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CASE REPORT/*OPIS PRZYPADKU*

Paradoxical bronchoconstriction due to salbutamol MDI

Paradoksalny skurcz oskrzeli wywołany salbutamolem w inhalatorze ciśnieniowym z dozownikiem (MDI)

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ABSTRACT

An 18-year-old female student presented to us with a history of episodes of nocturnal shortness of breath, precipitated on exposure to cold, for a duration of 6 years. Suspecting it to be due to bronchial asthma, the patient was subjected to spirometry. Pre-bronchodilator spirometry revealed abnormal pulmonary function, suggestive of obstructive lung disease. Postbronchodilator spirometry with a salbutamol metered-dose inhaler (MDI) showed a further decrease in pulmonary function, suggestive of bronchoconstriction. In such cases, it may lead to an erroneous diagnosis of chronic obstructive pulmonary disease or an inappropriate clinical response, leading to therapeutic implications. Here we report a case of a bronchial asthma patient showing paradoxical bronchoconstriction following use of a salbutamol metered-dose inhaler.

KEY WORDS

asthma, paradoxical bronchoconstriction.

STRESZCZENIE

Osiemnastoletnia studentka zgłosiła się do naszej poradni z powodu występujących od 6 lat nocnych epizodów duszności w reakcji na zimno. Z uwagi na podejrzenie astmy oskrzelowej u pacjentki wykonano badanie spirometryczne. Spirometria przed podaniem leku rozszerzającego oskrzela wykazała nieprawidłową czynność płuc wskazującą na obturacyjną chorobę płuc. Spirometria po podaniu leku rozszerzającego oskrzela (salbutamolu w inhalatorze ciśnieniowym z dozownikiem – MDI) ujawniła dalsze pogorszenie czynności płuc sugerujące skurcz oskrzeli. Takie przypadki jak opisywany mogą prowadzić do błędnego rozpoznania przewlekłej obturacyjnej choroby płuc lub nieodpowiedniej odpowiedzi klinicznej, co ma określone skutki terapeutyczne. W pracy opisano przypadek pacjentki z astmą oskrzelową, u której wystąpił paradoksalny skurcz oskrzeli po zastosowaniu salbutamolu w MDI.

SŁOWA KLUCZOWE

astma, paradoksalny skurcz oskrzeli.

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CLINICAL PRESENTATION

Bronchodilators are an important class of medications – administered either by inhalational, oral or intravenous routes – used in the treatment of chronic obstructive airway diseases. All classes of bronchodilators, namely, β_2-agonists, muscarinic antagonists and methylxanthines, have the potential to cause paradoxical bronchoconstriction, out of which the β_2-agonists have been most commonly reported. Here we present a case of an asthma patient who showed paradoxical bronchoconstriction, probably to an excipient in the salbutamol metered-dose inhaler (MDI).

An 18-year-old girl presented to the out-patient department with complaints of episodes of shortness of breath associated with cough and minimal mucoid expectoration, predominantly nocturnal, precipitated on cold exposure for the last 6 years. There was no history of fever or any other cardiorespiratory symptoms. There was no history suggestive of atopy. On examination, the patient was found to have a pulse rate of 84 per min, BP of 110/70 mm Hg, respiratory rate of 18 per min with oxygen saturation of 98% in room air, and normal body temperature. Auscultation of the chest revealed normal vesicular breath sounds. A provisional diagnosis of bronchial asthma was made and the patient was subjected to further evaluation. Chest radiograph did not reveal any significant abnormality. A spirometry test, measuring forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio, was performed before and 15 min after administration of 400 µg of salbutamol via an MDI. Pre-bronchodilator spirometry revealed abnormal pulmonary function suggestive of obstructive lung pathology. The postbronchodilator spirometry result showed further reduction in pulmonary function indicating bronchoconstriction where FEV_1 decreased by 570 ml (36%). Her post-bronchodilator spirometry was suggestive of a chronic obstructive pulmonary disease (COPD) pattern where the FEV_1/FVC ratio was lower than 0.7 as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The patient was followed up 2 days later for repeat bronchodilator spirometry using nebulized salbutamol (2.5 mg), which showed a significant increase in the airflow with an increase in FEV_1 of 700 ml (47%) suggestive of significant post-bronchodilator reversibility. This time the postbronchodilator FEV_1/FVC was more than 0.7, suggestive of a reversible airway disorder. This suggested that the paradoxical bronchodilator response was due to an excipient present in the salbutamol MDI. She was treated for asthma with inhaled corticosteroids, after which she showed significant improvement.

OBSERVATIONS AND EVIDENCE

Paradoxical bronchoconstriction is defined as sudden onset of unanticipated contraction of the smooth muscles of the airway in the walls of the bronchi occurring soon after administration of inhalational aerosols [1]. The response is termed paradoxical, because bronchodilation and the resultant increase in FEV_1 and/or FVC is normally expected following inhalation of a bronchodilator agent. Paradoxical responses have been reported to occur due to the effect of the bronchodilator drug as well as various other contents or the dosage forms of the drug (Table 1) [1–3]. All salbutamol preparations, except levosalbutamol, are racemic mixtures, composed of a 1 : 1 ratio of (R)-isomer and (S)-isomer of salbutamol. The (R)-isomer, also known as levosalbutamol, has bronchodilatory, bronchoprotective and ciliary stimulatory properties, and the (S)-isomer has been shown to be devoid of bronchodilatory activity and also opposes the actions of R-isomer. The (S)-salbutamol has been shown to increase bronchial hyper-responsiveness and promote smooth muscle contraction causing bronchospasm. There are fewer reports of bronchospasm in response to levosalbutamol than to salbutamol.

The various mechanisms that have been postulated to cause paradoxical bronchoconstriction include IgE mediated reaction to ingredients in MDI such as oleic acid used as a dispersant in MDI, irritation due to propellants such as hydrofluoroalkanes and chlorofluorocarbons, presence of S-isomer as a component of racemic mixtures, preservatives or turbulence of airflow due to inappropriate inhaler technique. There are also reports showing paradoxical bronchoconstriction following nebulized β_2-agonists, probably due to hyperosmolality or acidity of the preservatives such as benzalkonium chloride in the respirator solutions [4, 5].

In the present case, the pre-bronchodilator spirometry showed a decreased FEV_1/FVC ratio of 65.1 as well

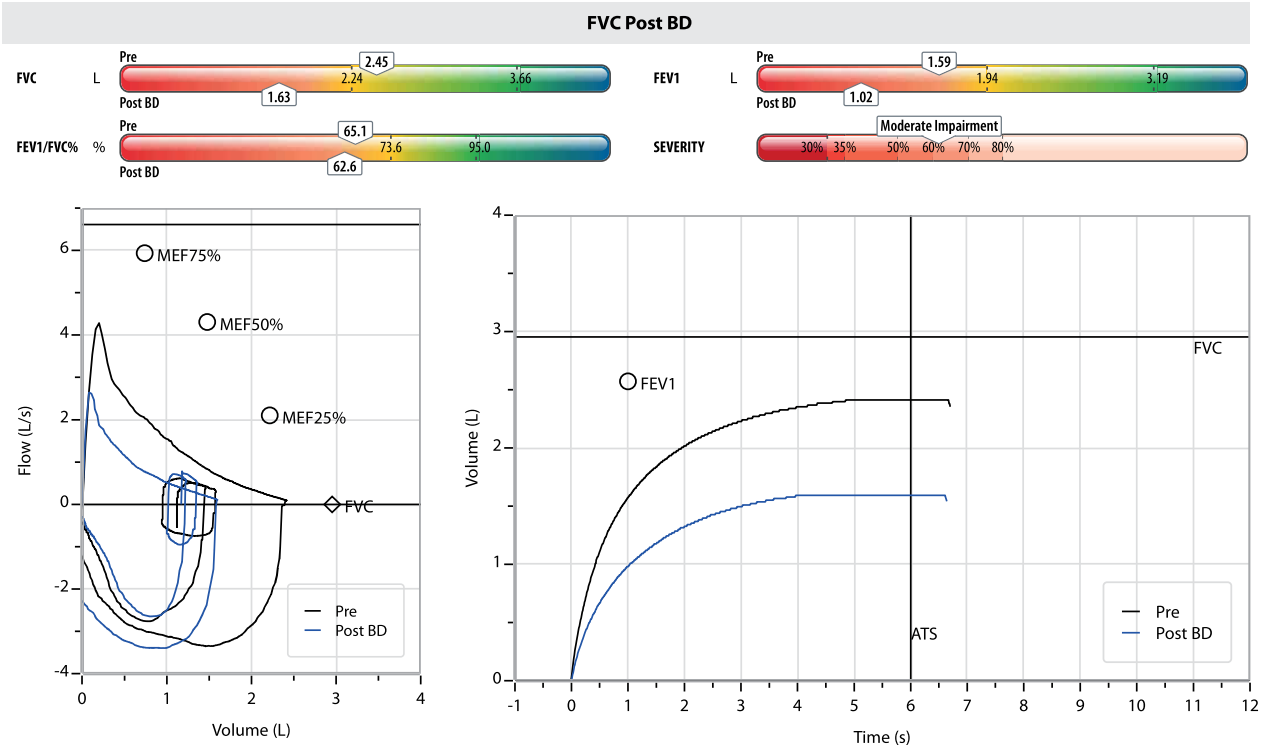
TABLE 1. Contents of bronchodilator preparations

Inhaled β_2-agonists delivered by MDI	Inhaled β_2-agonists nebulization solutions
Propellants (HFA)	Saline
Sorbitan	Benzalkonium chloride
Oleic acid	Edetate sodium
Ascorbic acid	
Alcohol	
Soy lecithin	
Others – saccharin, menthol	

HFA – hydrofluoroalkane.

as decreased percent predicted FEV_1 (62%) suggestive of a mild obstructive abnormality (Fig. 1). As per the guidelines of the American Thoracic Society, significant postbronchodilator reversibility is defined as a 12% and 200 ml increase in either FEV_1 or the FVC. In our patient, 400 µg of salbutamol via an MDI produced a 570 ml (36%) decrease in FEV1 and a 820 ml (33%) decrease in FVC, thereby making the response paradoxical (Fig. 1). On the other hand, use of 2.5 mg of nebulized salbutamol led to an increase in FEV_1 of 700 ml (47%) and in FVC of 100 ml (4%), suggestive of significant postbronchodilator reversibility (Fig. 2). The bronchodilatory response to nebulized salbutamol and MDI ipratropium suggests that the paradoxical bronchoconstrictory response to salbutamol MDI was not due to the drug but was a reaction to an excipient.

Wilkinson *et al.* compared post-inhaler FEV_1 in six patients who showed paradoxical bronchoconstriction to



Interpretation:

Confirm Report **Signature:** _____

		PRE					POST BD				
		Meas.	Normal Range	Pred	% Pred	z score	Meas.	Change	% Change	% Pred	z score
FVC	L	**2.45**	2.24 - 3.66	2.95	83	-1.16	**1.63**	-0.81	-33	55	-3.07
FEV1	L	**1.59**	1.94 - 3.19	2.57	62	-2.56	**1.02**	-0.57	-36	40	-4.07
FEV1/FVC%	%	**65.1**	73.6 - 95.0	84.3	77	-2.95	**62.6**	-2.4	-4	74	-3.33
PEF	L/s	**4.28**	5.13 - 8.09	6.61	65	-2.58	**2.64**	-1.63	-38	40	-4.41
FEF25-75%	L/s	**0.99**	2.59 - 5.39	3.99	25	-3.52	**0.62**	-0.37	-37	16	-3.96
MEF25%	L/s	**0.48**	0.96 - 3.23	2.10	23	-2.35	**0.36**	-0.11	-24	17	-2.51
MEF50%	L/s	**1.18**	2.49 - 6.11	4.30	28	-2.84	**0.71**	-0.47	-40	17	-3.27
MEF75%	L/s	**2.21**	3.71 - 8.15	5.93	37	-2.76	**1.36**	-0.84	-38	23	-3.38
FEV6	L	**0.00**	---	-	-	-	**0.00**	0.00	-	-	-
FEV1/FEV6%	%	**0.0**	---	-	-	-	**0.0**	0.0	-	-	-

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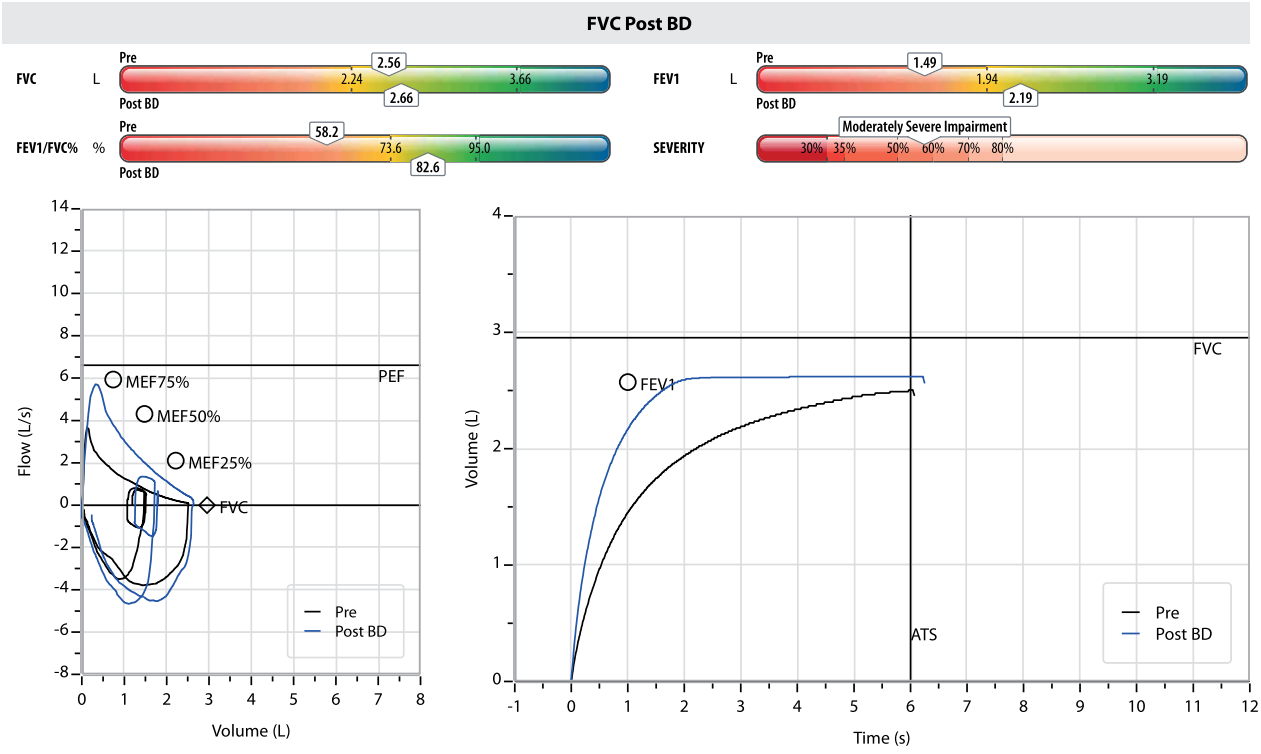
FIGURE 1. Pre- and post-bronchodilator spirometry with MDI salbutamol



Interpretation:

Confirm Report **Signature:** _____

		PRE					POST BD				
		Meas.	Normal Range	Pred	% Pred	z score	Meas.	Change	% Change	% Pred	z score
FVC	L	**2.56**	2.24 - 3.66	2.95	87	-0.91	**2.66**	0.10	4	90	-0.68
FEV1	L	**1.49**	1.94 - 3.19	2.57	58	-2.85	**2.19**	0.70	47	85	-0.98
FEV1/FVC%	%	**58.2**	73.6 - 95.0	84.3	69	-4.02	**82.6**	24.4	42	98	-0.27
PEF	L/s	**3.67**	5.13 - 8.09	6.61	56	-3.27	**5.71**	2.04	56	86	-1.00
FEF25-75%	L/s	**0.83**	2.59 - 5.39	3.99	21	-3.72	**2.03**	1.20	145	51	-2.31
MEF25%	L/s	**0.40**	0.96 - 3.23	2.10	19	-2.45	**1.14**	0.73	179	54	-1.39
MEF50%	L/s	**0.97**	2.49 - 6.11	4.30	23	-3.03	**2.28**	1.30	134	53	-1.84
MEF75%	L/s	**1.83**	3.71 - 8.15	5.93	31	-3.04	**3.88**	2.04	111	65	-1.52
FEV6	L	**0.00**	---	-	-	-	**0.00**	0.00	-	-	-
FEV1/FEV6%	%	**0.0**	---	-	-	-	**0.0**	0.0	-	-	-

Technician QC Pre: A B C D E F

Technician QC Post: A B C D E F

FIGURE 2. Pre- and post-bronchodilator spirometry with nebulized salbutamol

salmeterol via MDI but not to salmeterol Diskhaler, suggesting bronchoconstriction to a component in the MDI but not the active molecule [6]. The importance of this case can be summarized as follows:

1. Post-bronchodilator $FEV_1/FVC < 0.7$ is used as a criterion to diagnose COPD. However, in cases like this when there is a paradoxical response to bronchodilators, the label of COPD may be erroneous and should be reviewed after using another bronchodilator or preparation.
2. Bronchodilator reversibility may be negative, i.e., it does not satisfy the criteria for reversibility (12% and 200 ml increase in FEV_1 or FVC), but in cases where the changes indicate a significant decrease, this might also indicate a positive test, which may be demonstrated by an appropriate bronchodilator. This implies that a significant decrease in pulmonary function after bronchodilator administration is a basis to suspect possible bronchodilator reversibility.

3. Finally, emphasis should be placed on the clinical history of seasonal and diurnal variation to suspect and diagnose asthma, and in cases where the spirometry results are misleading, it is important to seek the exact reason for this.
4. Some patients with a diagnosis of asthma may complain of no benefit or worsening of symptoms on taking bronchodilators, which should lead one to suspect and rule out paradoxical bronchoconstriction [1].

CLINICAL OUTCOME

It is critical that physicians become aware of the phenomenon of paradoxical bronchoconstriction and appreciate the implications in a patient with suspected obstructive airway disease. In an appropriate clinical setting, this might imply hyper-reactivity to one or more component in the aerosol preparation leading to falsely negative bronchodilator responses as well as symptomatic worsening in patients.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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