Spacers and Valved Holding Chambers—The Risk of Switching to Different Chambers

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Spacers are pressurized metered-dose inhaler (pMDI) accessory devices developed to reduce problems of poor inhaler technique with pMDIs. Spacers that feature a 1-way inspiratory valve are termed valved holding chambers (VHCs); they act as aerosol reservoirs, allowing the user to actuate the pMDI device and then inhale the medication in a 2-step process that helps users overcome challenges in coordinating pMDI actuation with inhalation. Both spacers and VHCs have been shown to increase fine particle delivery to the lungs, decrease oropharyngeal deposition, and reduce corticosteroid-related side effects such as throat irritation, dysphonia, and oral candidiasis commonly seen with the use of pMDIs alone. Spacers and VHCs are not all the same, and also are not interchangeable: the performance may vary according to their size, shape, material of manufacture and propensity to become electrostatically charged, their mode of interface with the patient, and the presence or otherwise of valves and feedback devices. Thus, pairing of a pMDI plus a spacer or a VHC should be considered as a unique delivery system. In this

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Abbreviations used
pMDI- Pressurized metered-dose inhaler
VHC- Valved holding chamber

Rostrum we discuss the risk potential for a patient getting switched to a spacer or VHC that delivers a reduced dose medication.

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Key words: *Spacer; Valved holding chamber; Inhalers*

INTRODUCTION

Pressurized metered-dose inhalers (pMDIs) are the most widely used devices for delivery of aerosol medications due to their effectiveness and relative simplicity of use.[1] However, an important weakness of pMDIs is their propensity to be used suboptimally or incorrectly,[2] a problem that has been recognized since their inception and that is unfortunately still present today.[3] In a survey conducted among persons referred by family physicians, internists, surgeons, and pulmonologists for routine spirometry, only 10.8% of the subjects correctly performed all the maneuvers recommended for self-administration and 24.7% failed to perform more than half the maneuvers adequately.[4] A review of 2123 patients with asthma by the National Services for Health Improvement found that, without training, 86% failed to properly use their inhaler.[5] Even with inhaler training, some people will revert to bad technique, and some will not benefit from training.[6] One of the most common errors associated with pMDIs is the lack of coordination between inhaler actuation and inhalation.[2] Coordination between inhalation and generation of the aerosol, so that the inhaler should be activated just after onset of inspiration, is crucial to increase drug deposition in the lung during pMDI use.[7] In the CRITIKAL study, poor coordination between inhaler activation and inhalation led to a greater likelihood of uncontrolled asthma symptoms and a higher rate of exacerbations.[8]

Spacers and valved holding chambers (VHCs) are medical devices, made of either polycarbonate plastics or metal, that interface with the pMDI. They are shaped like a tube with openings at both ends: one opening is the mouthpiece that is placed into the mouth (or a facemask fitting the spacer with a tight seal) and the other opening is where the pMDI is inserted.[9-11] In this way, they provide additional space for the aerosol plume to develop.[9-11] In fact, with either a spacer or a VHC, the aerosol flows from the pMDI into the chamber, thus allowing deceleration of the aerosol plume and, in the case of VHCs, trap the aerosol cloud until the patient inhales from the chamber rather than directly from the pMDI.[9-11] This greatly reduces oropharyngeal drug deposition via retention of large aerosol particles within the holding chamber, thus reducing the potential for corticosteroid-related local side effects (ie, candidiasis and dysphonia) and systemic absorption.[9-11] Although the terms "spacer" and "VHC" are frequently used interchangeably, the former is a generic term for any open tube, sometimes made from household items such as toilet paper rolls or plastic soda bottles,[12,13] placed on the mouthpiece of the pMDI to extend its distance from the patient's mouth.[9-11] However, a VHC is a spacer that is manufactured with a 1-way, low-resistance valve to regulate inspiratory flow and prevent exhalation into the device.[9-11] The newer VHCs such as the AerochamberFlow-Vu (Trudell Medical International, London, Ontario, Canada), the Opti-Chamber Diamond (Philips Respironics, Guildford, Surrey, UK), or the InspiraChamber (Lupin Pharmaceuticals, Pune, Maharashtra, India) have an alert whistle to provide feedback on correct inspiratory flow.[14] The VHCs are generally preferable to simple spacers because the latter, because of the lack of a 1-way valve, are susceptible to dispersal of the aerosol within due to uncoordinated exhalation into the chamber. In addition, VHCs substantially lessen the need of inhaler actuation-inhalation coordination, which is problematic for both adults[1,2] and children.[15] As a result, VHCs may increase pulmonary deposition of drug suspensions[16] and, compared with the pMDI alone, may improve clinical outcomes including airway hyperresponsiveness,[17] lung function,[18-20] and asthma control,[21] with a reduction in the requirement for oral corticosteroids.[22] Accordingly, the use of VHCs is firmly recommended in international guidelines on the management of asthma[23-25] and chronic obstructive pulmonary disease[26] (Table I), particularly in patients prone to pMDI handling errors.[27] Although patients who have correct technique with pMDIs may not derive any benefit from the use of VHCs,[27] the latter reduce oropharyngeal deposition of large aerosol particles emitted from a pMDI, even with "perfect" technique.[28]

Although the potential benefits of spacers/VHCs are clear, there is less consensus as to whether there are any meaningful differences between different devices. There is substantial, occasionally contradictory, literature detailing the relative performance of a large number of different spacers or VHCs.[29] It is well established from *in vitro* studies that a specific VHC may perform differently with different drugs[30-32] or a specific drug may perform differently in terms of emitted fine particle mass if inhaled through different VHCs.[33] Thus, substitution of one type of spacer or VHC with another may have both safety and clinical implications unless otherwise proven as equivalent through *in vitro* and/or *in vivo* studies. Hatley et al[34] found that the aerodynamic particle size distribution of albuterol aerosols obtained by 2 antistatic VHCs was similar but significantly different from that obtained by using a conventional VHC. Recently, D'Vaz et al[35] reported no difference in the bronchodilator response, as assessed by FEV_1 changes, to salbutamol inhaled through different spacers in children with asthma.[35] Accordingly, radiolabeled aerosol studies found equivalent lung deposition of aerosol using different spacers.[36] However, detection of differences in the bronchodilator response to an agent delivered by different devices may be difficult due to the potentially confounding effects related to the patient inhalation technique, as well as due to the variability in the levels of airway narrowing, especially when such variability is not adequately accounted for in patient selection.[18,19] In addition, even low doses of bronchodilators delivered by virtually any inhalation device may produce near-maximal bronchodilator responses falling on the flat part of the dose-response curve.[18,19,37] Although some studies failed to show significant differences in lung deposition between different spacers/VHCs,[36] others found that large-volume (≥750 mL) resulted in greater whole lung deposition compared with smaller devices.[38] Differences in the

TABLE I. Guidelines recommending spacer or VHCs

Institution	Year	Recommendation(s)
American Association of Respiratory Care	2007	A spacer/VHC should be used with an MDI; a spacer/VHC with facemask is appropriate for patients (usually < 3 y) unable to use a mouthpiece.
American College of Chest Physicians/American College of Allergy, Asthma & Immunology	2005	For patients who have trouble coordinating inhalation with device actuation, the use of a spacer (with a valve) may obviate this difficulty; the use of spacers is mandatory for infants and young children.
British Thoracic Society/Scottish Intercollegiate Guidelines Network	2012	Children and adults with mild and moderate exacerbations of asthma should be treated by bronchodilators given from a pMDI + spacer/VHC, with doses titrated according to clinical response; in children aged 0-5 y, pMDI + spacer are the preferred method of delivery of β2 agonists or inhaled steroids; the spacer should be compatible with the pMDI being used.
Canadian Pediatric Asthma Consensus Guidelines	2005	The use of a VHC with pMDI is strongly recommended for children.
Canadian Thoracic Society	2010	The addition of a VHC with mouthpiece is helpful in overcoming poor hand-mouth coordination and reducing side effects, with increased drug delivery and lung deposition; VHCs with facemask attachments are useful for the elderly, who can use 4-6 tidal breaths for each actuation of the medicine.
Global Initiative for Asthma	2017	pMDI + dedicated spacer/VHC with facemask is the preferred delivery system for children aged 4 y and younger; pMDI + dedicated spacer/VHC with mouthpiece is the preferred delivery system for children aged between 4 and 6 y.
Global Initiative for Chronic Obstructive Lung Disease	2014	For the MDI, the addition of a large- or small-volume spacer often overcomes coordination problems, and improves lower airway deposition and clinical benefit.
International Primary Care Respiratory Group	2006	The preferred device for administering inhaled asthma medication for infants and young children is a pMDI with a spacer and face mask; as the child's ability to co-operate improves (often around the age of 4-6 y), a spacer with a mouthpiece can be used rather than a facemask.
National Heart, Lung, and Blood Institute	2007	All patients taking inhaled steroids should use a pacer/VHC; patients younger than 5 y should use a spacer/VHC with facemask for inhaled steroids.
Dutch College of General Practitioners (NHG) guidelines asthma and COPD	2014	Children: pMDIs should always be used in combination with a spacer/VHC. Adults: pMDIs should always be used in combination with a spacer/VHC, unless the patient can use a pMDI adequately.
National Institute for Clinical Excellence (UK)	2010	Spacer/VHC recommended with a facemask where necessary for both corticosteroids and bronchodilators (children younger than 5 y); a pMDI used with an appropriate spacer/VHC is first choice for corticosteroids (children aged 5-15 y); for patients with chronic obstructive pulmonary disease, pMDI alone is rarely suitable for use with the elderly; the spacer should be compatible with the patient's pMDI.

study design and methodology may account for these contradictory results.

Dissanayake et al[39] set out to address the impact of spacer design on drug delivery performance and look at potential implications for clinical use. Four similarly sized chambers were compared "out of the box" in terms of statistical equivalence with the most widely prescribed, nonconducting VHC, Aerochamber Plus chamber (Trudell Medical International) with respect to retention of drug particles within the device and the aerodynamic particle size distribution of the drug particles delivered. The authors found that only the Aerochamber Flow-Vu chamber demonstrated an equivalent profile of dose retention and delivery versus the reference chamber. The Compact Space Chamber Plus (Medical Developments, Victoria, Australia), the OptiChamber Diamond, and InspiraChamber devices all retained approximately twice as much drug, delivering around half the dose and showing nonequivalent performance compared with the Aerochamber Flow-Vu chamber and the reference chamber (pretreated AerochamberPlus chamber). Thus, the performance of VHCs that resemble one another in terms of appearances and dimensions may differ markedly, implying that VHCs should not automatically be considered interchangeable.[39] Although equivalent performance between different VHCs has been demonstrated,[34] a recent *in vitro* study[40] and a literature review[14] provide further support for the results found by Dissanayake et al.[39] In considering the important attributes of such delivery devices, the review notes a shift in emphasis from chamber size and shape to other aspects, such as consistency of drug delivery, static charge reduction, valve performance, and factors optimizing facemask effectiveness, such as flexibility and seal.[14] Because differences exist between different spacers or different VHCs, which in some cases are sufficiently large that meaningful and overt clinical differences would be anticipated as a result, each pMDI spacer/VHC combination should be treated as a unique inhaled medication delivery system.[29] In this connection, the European Medicines Agency guidance recommends that the development and registration process for drug products delivered by pMDIs include testing and supporting *in vitro* and *in vivo* data of the pMDI when used with at least 1 named spacer/VHC.[41] In addition, the European Medicines Agency guidance states that patients with asthma with well-controlled disease by inhaled medications delivered through pMDIs plus spacer/VHC should always use the same type of spacer/VHC and not switch to a different spacer/VHC that may deliver different amounts of drugs.[41]

The European Union registration documentation for pMDIs (Summary of Product Characteristics and Patient Information Leaflet) specifically notes that the VHC to be used should be based on the device used in the product development/registration studies. In case of a spacer/VHC substitution, appropriate equivalency data for the alternative device must be presented.[41] Surprisingly, at variance with European Medicines Agency, other regulatory authorities, such as for instance the US Food and Drug Administration, do not require data for a specific named spacer to support pMDI approval. However, in a draft Food and Drug Administration Chemistry, Materials and Controls Industry guidance for orally inhaled products issued in 1998 by the Center for Drug Evaluation and Research, there is recognition that clinical efficacy assessment of pMDI-delivered aerosols requires consideration of the presence of a spacer/VHC.[42]

CONCLUSIONS

There is published evidence that the union of a particular pMDI and a given spacer/VHC is considered a specific inhaled medication delivery system. Therefore, we recommend physicians to focus on selecting the most appropriate spacer/VHC for the patient and their pMDI(s), given the weight of clinical evidence available. Although the noninterchangeability of VHCs is recognized,[14,34,40] we also recommend clinicians to monitor for any changes in disease control if the patient's VHC was switched. Furthermore, we believe that pharmacists need to appreciate that spacers/VHCs may deliver different amounts of drug from the pMDI and therefore substitution of a different device from that prescribed by the physician may have an impact on the patient. Finally, regulatory authorities need to be aware of the risks inherent in the current approval process of spacer VHCs through CE mark registration and look for improvements to, at the very least, restrict the ability of devices with serious design/quality flaws to be approved and used by patients.

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