

# Paradoxical bronchoconstriction caused by $\beta_2$ -adrenoceptor agonists

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## ABSTRACT

**Introduction:** Salbutamol and terbutaline are short-acting  $\beta_2$  adrenergic agonists that produce bronchial smooth muscle relaxation and are widely used in obstructive pulmonary diseases. Nevertheless, their use has been the cause of a paradoxical bronchoconstriction, which is a rare and potentially serious adverse reaction. The aim of this study is to report a case of paradoxical bronchoconstriction caused by  $\beta_2$  adrenergic agonists.

**Methods:** This case is about a 50-year-old asthmatic patient who describes a history of repeated acute asthma attacks after salbutamol inhalation or terbutaline nebulization. A double-blind crossover study was performed over 3 days, in order to compare the effects of each bronchodilator. Forced expiratory volume in 1 second ( $FEV_1$ ), forced vital capacity (FVC), and maximal expiratory flow 25-75 (MEF25-75) were measured.

**Results:** On the first day, a bronchoconstriction caused by deep and repeated inhalations was eliminated. On the second day, an airway obstruction was confirmed by a decrease in  $FEV_1$  at 40% from baseline values after nebulization of a standard dose of terbutaline. On the third day, a spirometry was performed before and after nebulization of a standard dose of ipratropium bromide, and there were no significant changes in the spirometric parameters. Finally the patient was discharged with a written warning mentioning the danger of salbutamol and terbutaline use.

**Conclusion:** Salbutamol and terbutaline are generally well-tolerated  $\beta_2$  adrenergic agonists. Nevertheless, in rare cases, these substances can cause a paradoxical bronchoconstriction. Doctors must therefore remain vigilant about its side effect and possibly investigate each case.

**Keywords:** Asthma, Bronchoconstriction, Bronchodilators,  $\beta_2$  adrenergic agonists, Spirometry

## Background

Salbutamol and terbutaline are both short-acting  $\beta_2$ -adrenoceptor agonists that are believed to exert their maximal therapeutic effect through bronchodilation. Activated  $\beta_2$ -adrenergic receptors promote their binding to a stimulating G protein called Gs. This binding stimulates adenylyl cyclase, which in turn activates the intracellular cyclic adenosine monophosphate (cAMP) that phosphorylates several relaxation proteins. In bronchial smooth muscle, activated protein kinase inhibits both myosin and phosphoinositide

light chain kinase hydrolysis. In addition, it promotes the exchange of calcium/sodium, which results in a decrease in intracellular calcium concentration, and stimulates the Na<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase (ATPase) pump.

This discovery justifies the use of these substances as a pillar of the treatment of bronchial obstruction in addition to their safety and efficiency (1-5).

Nevertheless, use of salbutamol and terbutaline has been the cause of paradoxical bronchoconstriction, which is a rare and potentially serious adverse event requiring vigilance by treating physicians (6,7).

We describe a case of paradoxical bronchoconstriction in an asthmatic patient caused by  $\beta_2$ -adrenoceptor agonists objectively demonstrated with an appreciable decrease of forced expiratory volume in one second ( $FEV_1$ ) in a double-blind crossover study.

## Methods and Results

This case is about a 50-year-old asthmatic patient with no other past medical history and whose body mass index was 20.7 kg/m<sup>2</sup>. He described a history of repetitive acute attacks of asthma after inhalation of salbutamol. Asthma was

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**TABLE I** - Spirometric parameters before and after salbutamol inhalation

Spirometric parameters	Baseline spirometry		After salbutamol		
	Measured	% Predicted	Measured	% Predicted	% Changing
FEV <sub>1</sub>	2.36 L	74	1.76 L	55	-25
FVC	3.57 L	91	3.36 L	86	-6
FEV <sub>1</sub> /FVC	66%	–	52%	–	-21
FEF25-75	1.34 L	36	0.68 L	18	-49

FEF25-75 = FEF between 25% and 75% of the FVC; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.

diagnosed 5 years earlier, based on clinical arguments without neither atopy nor spirometric confirmation. The patient was then treated with inhaled corticosteroids and salbutamol for 3 years. During this period, the patient continued to have respiratory symptoms such as wheezing and dry cough after taking medication. In April 2016, the patient presented dramatic symptoms after taking a standard dose of terbutaline via nebulizer and developed a respiratory failure requiring intubation and hospitalization in an intensive care unit.

As part of the follow-up of his disease, the patient was sent to our pulmonary function department in August 2017. Spirometry and bronchodilator reversibility test were carried out by a "CareFusion MicroLab" spirometer, and spirometry was performed by experts in respiratory functional exploration according to the latest American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations. Predicted values were obtained according to reference equations from the work of Stocks and Quanjer (8).

Baseline spirometry revealed a small airways obstruction, which is defined by a normal forced vital capacity (FVC), a normal FEV<sub>1</sub>/FVC ratio, and a decrease of at least one forced expiratory flow (FEF): FEF50%, FEF25%, or FEF between 25% and 75% of the FVC (FEF25-75). During bronchodilator reversibility test, the patient developed an explosive cough and dyspnea just after salbutamol inhalation (400 µg) by metered dose inhaler (MDI). A decrease in FEV<sub>1</sub> at 25% from baseline was noticed (Tab. I). An administration of ipratropium bromide via nebulizer restored basic spirometric values.

In the light of this ascertainment, we studied the influence of terbutaline and ipratropium bromide on bronchial reactivity. A double-blind crossover study was performed, over 3 days; neither the patient nor the technician knew the composition of the nebulization in order to compare the effects of each bronchodilator on bronchial reactivity. An informal consent was obtained and the patient was asked to avoid using bronchodilators for at least 12 hours prior to the study. FEV<sub>1</sub>, FVC, and FEF25-75 were measured and the patient was monitored by blood oxygen saturation.

On the first day, a basic spirometry was performed with eight measurements in order to eliminate bronchoconstriction due to deep inhalation during spirometry testing. No significant changes compared to baseline spirometry were found (Tab. II).

On the second day, a spirometry was planned before and 15 minutes after a nebulization of a standard dose of terbutaline made up to a total volume of 5 mL with 0.9% saline

**TABLE II** - Spirometric parameters during repeated spirometry testing

	FEV <sub>1</sub>	FVC	FEV <sub>1</sub> /FVC (%)
<b>Baseline or 1st spirometry</b>	2.41 L (75%)	3.27 L (83%)	73
<b>2nd spirometry</b>	2.36 L (74%)	3.11 L (79%)	75
<b>3rd spirometry</b>	2.29 L (71%)	3.15 L (80%)	73
<b>4th spirometry</b>	2.35 L (73%)	3.19 L (81%)	73
<b>5th spirometry</b>	2.30 L (71%)	3.11 L (79%)	73
<b>6th spirometry</b>	2.42 L (75%)	3.22 L (82%)	75
<b>7th spirometry</b>	2.31 L (71%)	3.20 L (81%)	72
<b>8th spirometry</b>	2.35 L (73%)	3.22 L (82%)	72

FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.

solution (5 mg/unit). The patient was initially asymptomatic, but nebulization was interrupted because of important dyspnea, coughing, wheezing, and discrete cyanosis. Physical examination revealed a wheezing, sinus tachycardia at 110 per minute, and blood oxygen saturation at 85%. There was no urticaria, pruritus, or macular rash. The spirometry was performed earlier because of the reaction and revealed an airway obstruction confirmed by a decrease in FEV<sub>1</sub> at 40% from baseline spirometry (Tab. III).

On the third day, a spirometry was performed before and 30 minutes after a nebulization of a standard dose of ipratropium bromide made up to a total volume of 5 mL with 0.9% saline solution (0.5 mg/unit). There were no significant clinical or spirometric changes (Tab. IV). Finally, the patient was discharged with a written warning mentioning the danger of salbutamol and terbutaline use via MDI or nebulizer solutions.

## Discussion

Currently, inhaled β<sub>2</sub>-adrenoceptor agonists are generally used in the treatment of acute asthma attacks, based on their effectiveness and relative safety. However, in rare cases, they may cause unexpected adverse effects such as paradoxical bronchoconstriction.

Paradoxical bronchoconstriction was recorded in this patient each time he used β<sub>2</sub>-adrenoceptor agonists, whether with salbutamol via MDI or terbutaline via nebulizer. Many

TABLE III - Spirometric parameters before and after terbutaline nebulization

Spirometric parameters	Baseline spirometry		After terbutaline		
	Measured	% Predicted	Measured	% Predicted	% Changing
FEV <sub>1</sub>	2.36 L	74	1.41 L	44	-40
FVC	3.11 L	79	2.82 L	72	-9
FEV <sub>1</sub> /FVC	75%	-	40%	-	-35
FEF25-75	2.22 L/s	51	0.79 L/s	18	-64

FEF25-75 = FEF between 25% and 75% of the FVC; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.

TABLE IV - Spirometric parameters before and after nebulization of ipratropium bromide

Spirometric parameters	Baseline spirometry		After ipratropium bromide		
	Measured	% Predicted	Measured	% Predicted	% Changing
FEV <sub>1</sub>	2.54 L	79	2.59 L	80	+2
FVC	3.78 L	76	3.85 L	79	+2
FEV <sub>1</sub> /FVC	64%	-	67%	-	+3
FEF25-75	1.89 L	43	1.97 L/s	45	+4

FEF25-75 = FEF between 25% and 75% of the FVC; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.

factors have been excluded before reaching the conclusion of paradoxical bronchoconstriction.

First, in some asthma patients, deep inhalation can produce paradoxical bronchoconstriction during spirometry testing (9). This is why we performed the test on the first day with more than three measurements, but no spirometric changes were found. Second, double-blind crossover study was performed to avoid psychological response to spirometry testing. In fact, psychological stress can exacerbate clinical symptoms in patients with asthma (10). Third, several studies suggested that excipients (as chlorofluorocarbon propellants and surfactants) or preservatives (as benzalkonium chloride) in MDIs have been incriminated in paradoxical bronchoconstriction due to a bronchial irritation (11,12).

In our case, this possibility was rejected because the same response was seen after nebulization of terbutaline solution, which did not contain foreign substances as preservatives or stabilizers. In fact, excipients of our terbutaline solution were sodium chloride, sodium edetate, and hydrochloric acid.

In addition, osmolarity of liquids of nebulization may induce bronchoconstriction. Hyperosmolar buffers have been shown to cause histamine release from normal human basophils and mast lung cells (13,14). Saline solutions that are hypotonic or hypertonic are both able to induce bronchoconstriction (15). For these reasons, we used isotonic saline in all nebulizer solutions.

This bronchoconstriction was most likely related to an adverse reaction to  $\beta_2$ -adrenoceptor agonists. It is, however, difficult to specify their exact action mechanism on bronchi during this paradoxical reaction. A number of questions remain to be answered with a biocellular study.

All possibilities should be taken into account. It is dangerous to reject a possible cause of asthma mortality. Doctors

and patients should be aware that although  $\beta_2$ -adrenoceptor agonists do not generally produce adverse effects, it may aggravate symptoms. This adverse reaction needs to be considered as one of the possible causes of sudden death or acute asthma attack.

Finally, some precautions should be taken with the use of  $\beta_2$ -adrenoceptor agonists. Since short-acting  $\beta_2$ -adrenoceptor agonists represent the first-line treatment of acute asthma (2,3), any discrepancy between a good adherence to treatment and refractory symptoms should lead the physician to suspect paradoxical bronchoconstriction. In this case, the patient should be treated with other bronchodilators such as anticholinergics.

Similar reactions should lead to a new assessment including a full spirometric study with bronchial reversibility tests as well as the above-cited protocol, in order to define the causative agent.

## Conclusion

$\beta_2$ -adrenoceptor agonists are an important and well-tolerated pharmacological class in the management of asthma. In rare cases, salbutamol and terbutaline may cause unusual paradoxical bronchoconstriction, whose mechanism remains unknown. Therefore, physicians must be vigilant about this potentially serious side effect and investigate each case.

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