistance to low inhalation flow rates and could only partially block exhaled air, while the other one could close completely but showed high resistance to inspiration at low flow rate. Lower drug output can be explained by high resistance to low flow rate, causing poor opening of the valve at the beginning of the inspiration, and the valve not closing during expiration, causing exhalation inside the chamber. Given the preponderant role of inspiratory valves in the proper functioning of VHCs, it is essential to properly analyze their characteristics, especially at low flow rates. Inspiratory valves must function effectively to not compromise drug delivery.

References :

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