Focus on pMDI and VHC; Past, Present, Future!

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SPACERS AND VALVED AEROSOL RESERVOIRS or ‘holding chambers’ (VHC), to assist delivery of aerosols generated by pressurized metered dose inhalers (pMDIs), have been one of the most important achievements in aerosol therapy over the past 3 decades. Starting as simple tubes or Styrofoam coffee cups, they have undergone a substantial evolution and are now integral to the delivery of aerosol medications. Advantages of VHC include 1) Overcoming the problem of coordination between aerosol discharge from MDIs and inhalation; 2) Small particle selectivity and targeting to the lower respiratory tract (LRT) reducing the oropharyngeal dose by about 90%. The latter effect also reduces the systemic dose of corticosteroids and bronchodilators. VHC, therefore, minimize multiple undesirable side effects including hoarseness, the metallic taste of some inhaled medications, cold freon effect in children and systemic effects (tremor, tachycardia, anxiety, rare adrenal insufficiency, and glaucoma).

The supplement provided with this issue of JAMPDD presents an overview of how far VHC science has come since the earliest, large, and impractical reservoir devices were first conceived in the mid-1970s. It describes the state of the art approach to the study and evaluation of various aspects of VHCs using the new OptiChamber Diamond VHC and the LiteTouch face mask, both developed by Philips Respironics, as a ‘case study’. The supplement includes studies ranging from basic aerosol science to preclinical evaluation of the OptiChamber Diamond VHC in comparison with similar devices.

The history section by Nikander et al.⁽¹⁾ provides a summary of the background and evolution of VHCs over the past 45 years. It is a fascinating story of VHC development as ongoing research improved our understanding of VHC structure and function. Readers will doubtless enjoy following the scientific twists and turns as in good Holmesian fashion clinicians and engineers identified problems and found solutions.

Although it appears that we are nearing the epilogue, there is still a sequel waiting to be drafted. I am sure that this will be produced during the next few years and the authors have set the stage for the next chapter.

Particularly interesting is the 65-year-old story of the 12-year-old girl with asthma who was fed-up with administering epinephrine to herself with a squeeze-bulb nebulizer that tended to flood her schoolbag. She asked her father, an

engineer at the Riker Co, if he could develop a canister of the medication based on the system that Riker had developed during WW2 for spraying insecticide used by the US army in the Far East. The result was the pMDI, followed later by spacers and VHCs, which arose out of the need to overcome the difficult-to-coordinate aerosol discharge and simultaneous inhalation. These devices made it possible to dissociate aerosol discharge and inhalation and improved aerosol targeting to the LRT.

So here are we, scientists, manufacturers, clinicians, and inventors, and there is that girl who, by asking the right person the right question, triggered the development of a unique aerosol delivery system that filled an important need and has stood the test of time!

Reading Nikander et al, I considered how much I have been influenced by parents and by their children’s needs over the years and how those needs led me to undertake research to find solutions to those problems. As a pediatric pulmonologist, it was parents’ frequent complaints about the difficulty of administering aerosol therapy to their children, particularly those under 4 years of age, which led my colleagues and me to think about devising solutions.

To paraphrase William Osler, listen to the patient, and to the caregivers; their questions should become the research that provides answers that improve the quality of life of our patients!

Hatley et al.⁽²⁾ describe the *in vitro* properties of various VHCs with particular reference to the new OptiChamber Diamond VHC. They compared the aerodynamic particle size distribution (MMAD & GSD) of two HFA-pressurized pMDIs, beclomethasone solution and albuterol suspension at two airflow velocities, using three VHCs (OptiChamber Diamond, AeroChamber Z-Stat, AeroChamber Plus) compared to pMDI alone and the effect of washing the VHCs with detergent to further minimize static effects, if any. The results, presented in reader-friendly Forest plots, confirmed numerous previous studies that the VHC reduces the total delivered dose at the mouth by removing 80%–90% of the drug contained in large particles (MMAD ~5–10 μ m) that are, when the pMDI is used alone, aerodynamically removed in the oropharynx by impaction. These results, more pronounced at low flows, make sense given that evaporation of propellant from large particles results in smaller particles during their residence within the chamber. Both anti-static

chambers used in the study (OptiChamber Diamond and AeroChamber Z-Stat) had comparable results for the two flow rates tested, as well as for the two formulations. Both were better than the pMDI alone or than the nonstatic VHC. Washing the OptiChamber Diamond VHC, taken from the original package before using it for the first time, had no additional influence on its aerosol characteristics, confirming that the aerosol was not influenced by static charge after it emerged from the nozzle of the pMDI boot.

Slator et al.⁽³⁾ describe a set of experiments designed to evaluate the impact of inhalation delay and airflow velocity on the *in vitro* delivery of aerosol from four different VHCs (OptiChamber Diamond, AeroChamber Z-Stat, AeroChamber Plus, Volumatic). Although the subject has received considerable attention in the past, the authors created a very sophisticated and accurate custom-built inhalation-delay test rig, which enabled automation of precise inhalation delays (0, 5, or 10 seconds). They also evaluated various airflow velocities. While the study was designed primarily to address FDA regulatory issues, development of the automated solenoid-controlled test rig is a positive step in improving the precision of testing the impact of inhalation delay.

All VHCs studied showed a reduction in the total emitted dose when the duration of the delay between aerosol discharge into the VHC and evacuation of the device increased, emphasizing the need for some degree of cooperation by the patient or caregiver. They showed that, on average, there was a statistically significant reduction in total dose emitted after a delay of 10 seconds. Furthermore, the emitted dose increased with increased airflow. This effect was significantly greater with nonstatic VHCs compared to static VHCs.

Whereas the articles referred to above confirm previous studies by several investigators, the study by Xu et al.⁽⁴⁾ constitutes a new approach to the evaluation of the VHC which takes into account a relatively neglected area, namely the face mask. As the authors note, the interest in face mask design and mask properties is relatively recent. Even less explored is the evaluation of face mask performance. It is very important to consider that, in practice, face masks are attached to human faces. Thus, when modeling aerosol delivery, it is crucial to study masks under relatively realistic conditions. Xu et al. used realistic face models, as well as clinically relevant airflows, testing six VHCs with face masks (OptiChamber Diamond with LiteTouch face mask, AeroChamber Z-Stat and AeroChamber Plus both with ComfortSeal face mask, Pocket Chamber and Pocket Chamber Antistatic with standard face mask, and Volumatic with Silicone face mask). In addition, they used a pulley system to deliver a measured constant (1.9 kg) force onto the face masks including more realistic 3-D 'faces' rather than a flat planar surface. An important lesson from Xu's study was that minimal leakage occurred when vertical head tilt was avoided, suggesting that minimizing facial tilt minimized distortion of the flexible face mask rim. These authors recognized the limited age range of their model faces. For example, our group averaged faces from almost 300 children to establish validated average small, medium, and large clusters of faces from which 'average' small, medium, and large facial dimensions were derived.⁽⁵⁾ How to best to estimate an individual face from average faces is an important topic for future study.

In addition to 'fit,' force applied to the face mask, in order to achieve a seal, is increasingly recognized as an important

factor in face mask design. Clearly, the force applied to the face mask will influence the seal. However, with small children, application of too great a force may result in mask distortion/herniation, discomfort and fear, causing rejection of the face mask and or crying, which has been shown to decrease aerosol delivery greatly. Addressing the force parameter is therefore important and the study by Xu et al.⁽⁴⁾ establishes an improved methodology to better evaluate this interesting and important feature of face mask design. The importance of differences in sealing force and its effect on seal and drug delivery will be important in comparing mask designs with reported values ranging from 1.9 kg⁽⁴⁾ to 200–400 grams (preliminary work from our group,⁽⁶⁾ as well as the study of Minh⁽⁷⁾ in this issue), suggesting that measuring techniques and face mask design affect the assessment of the seal. Minh et al.⁽⁷⁾ evaluated a new device for measuring flow and force during application of pMDI + VHC with face mask in 30 children aged 1–4 years of age. This innovative approach uses an electronic device—a Facemask Datalogger—to measure the applied force when positioning a custom instrumented OptiChamber Diamond VHC with LiteTouch face mask onto children's faces. The mean application force in the Minh study was only 4 N equal to 411 g, and the mean time needed to empty the VHC was 4.5 sec. Results of Minh et al. were similar to reported findings from our group. Using a mechanically applied mass, we found a good seal with only 200 g of force.⁽⁶⁾ Both the electronic and mechanical systems results suggest that the forces needed to seal the face masks (e.g., Soothermask™ and LiteTouch™ masks) to children's 'faces' under specified conditions may be less than previously assumed.⁽⁸⁾ Whether this difference is related to the actual face mask design and configuration has not been fully answered, and clearly further studies are needed. Doubtless, the topic of applied force, its measurement, and its incorporation into face mask design and evaluation will receive more attention in the near future. Another important factor (not discussed in the present supplement) that should be considered in the future evaluation of new VHCs and associated masks is mask dead space in particular, for pediatric applications.^(9,10)

Closer to real life, Ditcham et al.⁽¹¹⁾ used scintigraphy to compare lung deposition between mouth pieces and face mask delivery of labeled albuterol through a pMDI connected to the OptiChamber Diamond VHC used with standard mouthpiece or the LiteTouch face mask. In contrast to previous studies, these authors attempted to correlate aerosol deposition with narrative data relating to tolerance and compliance in a group of children 3–5 yrs of age. This is a welcome approach but their tolerance data may not be applicable to a younger (<3 years) population of mask users where mask acceptance is more critical. In addition, inspection of their scintigraphic scans suggests that they may have some interesting data suitable for future publication. The images clearly show facial and nasal deposition with the facemask, (absent with the mouthpiece) a factor that may be important in facial and nasal adverse effects. How that deposition relates to leaks, force, face mask design, and breathing pattern may lead to important future face mask designs.

Another important finding from the Ditcham study was the similarity between face mask and mouthpiece aerosol delivery to the LRT. These results confirm recent *in vitro* and *in vivo* studies^(12,13) and reassure clinicians about the efficacy of face mask (vs. mouth piece) breathing for aerosol

delivery in young patients contrary to older data from Chua⁽¹⁴⁾ that projected the opposite based on data from somewhat older (>6 year-old) children.

It is most timely to have a JAMRDD supplement devoted entirely to valved holding chambers with particular emphasis on face masks and pediatric applications. It provides an excellent overview of the past and sets the stage for future developments that will doubtless lead to improvements in the aerosol science and future clinical applications of valved aerosol holding chambers and masks, particularly in infants and toddlers.

Author Disclosure Statement

The author has patent rights for devices for delivering aerosols to infants.

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