should report DLCO as percent predicted and properly adjust it for lung volume. The American Thoracic Society recommends adjusting predicted values (not measured values) for altitude and hemoglobin and makes clear that the DLCO/alveolar volume (VA) ratio does not correct for lung volume.\(^2\)

DLCO and the DLCO/VA ratio change with lung volume as would be expected with changes in surface area for diffusion. Percent predicted for DLCO adjusted for lung volume (D\(\text{aco}\)) and DLCO/VA ratio adjusted for lung volume (K\(\text{aco}\)) also should be reported, using the following equations: D\(\text{aco}\) predicted = DLCO predicted \(\times (0.58 + 0.42 \times \text{VA} / V_{Atlc})\) and K\(\text{aco}\) predicted = K\(\text{co}\) predicted \(\times (0.42 + 0.58 / \text{VA} / V_{Atlc})\), where K\(\text{co}\) = carbon monoxide transfer coefficient and V\(\text{Atlc}\) = predicted VA at total lung capacity.\(^3\)

It also would be helpful to know whether CMS affects spirometry (FEV\(_1\) and vital capacity) and lung volume. Percent predicted carbon monoxide diffusing capacity for lung volume (143\% vs 130\% \pm 23\%, \(P = .30\)), carbon monoxide diffusing capacity adjusted for lung volume (142\% \pm 20\% vs 143\% \pm 23\%, \(P = .92\)), and carbon monoxide diffusing capacity per unit of alveolar volume adjusted for lung volume (137\% \pm 14\% vs 145\% \pm 23\%, \(P = .29\)) were similar in patients with CMS and control subjects.

These additional data further strengthen our conclusion that the large differences in pulmonary-artery pressure responsiveness between patients with CMS and healthy control subjects are not related to differences in the pulmonary microcirculation between the two groups.

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**Response**

To the Editor:

In our recent article in CHEST,\(^1\) we suggested that in patients suffering from chronic mountain disease (CMS), the exaggerated increase in pulmonary-artery pressure during mild exercise is not related to a difference in the extent of the pulmonary microcirculation because carbon monoxide diffusing capacity was comparable in patients with CMS and control subjects.\(^1\) Johnson suggests that to reinforce this conclusion, the data should be analyzed further and reported as percent predicted values adjusted for lung volume. Percent predicted carbon monoxide diffusing capacity (143\% \pm 22\% vs 157\% \pm 25\%, \(P = .15\)), carbon monoxide diffusing capacity per unit of alveolar volume (137\% \pm 13\% vs 130\% \pm 23\%, \(P = .30\)), carbon monoxide diffusing capacity adjusted for lung volume (142\% \pm 20\% vs 143\% \pm 23\%, \(P = .92\)), and carbon monoxide diffusing capacity per unit of alveolar volume adjusted for lung volume (137\% \pm 14\% vs 145\% \pm 23\%, \(P = .29\)) were similar in patients with CMS and control subjects. These additional data further strengthen our conclusion that the large differences in pulmonary-artery pressure responsiveness between patients with CMS and healthy control subjects are not related to differences in the pulmonary microcirculation between the two groups.

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**How to Compare Two Different Metered-Dose Inhaler-Valved Holding Chambers in the Administration of Salbutamol**

To the Editor:

I read with interest the correspondence by Di Berardino et al (February 2010)\(^4\) to see how the difficult task of inhalation product comparison has been addressed.\(^4\) I agree that different valved holding chambers (VHCs) that are available for inhalation should not be used without evidence of equivalent efficacy/safety and compatibility between pressurized metered-dose inhalers (pMDIs) and VHCs, but I think that the authors’ proposal is not enough to ensure the correct delivery of aerosolized drugs. Conversely, it seems to be an excuse to use a new VHC without the required evidence.

The clinical response to a specific pMDI cannot be assumed to be equivalent if a different spacer is used or if a different pMDI is used with the same spacer. The development of a pMDI should always include the testing of at least one specific named spacer for use with the particular pMDI, which should be stated in the labeling. If the spacer is to be replaced subsequently by an


References

alternative spacer, appropriate in vitro or in vitro and clinical data must be presented.\textsuperscript{3}

The proposed “amount of drug within the respirable range” is not enough to ensure equivalence from an in vitro point of view since the whole aerodynamic particle size distribution has to be compared.\textsuperscript{3} If comparative in vitro determination using a validated method does not show equivalence, a clinical comparison is required. This clinical comparison must include an assessment of systemic safety through investigation of equivalence based on pharmacokinetic data or pharmacodynamic data.\textsuperscript{3}

From an efficacy viewpoint the study must be sensitive enough to discriminate between spacers. For a study to have assay sensitivity at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other. Consequently, the proposed study design to assess “improvement of spirometric parameters” does not comply with the regulatory requirements\textsuperscript{3,5} and the state of the art,\textsuperscript{3} consisting of the estimation of the relative potency. Furthermore, the authors have neither compared the results statistically nor predefined the acceptance range to conclude that both VHCs are equivalent. Therefore, it is not possible to conclude that “both of the VHCs tested were suitable for use in the delivery of salbutamol.”\textsuperscript{1} The new VHC should be compared properly to be used and it should be used only with those pMDIs investigated.

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Response

To the Editor:

In reply to the response by García-Arieta regarding our previous correspondence, we are pleased to see that we have attained our initial objective of drawing attention to and provoking discussion on the unacceptable situation concerning drug delivery through pressurized metered-dose inhalers (pMDI) and spacers. The main problem is that summaries of product characteristics of drugs in pMDIs currently available on the market often do not contemplate the use of valved holding chambers (VHCs), even if evidence suggests that they should not be used without them in order to avoid oropharyngeal deposition, and do not report instructions for use or therapeutic dose when administered with specific VHCs. Moreover, it has even been suggested that plastic or glass bottles can be used instead of VHCs. On the basis of this evidence, many patients probably do not use drugs properly delivered by pMDIs and do not receive the optimal therapeutic dose.

We agree that if a pMDI has been designed for use with a specific spacer it should always be used with this named spacing device. In this case, however, both should be present in the same package to avoid misuse and must be reported in the product warnings, for example, “These instructions are not necessarily valid when this pMDI is used with other spacers.”

Aerosol therapy is a complex process that depends on nebulizer performance and patient features. In order to avoid errors, these variables should be studied separately. The amount of drug within the respirable range is an objective parameter to quantify the amount of drug available at the end of the spacer system and potentially capable of reaching the lower airways. This simple method has been suggested to standardize first-step aerosol therapy delivery and is currently the only way of assessing the effective amount of drug administered. Moreover, if comparative in vitro determination does not show equivalence, it is highly likely that either will clinical comparison. If pMDI drugs are to be used with different spacers, instructions must be given about how to make the same effective amount of drug to be administered available at the end of each spacer. Our results were supported by statistical analysis, particularly a general linear model for repeated measures using type of treatment and sex as factors and age as covariate. FEV\textsubscript{1} (\(F = 28.733; P < .001\)) and peak expiratory flow (\(F = 25.879; P < .001\)) were shown to increase significantly after both treatments.

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