HFA–BDP and its implications for the quiet zone

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Introduction

It is difficult to assess changes in the function of small airways using conventional measures of pulmonary function since these measurements are relatively insensitive, variable and/or physiologically non-specific. Recent advances in high-resolution computed tomography (HRCT) imaging have made it possible to obtain non-invasive reproducible measurements of structure–function relationships within the lung. This technique has great potential for diagnosing changes in small airway function and in assessing response to drug treatment.

This article will outline the role of HRCT in elucidating the effects of HFA-BDP within the small airways. The data presented herein have been adapted from References 1–3.

High-resolution computed tomography to assess small airways function

High-resolution computed tomography (HRCT) is a non-invasive imaging technique that can be used to assess pulmonary structure–function relationships (4–6). It allows direct radiographic evaluation of luminal calibre and wall thickness of macroscopic airways >2 mm in diameter (7), although direct measurement of changes in the calibre of the small airways (<2 mm in diameter) is not yet possible. However, HRCT can be used to indirectly assess the small airways by measuring the regional air trapping that results from small airways narrowing and the hyperreactivity of the small airways to methacholine (8,9). HRCT is also more sensitive than spirometry (8,10) in providing an accurate and reproducible assessment of small airways changes in mild asthma.

Regional air trapping can be assessed by analysis of lung attenuation curves (LAC) which represent the frequency distribution of lung attenuation units within axial sections in a region of interest; a shift to the left (to lower attenuation) in the LAC at a given standardized lung volume (usually residual volume) reflects an increase in air trapping, whereas a shift to the right (to higher attenuation) reflects improvement in air trapping that may be attributed to therapeutic efficacy (8).

Thus, functional HRCT provides reproducible measurements of cross-sectional area of macroscopic airways, as well as regional attenuation characteristics reflecting the patency of peripheral airways. This imaging technique is thought to be more sensitive than pulmonary function tests in the early stages of chronic airways disease and has considerable potential for use in the diagnosis and longitudinal evaluation of patients.

Inhaled corticosteroids and the small airways

As prophylactic agents, corticosteroids have been the cornerstone of asthma treatment. Inhaled corticosteroids (ICS) have now become established as first-line treatment for patients with persistent asthma (11,12).

It is clear that anti-inflammatory treatment needs to be directed to both large and small airways to achieve maximal suppression of inflammation (13). However, only about 10% of the steroid dose generated from chlorofluorocarbon (CFC)-based metered-dose inhalers reaches the lower respiratory tract with the greater part of the medication being deposited in the large airways (14).

The most widely used ICS preparations in Europe are beclomethasone dipropionate (BDP), budesonide and fluticasone propionate, with BDP being the first and still the most commonly prescribed ICS. BDP reformulated with the alternative propellant, hydrofluoroalkane (HFA)-134a, results in a solution preparation that delivers an aerosol with a much smaller mean particle size (MMAD 0.8–1.2 μm) than that of the suspension aerosols generated by conventional chlorofluorocarbon 11/12 (CFC)-based metered-dose inhalers of BDP (MMAD 3.5–4 μm). The availability of an extrafine corticosteroid aerosol raises the possibility of more effective delivery of inhaled anti-inflammatory medication to the lung periphery in asthmatic patients and thus more effective suppression of inflammation and improved function of the small airways in asthma.

HFA-BDP and the small airways

HRCT was used to address the hypothesis that, compared to a CFC-based inhaled corticosteroid [beclomethasone dipropionate (BDP)] (Beclovent™), 3 M HFA-BDP...
(QVAR™, 3M Pharmaceuticals, St Paul, MN, U.S.A.), administered in the same low dose (50 μg puff⁻¹ ex-nasow, two puffs twice daily), would lead to greater improvement in small airways patency in patients with mild-to-moderate persistent asthma \( (\text{FEV}_1 \geq 60\% \text{ predicted; } PC_{20} \leq 4 \text{mg ml}^{-1}) \) after a one month course of treatment. Changes in small airways patency were assessed indirectly using a validated thoracic HRCT technique for quantitating changes in regional hyperinflation (8, 10).

Variations in lung attenuation as an indirect measure of air trapping were characterized in two ways from the LAC: median lung attenuation and the lowest 10th percentile of the frequency distribution (15). Lung attenuation was assessed on these parameters for the regions of interest in the right upper and lower lobes at the different measurement times. Automated routines divided axial right lung sections into three area-equivalent gravitational zones: anterior (non-dependent), middle and posterior (dependent), intended to correspond roughly to West’s three physiologic zones (16) (Fig. 1). At any axial level, whole lung as well as regional (gravitational zone) measurements were obtained.

The average median pre-methacholine lung attenuation increased by 39 units in the HFA group between the two visits (indicating less regional air-trapping) but remained essentially unchanged in the CFC group (Table 1).

At the baseline visit, the reduction in lung attenuation after methacholine (indicating worsening regional air-trapping in response to methacholine) is similar for the HFA and CFC groups (-29 vs. -26, respectively; \( P=0.90 \)). In contrast, at the post-treatment visit, the magnitude of the decrease in lung attenuation in response to methacholine is reduced in the HFA group compared to the baseline response in the same subjects (-17 vs. -29), while the magnitude of the decrease in lung attenuation following methacholine compared to the baseline response is augmented in the CFC group. The difference in the effects of the two treatments (HFA vs. CFC) on response to methacholine is statistically significant \( (P=0.04) \), implying a relatively more favourable effect on regional hyperreactivity after treatment with HFA- than with CFC-BDP. Moreover, the lung attenuation response to methacholine improved (i.e. lung attenuation decreased less, implying less increase in regional air-trapping induced by methacholine) significantly more often following treatment with HFA-BDP than CFC-BDP.

In summary, this study demonstrates a greater efficacy of HFA-BDP compared to CFC-BDP in reducing regional air-trapping, as assessed by changes in the regional distribution of lung attenuation. In addition, greater efficacy of HFA-BDP is also shown in reducing regional airways hyperreactivity, as determined by changes in regional air-trapping after bronchoprovocation with

![Image: Axial lung section divided into three area-equivalent gravitational zones (anterior or non-dependent, middle, and posterior or dependent), corresponding to West's three physiologic zones (16).](image)

**Table 1.** Median lung attenuation at RV, pre-methacholine, mid lung zone, RLL

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC (n = 15)</td>
<td>-695 ± 72*</td>
<td>-692 ± 61</td>
<td>3</td>
</tr>
<tr>
<td>HFA (n = 16)</td>
<td>-674 ± 89</td>
<td>-635 ± 77</td>
<td>39</td>
</tr>
</tbody>
</table>

*Hounsfield units (HU); mean ± sd

Source: Ref. 1.

**Table 2.** Median lung attenuation at RV, mid lung zone, RLL

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-MCT</th>
<th>Post-MCT</th>
<th>Δ</th>
<th>Pre-MCT</th>
<th>Post-MCT</th>
<th>Δ</th>
<th>ddΔ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC (n = 9)</td>
<td>-690 ± 93*</td>
<td>-716 ± 84</td>
<td>-26</td>
<td>-680 ± 75</td>
<td>-740 ± 80</td>
<td>-60</td>
<td>34</td>
</tr>
<tr>
<td>HFA (n = 11)</td>
<td>-692 ± 68</td>
<td>-721 ± 70</td>
<td>-29</td>
<td>-646 ± 57</td>
<td>-663 ± 80</td>
<td>-17</td>
<td>12*</td>
</tr>
</tbody>
</table>

*HU; \( P<0.04 \); difference from \( \Delta \Delta \) for CFC group.

Source: Ref. 1.
methacholine, again assessed by analysing changes in the distribution of lung attenuation. These differences between the effects of the two formulations of BDP on regional air-trapping and regional hyperreactivity are consistent with the greater penetration of the smaller airways by the extra-fine HFA, compared to the larger particle size CFC, corticosteroid aerosol previously demonstrated by radio-labelled aerosol deposition studies (17).

Conclusion

In conclusion, functional imaging provides a sensitive new tool for assessing the long-term effect of corticosteroid aerosols on small airways function. Using this new assessment tool it has been shown that the extrafine HFA-BDP aerosol appears to have greater efficacy than the same dose of the larger particle size CFC-BDP aerosol on small airways function, most likely due to the more effective delivery of the extrafine corticosteroid aerosol to the lung periphery. Additional studies are needed in larger numbers of patients with asthma of varying severity over longer periods of time to assess further the impact of targeting the small airways for treatment with anti-inflammatory agents on lung function and other clinical outcomes.

References