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Evidence of pneumoconstriction in asthmatics

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ABSTRACT

Introduction: In asthma, bronchial smooth muscle contraction is responsible for the obstructive ventilatory defect that may be relieved by the administration of bronchodilators. It has been observed that deep inspiration causes dilation of the airways in both asthmatic and nonasthmatic subjects. Pneumoconstriction is a rare manifestation of the contractile cells present in the perialveolar space leading to a restrictive defect in asthmatics. **Case study:** We present the lung function tests of two asthmatic patients (a boy and a woman) depicting a restrictive defect (pneumoconstriction) that disappeared after salbutamol administration while no improvement was noted in the spirometric data. **Results:** We observed a particular static lung volume distribution that could be explained by a concept of cellular mechanoresponsiveness called “glassy dynamics” applied to smooth muscle cells. **Conclusion:** We concluded that the presence of contractile interstitial cells in the perialveolar space could be responsible for the observed anomalies reflecting pneumoconstriction. We explained the observed distribution of static lung volumes by the glassy dynamics of cytoskeleton, a concept that had no clinical validation.

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KEYWORDS

Asthma; glass dynamics; pneumoconstriction; restrictive spirometric pattern; smooth muscle

Introduction

Bronchial smooth muscle contraction is a hallmark of asthma. Smooth muscle cells (SMCs) or contractile interstitial cells that contain fibrillar bundles as well as actin were described in pulmonary alveolar septa of human lung for a long time [1]. A direct contractile response at the level of the alveolar wall and/or the alveolar duct has been demonstrated in vitro in human tissue [2] and regional pneumoconstriction induced by alveolar hypocapnia seems to be an important homeostatic mechanism for optimization of ventilation-perfusion matching. We present two case reports illustrating the same observation, i.e. pneumoconstriction.

Case study

The two patients are non-smoking Caucasian allergic (rhinitis and positive skin prick tests) asthmatics (typical symptoms and positive bronchodilator response in their past history) and their characteristics are described in Table 1. Pulmonary function tests (spirometry, body plethysmography) were performed according to international recommendations, and special attention was used to assure the accuracy and the reproducibility of function residual capacity (FRC) measurement. Reversibility testing used salbutamol 400 µg. The two patients have

discontinued asthma treatment at least 6 months before presentation.

Results

Table 1 shows in the two patients an inhomogeneous reduction of static volumes, i.e. more pronounced at low lung volumes, which is fully reversible while spirometry parameters are within normal range.

Discussion

The two patients depicted similar functional characteristics: absence of obstructive defect ($FEV_1/VC > -1.64$ Z-score) and a restrictive defect (total lung capacity [TLC] < -1.64 with plethysmography), ruling out small airways obstructive syndrome or pseudo-restrictive syndrome, a frequent trap in asthma [3]. The particular distribution of static volumes ($TLC (\%) > FRC (\%) > RV (\%)$) due to a similar volume reduction in mL of the three static volumes could be explained by the so-called “glass dynamics” of the cytoskeleton of SMCs [4]. This phenomenological hypothesis describes cytoskeletal mechanoresponsiveness of SMC as a glassy material implying that relaxation times are distributed as a power law, with a great many relaxation processes contributing when the

Table 1. Patients' characteristics.

Characteristics	Patient 1			Patient 2	
	One year before	Baseline	Bronchodilator response	Baseline	Bronchodilator response
Age, years		11		53	
Sex		Male		Female	
BMI, kg/m ²		18.7*		21	
Asthma control (GINA: 0–4)		0		1	
Spirometry					
FEV ₁ , L	2.14	2.12	2.25	2.07	2.14
FEV ₁ , % predicted	101	91	97	81	83
FEV ₁ , z-score	0.07	−0.82	−0.32	−1.41	−1.21
MEF _{25–75%} , L/s	2.27	1.86	2.14	2.7	2.51
MEF _{25–75%} , predicted	94	70	80	108	100
MEF _{25–75%} , z-score	−0.27	−1.44	−0.91	0.24	0
FVC, L	2.48	2.71	2.76	2.38	2.54
FVC, % predicted	100	99	101	74	79
FVC, z-score	0.01	−0.11	0.05	−1.9	−1.53
sVC [†] , L	2.53	2.72	2.75	2.19	2.3
sVC, % predicted	101	99	100	77	80
sVC, z-score	0.11	−0.12	−0.02	−1.59	−1.33
FEV ₁ /FVC, %	85	78	81	87	84
FEV ₁ /FVC, % predicted	100	91	95	109	105
FEV ₁ /FVC, z-score	−0.07	−1.17	−0.69	1.16	0.63
Plethysmography					
TLC, L	3.34	3.04	3.57	3.35	4.33
TLC, % predicted	100	84	99	71	92
TLC, z-score	0.03	−1.68	−0.14	−2.26	−0.62
FRC, L	1.43	1.13	1.58	1.64	2.59
FRC, % predicted	86	62	87	63	99
FRC, z-score	−0.89	−2.48	−0.77	−1.95	−0.05
RV, L	0.81	0.32	0.81	0.97	1.78
RV, % predicted	101	38	97	56	103
RV, z-score	0.05	−2.48	−0.10	−2.16	0.15

*The corresponding z-score is 0.60.

†SVC: slow expiratory VC in the child and slow inspiratory VC in the adult.

Predicted values for static volumes and SVC were calculated according to Koopman et al. [6] (for the pediatric case) and according to Quanjer et al. [7] (for the adult case). Predicted values for spirometric variables were calculated according to Global Lung Initiative reference equations [8].

frequency of the imposed deformation is small but fewer as the frequency is increased and slower processes became progressively frozen out of the response. We hypothesize that this particular dynamic applies for the contractile interstitial cells present in the perialveolar space.

This phenomenological description of the contracted state of the SMC explains the decrease in FRC, i.e. pneumoconstriction (Figure 1). The static volume corresponding to FRC results from the equilibrium of two opposing forces—the retracting force of the lung (blue arrow on Figure 1) and the distending force of the chest wall (black arrow on Figure 1). In presence of pneumoconstriction, an additional retracting force is present (red arrow in Figure 1) corresponding to the tension of SMC. Thus, the measured FRC is reduced. During deep inspiration, the alveolar SMC are then subjected to stretching that results in the fluidization of the cytoskeleton and thereby reducing the tension in the cell [4]. This phenomenon removes the additional retraction force and normalizes the volume measured after this maneuver (forced vital capacity [FVC] in both patients and expiratory slow vital capacity [VC] in the child, while inspiratory VC is reduced in the adult). Thus, the observed

relationship between the measured static volumes (relative to the predicted values) is straightforward. The percentage reduction in TLC is less than the percentage reduction in FRC (since TLC is a larger volume in absolute value), and the percentage reduction of FRC is lower than that of RV (RV is the smallest volume). The decrease in TLC (< -1.64 Z-score) characterizes a restrictive defect, which has already been observed in asthmatic patients [5].

The SMC constriction was completely relieved by the administration of bronchodilator and the static volumes were all normalized, as can be seen in Table 1. The absolute increase in each static volume was approximately the same (450 ml in the pediatric case and 1000 ml in the adult case). No improvement was observed on the spirometric variables, thus concluding to a purely parenchymal effect (no bronchoconstriction).

We hypothesize that asthma may lead to SMC contraction involving bronchi, bronchioles, and/or parenchyma that is functionally associated with either obstructive defect ($FEV_1/VC < -1.64$ Z-score), small airway obstructive pattern (FEV_1 and $VC < -1.64$, and FEV_1/VC and $TLC > -1.64$) or restrictive pattern ($TLC < -1.64$), respectively. Clinicians should evaluate bronchodilator

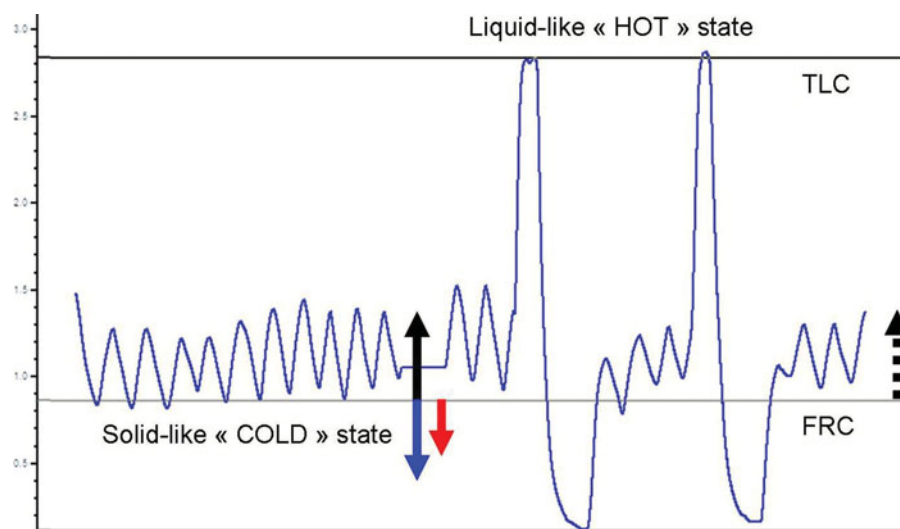


Figure 1. Physiological explanation of the observed anomalies during the plethysmographic measure of static volumes. The blue curve represents the tidal breathing of the patient followed by a complete exhalation from the TLC. The initial static volume (FRC) corresponds to the equilibrium of two forces (continuous arrows). The upward black arrow corresponds to the force exerted by the chest wall; the downward blue arrow corresponds to the elastic retraction force of the lung (increased by the retraction force of the SMC in the case of pneumoconstriction, red arrow). After fluidization of the SMC cytoskeleton, this retraction force decreases. The effect of the bronchodilators is represented by the upward dotted arrow. The bronchodilators will suppress the elastic retraction force of the SMC and as a consequence will normalize the FRC, as well as the other static volumes (TLC and RV).

response when facing an asthmatic patient with an isolated restrictive pattern (normal spirometry). The prevalence of this restrictive pattern (for instance, in more severe asthmatic patients), its reversibility, and clinical significance should be assessed prospectively.

Conclusion

We describe two cases compatible with pneumoconstriction in asthmatic patients. The observed distribution of static volumes could be explained by the glassy dynamics of smooth muscle cell.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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