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## Paradoxical Bronchoconstriction with Short-Acting Beta Agonist

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Study Design A  
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**Conflict of interest:** None declared

**Patient:** Male, 25  
**Final Diagnosis:** Paradoxical bronchospasm  
**Symptoms:** Dyspnea on exertion • shortness of breath  
**Medication:** Albuterol • levalbuterol  
**Clinical Procedure:** Pulmonary function testing  
**Specialty:** General and Internal Medicine





**Objective:** Unusual clinical course  
**Background:** Asthma is a common disease in the U.S. population. Initial therapy in the stepwise approach for asthma management is short-acting  $\beta_2$ -agonist (SABA) therapy as needed for symptom control. However, a significant adverse event that can occur with administration is bronchospasm. Here, we report a case of paradoxical bronchospasm with administration of SABAs during multiple pulmonary function tests (PFTs).

**Case Report:** A 25-year-old, non-smoking, African American male with a history of moderate asthma and allergic rhinitis treated with fluticasone/salmeterol diskus, albuterol hydrofluoroalkane (HFA) inhaler, and montelukast presented to our clinic complaining of recurrent episodes of acute shortness of breath immediately following each administration of albuterol for 4 weeks. PFTs were performed with levalbuterol (Xopenex) and albuterol (ProAir), yielding significant decrease in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Nebulized albuterol and ipratropium bromide also improved FEV1 and FVC. He was successfully transitioned to an ipratropium rescue inhaler for asthma exacerbations.

**Conclusions:** Paradoxical bronchoconstriction is the unexpected constriction of smooth muscle walls of the bronchi that occurs in the setting of an expected bronchodilatory response. This phenomenon has been observed with  $\beta_2$ -agonist-containing inhaler formulations and is an under-recognized adverse event. Theories suggest that the formulation excipients can trigger airway hyperresponsiveness in patients with allergically inflamed airways. Removal of excipients or use of anticholinergic inhalers improved respiratory function. Clinicians should be aware of paradoxical bronchospasm as an adverse effect with common inhaler formulations containing  $\beta_2$ -agonists and counsel patients accordingly in the appropriate clinical setting.

**MeSH Keywords:** Airway Remodeling • Albuterol • Anti-Asthmatic Agents

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## Background

Asthma affects 7.8% of the U.S. population and accounts for 3615 deaths annually [1]. Initial therapy in the stepwise approach for asthma management is short-acting  $\beta_2$ -agonist (SABA) therapy as needed for symptom control. Two of the most common SABA medications are albuterol and levalbuterol. Albuterol is a racemic mixture of (R)- and (S)- stereoisomers in a 1: 1 ratio. Levabuterol includes only the (R)-isomer in formulation. The (R)-isomer binds with 100 times greater affinity to  $\beta_2$  receptors. However, it is eliminated much more rapidly than the (S)-isomer. Albuterol has been proven to be non-inferior to levalbuterol [2], although levalbuterol use is increasing in clinical practice. While both medications are thought to be relatively safe, cases of unexpected bronchoconstriction or bronchospasm have been documented after administration. Here, we report a case of paradoxical bronchospasm with administration of SABAs during multiple PFTs.

## Case Report

A 25-year-old, non-smoking male with a history of moderate asthma and allergic rhinitis treated with Advair diskus (fluticasone propionate 250 mcg/salmeterol 50 mcg) 2 puffs twice daily, ProAir Hydrofluoroalkane (HFA) (albuterol 90 mcg) 2 puffs every 20 min as needed for shortness of breath, and Singulair (montelukast 10 mg) daily, presented to our clinic complaining of recurrent episodes of acute shortness of breath immediately following each administration of albuterol for 4 weeks. His Advair diskus dose had been decreased at his previous visit 8 months prior from 250/50 mcg to 100/50 mcg 2 puffs twice daily in line with step-down therapy with absence of exacerbations. He developed chest tightness and increased difficulty breathing starting almost immediately after dose reduction. He was still able to control symptoms and meet the physical demands of his job by increasing his Advair diskus 100/50 mcg from 2 puffs to 4 puffs twice daily and utilizing his ProAir inhaler more frequently for exacerbations, up to 4–5 times daily.

He presented for evaluation and pulmonary function testing at his earliest convenience. His pre-bronchodilator FVC was 4.17 L (76% predicted) and forced expiratory volume in 1 second (FEV1) was 2.19 L (50% predicted) at initial testing. After administration of 4 puffs Xopenex HFA (levalbuterol 90 mcg), his FVC decreased to 4.07 L (74% predicted) and his FEV1 decreased to 1.70 L (39% predicted). He was referred to our clinic for further workup.

On presentation to our clinic, he was hemodynamically stable and symptom free, with blood pressure of 119/60 mmHg, heart rate of 78 bpm, respiratory rate of 16 bpm, and oxygen saturation of 97% on room air. Lung volumes and repeat

PFTs were performed, showing his pre-bronchodilator FVC at 4.99 L (107% predicted) and FEV1 at 2.68 L (68% predicted) with lung volumes notable for end reserve volume (ERV) of 2.00 L (183% predicted), residual volume of 1.85 L (121% predicted), and total lung capacity of 6.27 L (91% predicted). Four puffs of ProAir HFA (albuterol 90 mcg) were administered via spacer and showed a decrease in FVC to 4.42 L (95% predicted) and FEV1 to 2.25 L (57% predicted). He remained asymptomatic despite his worsening PFTs. Given his air-trapping and worsening PFTs, a high-resolution chest computed tomography (CT) scan, absolute eosinophil count, alpha-1 antitrypsin level, neutrophil cytoplasmic antibody (ANCA) panel, complete blood count (CBC), comprehensive metabolic panel (CMP), and regional allergen skin test were ordered to exclude alternative diseases. His fluticasone/salmeterol was increased to 230 mcg and changed from diskus to HFA delivery, and he was scheduled for repeat PFTs with alternative bronchodilators.

Absolute eosinophil count (288/mcL), alpha-1 antitrypsin level (124 mg/dL), neutrophil cytoplasmic antibody (ANCA) panel (all <1: 20 titer units), CBC, and CMP were all within normal limits. High-resolution chest CT was without subpleural reticulation, honeycombing, bronchiectasis, or significant air-trapping. A regional allergen skin test revealed an elevated IgE to 1618 IU/ml (reference range 0–100 IU/ml) and multiple regional allergens including but not limited to cat dander, dog dander, cockroach, cedar, and grass.

Repeat PFTs were scheduled and the patient was instructed to not use his Advair and ProAir inhalers the evening prior and morning of testing. Unfortunately, he was unable to withhold medications entirely, given shortness of breath. His last administration of Advair prior to repeat PFT was 2–3 hours prior to testing. PFTs performed with nebulized albuterol sulfate 2.5 mg showed no change in FVC at 4.99 L (107% predicted), but there was an increase in FEV1 from 2.68 L (68% predicted) to 3.04 L (77% predicted) after administration. The patient was asked to return for a separate appointment for PFTs with ipratropium bromide (Atrovent HFA) to assess efficacy with the same instructions to withhold medications as stated above. He complied with instructions at this appointment. His FVC was unchanged before and after bronchodilator administration at 4.85 L (104% predicted). However, his FEV1 increased from 2.47 L (62% predicted) to 2.73 L (69% predicted) after 4 puffs of ipratropium bromide were administered. A summary of the patient's FEV1 with separate bronchodilators was compiled (Table 1). We chose not to test the patient free of his Advair, based on the increase of symptoms during trials of withholding prior to PFTs. We did not have access to placebo MDIs with excipients only.

The patient's albuterol HFA prescription was discontinued, and he was instructed to use an ipratropium HFA as needed for a

**Table 1.** Comparison table of percentage changes in forced expiratory volume in 1 second (FEV1) for different bronchodilators in the patient.

	FEV1 (L)	Percentage of predicted (%)	Percentage of change from baseline (%)
Encounter #1 pre-bronchodilator	2.19	50	N/A
Xopenex	1.70	29	-21
Encounter #2 pre-bronchodilator	2.68	68	N/A
ProAir	2.25	57	-11
Encounter #3 pre-bronchodilator	2.68	68	N/A
Nebulized albuterol	3.04	77	+9
Encounter #4 pre-bronchodilator	2.47	62	N/A
Atrovent	2.73	69	+7

rescue inhaler with continuation of his increased dose of fluticasone/salmeterol HFA daily. There were no reported symptoms after the transition of therapy.

## Discussion

Inhaled SABA-containing formulations are generally well-tolerated and are considered first-line therapy for asthma. Paradoxical bronchospasm is the unexpected constriction of smooth muscle walls of the bronchi that occurs in the setting of an expected bronchodilatory response. This phenomenon has been observed with  $\beta_2$ -agonist and is an under-recognized warning on package inserts for all dosage forms [3–5], occurring in up to 8% of patients [5]. Given that our patient experienced a decrease in pulmonary function with inhaled  $\beta_2$ -agonist formulations and an improvement in pulmonary function with nebulized  $\beta_2$ -agonist, we suspect the inactive ingredients in the inhalers caused bronchoconstriction. Inactive ingredients that are implicated in decreased pulmonary function attributable to hypersensitivity or irritant effects include oleic acid (an excipient in Xopenex HFA) [6,7] and ethanol (an excipient in ProAir HFA) [8,9]. Nebulized albuterol sulfate lacks these excipients and would not be expected to cause a similar response. Similar experiences with changes in formulations of  $\beta_2$ -agonist have been documented when comparing metered-dose inhalers (MDI) to nebulized formulations [10] with the rationale that the excipients rather than the  $\beta_2$ -agonist had caused the bronchoconstriction. This is further supported by our patient's lack of clinically significant response to Advair HFA, as the formulation contains only a suspension fluticasone propionate and salmeterol xinafoate in propellant HFA-134a and no other excipients [11].

It is well established that  $\beta_2$ -agonists, when used alone, can decrease pulmonary function, increase frequency of exacerbations, and increase responsiveness to methacholine [12]. This is believed to be secondary to an increase in airway responsiveness to allergens without change in bronchodilation effects of the medication. While studies have observed a tachyphylactic effect in respect to duration of bronchodilation, no such effect has been seen with peak bronchodilatory effects [13]. Animal models have shown long-term use of albuterol treatments with (R)-, (S)-, or (RS)-isomers are capable of precipitating an immediate allergic response and airway hyperresponsiveness in allergically inflamed airways [14]. Use of salmeterol alone is documented to worsen airway hyperresponsiveness and increase histological markers of inflammation, remodeling, and mucus hyperplasia when administered without inhaled corticosteroids [15]. Our patient had a history of allergic rhinitis, an elevated IgE level, and a grossly positive regional allergen panel, giving him a high likelihood of having allergically inflamed airways.

In addition, our patient had improvement in his pulmonary function with inhalation of ipratropium bromide. The excipients in our formulation (Atrovent HFA) included dehydrated alcohol and a similar propellant as in our other inhalers. We would have expected the formulation to cause similar decreases in pulmonary function given its excipients. We suspect that the anticholinergic properties of the medication suppressed the patient's response to the excipients, as animal models have demonstrated suppression of airway hyperresponsiveness and anti-inflammatory effects with tiotropium at higher doses [16]. When compared to albuterol monotherapy, larger studies have not shown convincing evidence that ipratropium generates a marked difference in PFTs [17,18]. However, it should be

noted that these studies did not identify allergic asthma and, to the best of our knowledge, no study has compared respiratory function with administration of anti-cholinergics to  $\beta_2$ -agonists in the setting of allergic asthma.

We further considered that 1,1,1,2-tetrafluoroethane, also known as HFA-134a, the propellant used in all 3 aerosolized formulations and his fluticasone/salmeterol formulation, might be a cause of the bronchospasm. We considered the propellant to be a less likely cause of the patient's symptoms given that hydrofluoroalkanes are potent smooth-muscle relaxants with effects demonstrated on bronchi [19] and there was absence of decreased pulmonary function with use of all inhalers utilizing HFA-134a as the propellant. We specifically would have expected our ipratropium inhaler (which contains similar excipients as the SABA formulations) to cause a decrease in pulmonary function; however, this was not observed in our testing. We did not feel it was safe to discontinue the patient's fluticasone/salmeterol HFA in order to assess its effects on the patient's PFTs.

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## Conclusions

We have demonstrated paradoxical bronchospasm with both albuterol HFA (ProAir) and levalbuterol HFA (Xopenex) formulations. While the exact mechanism underlying our findings remains unknown, we found acceptable alternative therapies for our patient using an ipratropium rescue inhaler (Atrovent) and nebulized albuterol. While we believe our patient's symptoms were most likely secondary to the excipients in his inhalers, clinicians should be aware of paradoxical bronchospasm as an adverse effect of  $\beta_2$ -agonist therapy and counsel patients in appropriate clinical settings.

## Statement

The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.