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MINIREVIEWS

Pitfalls in spirometry: Clinical relevance

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Abstract

Spirometry is one of the functional tests most used in respiratory medicine to assess lung function in health and disease conditions. Its success is grounded on solid principles of lung mechanics that state that maximal flow on expiration is limited by the physical properties of airways and lung parenchyma. In contrast, on inspiration, flow depends on the force generated by the inspiratory muscles. Reduced expiratory forced flow and volumes usually reflect a deviation from health conditions. Yet due to a complex interplay of different obstructive and restrictive lung diseases within the multiple structural dimensions of the respiratory system, flows and volumes do not always perfectly reflect the impact of the disease on lung function. The present review is intended to shed light on a series of artefacts and biological phenomena that may confound the clinical interpretation of the main spirometric measurements. Among them is thoracic gas compression volume, the volume and time history of the inspiratory manoeuvre that precedes the forced expiration, the effects of heterogeneous distribution of the disease across the respiratory system, and the changes in lung elastic recoil.

Key words: Spirometry; Thoracic gas compression volume; Volume history effects of the deep breath; Time history effects of the preceding inspiratory manoeuvre; Ventilation heterogeneities; Lung elastic recoil; Clinical interpretation

Core tip: Spirometry is usually taken as a marker of the disease and its progression independently of the condition. In the present review we partly challenge this notion by examining the role of different obstructive and restrictive lung diseases on a series of mechanisms that strongly affect the main spirometric parameters. Among them is thoracic gas compression volume, the volume and time history of the inspiratory manoeuvre that precedes the forced expiration, the effects of heterogeneous distribution of the disease across the respiratory system, and the changes in lung elastic recoil.

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INTRODUCTION

Current knowledge of the mechanisms determining forced expiratory flows and volumes in respiratory diseases is still incomplete. According to the principles of lung mechanics, maximum ventilation is achieved by activating the respiratory muscles to overcome resistive, elastic and inertial forces of the respiratory system[1-3]. During a forced inspiratory manoeuvre flow reaches a peak at about 50% of vital capacity (VC) because this is the volume at which the difference between the pleural pressure generated by the force of the inspiratory muscles[1] and the elastic, resistive and inertial pressures is maximal. Reducing inspiratory effort causes a parallel decrease in flow, which suggests that maximum inspiratory flow is limited by the force of the inspiratory muscles. Narrowing of extra- or intra-thoracic central airways may also

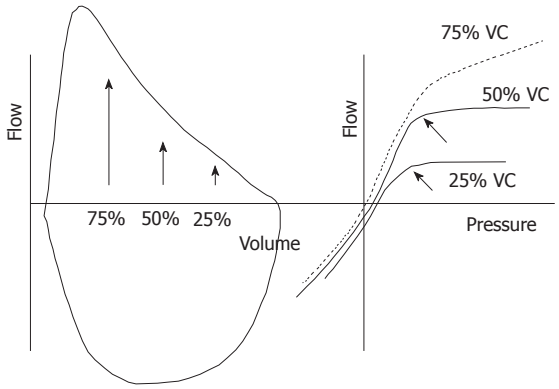

Figure 1 Relationship between maximum flow, volume and pleural pressure. Left panel: Flow-volume curves during inspiratory and expiratory manoeuvres. The arrows indicate the volume at 75%, 50%, and 25% vital capacity; Right panel: flow and pleural pressure (Ppl) relationships during expiratory manoeuvres at different lung volumes. At 25% and 50% vital capacity (VC) flow plateaus at different pressures (oblique arrows). In contrast, at 75% VC flow keeps increasing with the increase of pressure. The lack of increased expiratory flow at 25% and 50% VC despite the increase in Ppl supports the concept of expiratory flow limitation.

contribute to limiting inspiratory flow. During a forced expiration, flow depends on the mechanical properties of airways and lung over most of VC rather than the expiratory effort. A peak expiratory flow (PEF) is on average achieved in less than 120 ms after the start of the expiratory effort. Thereafter, flow decreases almost linearly with lung volume. That expiratory flow is limited during forced expiration can be demonstrated by plotting flow *vs* transpulmonary pressure at iso-volume: flow increases monotonically with pressure at high lung volume but then reaches a plateau at mid-to-low lung volumes (Figure 1). Several theories have been proposed to explain the phenomenon of expiratory flow limitation (EFL).

The equal pressure-point theory[4] predicts that during forced expiration, the driving force for flow, *i.e.*, alveolar pressure (Palv), decreases with decreasing lung volume to a point at which it equals pleural pressure (Ppl). This is called the equal pressure point (EPP). Under these conditions, the airways tend to collapse. Downstream from this segment, the airways will oscillate between different physical configurations depending on the fluctuation of intrabronchial relative to extrabronchial pressure. When this condition is achieved, flow becomes maximal and cannot increase no matter how the expiratory effort is increased or pressure at the mouth is lowered. The EPP first develops within the intrathoracic trachea and then shifts to the sublobar or segmental bronchi with the decrease in Palv. This model allows partitioning the airways located upstream from the EPP where flow is determined by Pel and upstream resistance, thus reflecting most of the structural changes occurring with lung diseases, and those lying downstream from the EPP where flow is controlled by central airways resistance.

Permutt *et al*[5] interpreted the EFL on the basis of a Starling resistor. In brief, with the gradual decrease of Palv when gas moves from the alveoli to the mouth, there will be a time when Palv decreases and reaches a critical value similar to Ppl. The collapsible segment will then narrow and self adjust in size in a way that inlet pressure equals Ppl and outlet pressure is determined by flow and resistance of the downstream segment.

More recently, the EFL phenomenon has been interpreted on the ground of the pressure-area (P-A) relationship and Bernoulli effect[1]. The concept here is that choke points (CP) form during a forced expiration depending on elastic properties of the airways and pressure loss necessary to accelerate gas from a large surface (alveoli) to central airways. As a result, the higher the airway size and stiffness of the airway wall at the CP the higher maximum flow and vice versa.

Recognition that maximum expiratory flow depends on the physical properties of the lung and airways upstream from the CP represents the most solid rationale for using spirometry in clinical practice and research to assess and locate the structural changes caused by respiratory diseases. Noninvasiveness of the technique, easiness to perform the manoeuvre, low cost of instrument, and standardization of the technique with reference equations explain the widespread use of spirometry around the world[6].

If all this fully supports the use of spirometry in respiratory medicine, the last two decades however, have brought to light a series of artefacts that may confound the interpretation of the spirometric signals and data in different respiratory diseases.

THORACIC GAS COMPRESSION VOLUME

During a forced expiration, the effort causes an increase in Palv that exceeds the pressure necessary to generate maximal flow[7,8]. This is a function of absolute lung volume and airflow resistance. As a result, part of the thoracic gas is compressed and the forced expiratory volume in 1 s measured at the mouth by spirometry (FEV_1) is therefore less than that simultaneously measured from the changes in a body plethysmograph ($FEV_{1\text{-PL}}$) which is void of the effects of thoracic gas compression (Figure 2, upper panel). This phenomenon results in a negative effort-dependence of FEV_1 and is clinically relevant for interpretation of lung function in disease as well as the changes occurring with medical interventions on airways or lung volume[9]. On average, in healthy subjects the difference between $FEV_{1\text{-PL}}$ and FEV_1 is about 4%[10]. However, in obstructive lung diseases this may reach values up to 100%[11,12], depending on airflow resistance and amount of intrathoracic gas. A typical example is shown in Figure 2, lower panel. This phenomenon is clinically relevant for interpretation of lung function in disease and with medical interventions on airways or lung volume. Unpublished data from our Lab show that for a given airflow resistance, the FEV_1 in Chronic obstructive pulmonary disease (COPD) is significantly higher in the patients with predominant bronchiolitis than emphysema. This is because in emphysema absolute lung

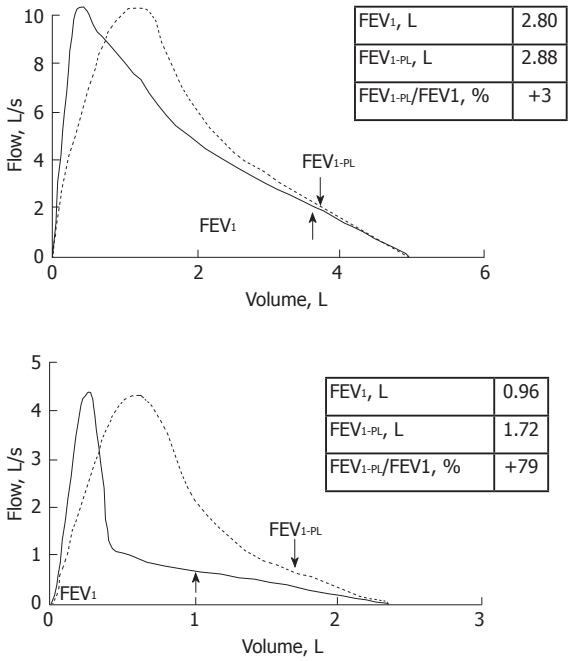

Figure 2 Effects of thoracic gas compression volume on spirometry. Flow at the mouth is plotted against volume integrated from the flow signal (continuous line) or measured in a volume-compensated body plethysmograph (dashed line). The FEV_1 at the mouth (FEV_1) and in the plethysmograph ($FEV_{1\text{-}PL}$) are indicated. The volume difference between the loops is the volume compressed within the chest wall during the forced expiratory manoeuvre (TGCV) and that does not contribute to the exhaled gas. Upper panel refers to a normal subject. The difference between $FEV_{1\text{-}PL}$ and FEV_1 is 3%. Lower panel refers to a patient affected by chronic obstructive pulmonary disease with prevalent emphysema. TGCV is very large because of lung hyperinflation in addition to airflow obstruction. $FEV_{1\text{-}PL}$ is 79% greater than FEV_1.

volume is higher than in chronic bronchitis. It follows that grading the disease on the FEV_1 as suggested by current international guidelines may lead to overestimate the severity of airflow obstruction in emphysema compared to chronic bronchitis and, as a result, overload the patients with inappropriate kind and amount of medications. In a recent study, Sharafkhaneh *et al*[11] reported that inhaling a bronchodilator agent was associated with a significant decrease in thoracic gas compression volume during forced but not tidal expiratory manoeuvres. This was due to a decrease in lung resistance and dynamic hyperinflation, and accounted for 23% of the increase in FEV_1, thus seriously confounding the interpretation of the dilator response based on the FEV_1. In other words, the FEV_1 significantly overestimated the number of positive bronchodilator responses. In another study, the same group showed that 40% of the increase in the FEV_1 after lung volume reduction surgery was explained by the decrease in thoracic gas compression volume (TGCV)[12]. Very recently, we examined the relationship between bronchial responsiveness or reversibility tests using FEV_1 and height and sex, which are major determinants of lung volume[9]. Airway responsiveness to methacholine was assessed in 54 asthmatics; bronchodilator response to salbutamol was assessed in 55 subjects with reversible airflow obstruction. The methacholine provocative dose was significantly greater using $FEV_{1\text{-}PL}$ than FEV_1, with this difference being significantly correlated with alveolar pressure, total lung capacity and height, and larger in males than females. Of the 55 subjects who responded to salbutamol with an increase of FEV_1 > 200 mL and > 12% of control, 28 did not show an increase of $FEV_{1\text{-}PL}$ above these thresholds. These subjects were significantly taller, predominantly males, with larger total lung capacity (TLC) and greater alveolar pressure than their counterpart. Thus, it appears that the bronchoconstrictor and bronchodilator responses are overestimated by standard spirometry in subjects with larger lungs because of the large TGCV.

Taken together, these findings strongly suggest that any changes in lung volume and/or airflow resistance no matter how they are achieved significantly confound the interpretation of the classical spirometric parameters.

VOLUME HISTORY EFFECTS OF THE DEEP BREATH

A second major factor that importantly affects spirometry is the full breath taken prior to full expiration. This was first described in 1961 by Nadel *et al*[13] in healthy subjects exposed to a constrictor agent. Taking a deep breath reversed the increase in airway resistance[13]. Subsequent studies proved that forced expiratory flow was higher during a maximal than a partial manoeuvre started from lower lung volume, and this increased with the severity of airway narrowing[14,15]. This effect on flow was also associated with a decrease in residual volume, suggesting that volume history modulates not only airway narrowing but also closure[16]. Studies conducted in asthmatics exposed to a provocative agent documented an increase in maximal compared to partial flow, thus suggesting bronchodilatation. Yet this was remarkably less than in healthy subjects. During natural asthma attacks indeed, the deep breath did not relieve bronchospasm or caused even more narrowing[17]. Similar responses were reported in COPD[18]. Reducing bronchial tone with a β_2-adrenoceptor agonist prevented maximal flow from increasing as much as partial flow, suggesting some modulation of airway tone by deep breath[19]. Reducing airway inflammation in asthma with inhaled steroids restored the bronchodilator effect of deep breath[20]. Thus, depending on the kind and severity of disease and medical interventions, the spirometric indexes are affected by the deep breath preceding the forced expiratory manoeuvre. Typical examples are shown in Figure 3.

In few asthmatic patients, taking one or more deep breaths may cause airway narrowing as suggested by important decrements of FEV_1[21]. This phenomenon was attenuated by a voltage-dependent Ca^{2+}-channel blocker, thus suggesting a myogenic response triggered by stretching airway smooth muscle cells.

These findings fuelled interest on the mechanisms causing airway narrowing. Based on the relative hysteresis hypothesis of Froeb *et al*[22], the airways dilate on inspi-

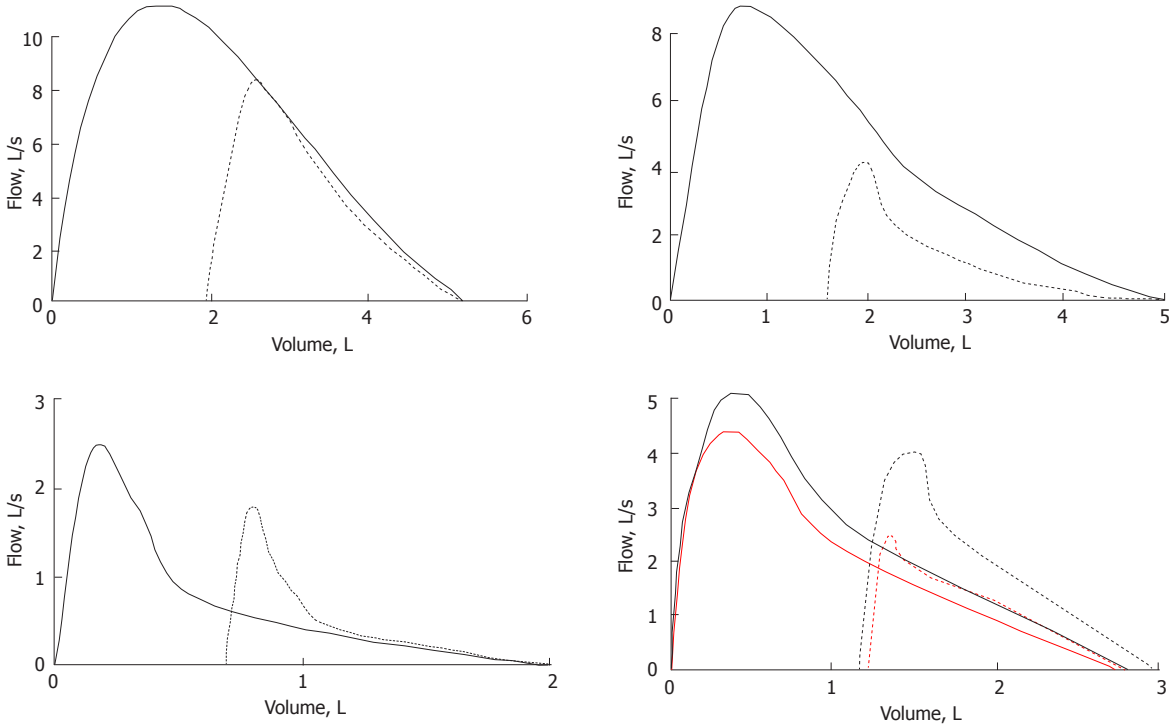

Figure 3 Examples of the effects of the deep breath on maximum flow and volume depending on the disease condition. Continuous and dashed lines are maximal and partial flow-volume loops, respectively. Upper left panel is a normal case. The slight increase in flow after DB suggests a decrease of normal bronchial tone presumably provided by the vagus nerve. Upper right panel is the case of a mild asthmatic subjects during a bronchial challenge. The increase in flow after the deep breath indicates that a substantial part of the constrictor response to the chemical agent is ablated with DB. Lower left panel is the case of a patient affected by chronic obstructive lung disease in which taking a DB is associated with a decrease of flow. This is presumably due to the involvement of the peripheral lung regions that contribute to the lung elastic recoil and/or loss of airway-to-parenchyma interdependence. Lower right lung is the case of an asthmatic subject before and after (red and balck lines, respectively) inhaling a bronchodilator agent. Isovolume flow measured during manoeuvres initiated from mid lung volumes (dashed lines) is higher than flow after a maximum lung inflation (continuous lines).

ration as a result of the increase in lung elastic recoil. However, because both airways and lung parenchyma are imperfect elastic materials, part of the energy stored on inspiration is dissipated on expiration. If this is the same for airways and lung parenchyma, then airway calibre and thus flow at a given lung volume will be the same on inspiration and expiration. If in contrast, it is the airways that mostly dissipate energy during cycling rather than lung parenchyma, then airway calibre will be larger on expiration than inspiration and the opposite will happen if pressure dissipates more within lung tissue than airways. This theory would suggest that the bronchodilator effect of the deep breath during induced bronchoconstriction might be the result of a decrease in airway smooth muscle tone when stretched by a large breath. Conversely, reducing airway smooth muscle tone by inhaling bronchodilators would reduce airway smooth muscle pressure dissipation, thus causing maximal flow to be less than partial flow. Similarly, an increase in airway wall stiffness due to chronic remodelling processes would prevent the airways from distending with large breaths. Finally, loss of pressure within lung parenchyma would result in a reduction of maximal below partial flow, though the underlying mechanisms at tissue or cellular level are unknown.

Altogether, these findings point out to the disease condition and severity as crucial modifiers of bronchial tone after a deep breath and thus classical spirometric indexes.

TIME HISTORY EFFECTS OF THE PRECEDING INSPIRATORY MANOEUVRE

Duration of the full inspiration preceding the forced expiratory manoeuvre also plays some role on the major spirometric indexes in different conditions such as health[23,24], airflow obstruction[24,25], cystic fibrosis[26], and interstitial lung disease[27]. In brief, under all these conditions, increasing the duration of the inspiratory manoeuvre and end-inspiratory pause is associated with a decrease in PEF and FEV_1 that is about 20%-30% compared with fast manoeuvres with no pause at maximal lung inflation. Loss of lung elastic recoil with the slow inspiratory manoeuvres has been suggested as the mechanism underlying the decrease in flow, though recruitment rate of closed or near closure airways might also play a role. The time history of the forced expiratory manoeuvres assumes clinical relevance mostly when inspiration is severely slowed down as a result of inspiratory muscles fatigue or severity of airway narrowing.

VENTILATION HETEROGENEITIES

Normal lungs exhibit structural and functional heteroge-

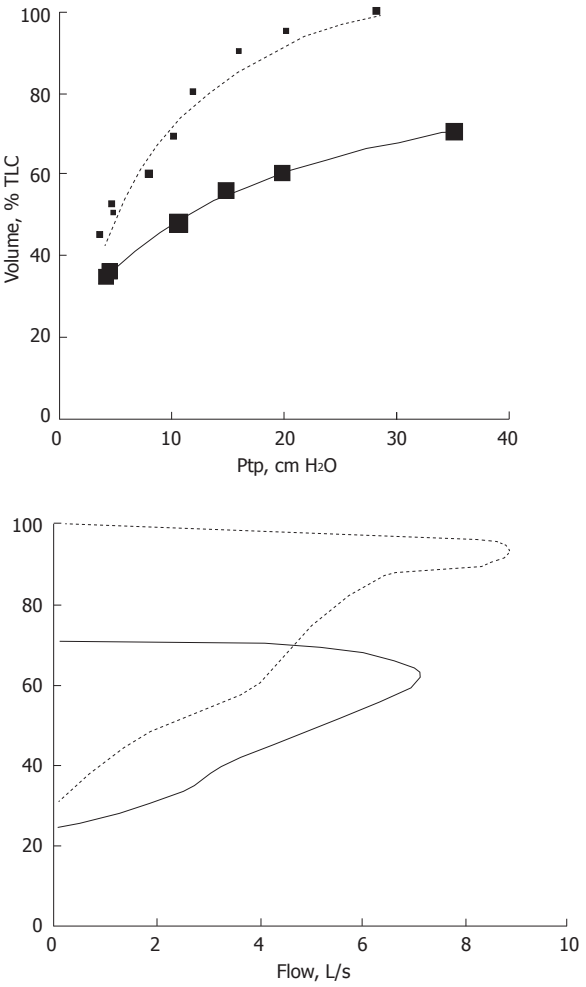

Figure 4 Effects of increased lung elastic recoil on maximal flow in a healthy subject (dashed lines) and a patients affected by pulmonary fibrosis (continuous lines). Upper panel: transpulmonary pressure (Ptp) is plotted *vs* lung volume; Lower panel: flow is plotted *vs* volume. With the increase in Ptp, maximal flow increases. This compensates for the decrease in FEV_1 expected from the decrease in total lung capacity (TLC).

neities[28-30] that contribute to modifying maximal flows and volumes.

For instance, central airways obstruction causes a decrease in maximum flow at high lung volume and a shift of the choke point to low lung volume[31]. This is because airway calibre, wall compliance, or both are reduced. Vital capacity is not reduced under these conditions because small airways are not affected by the disorder. In contrast, increasing peripheral airway resistance will cause flow to decrease over the entire range of lung volume, and choke point to shift to higher lung volume. This is because frictional and/or convective pressure losses are increased with a resulting decrease in transmural pressure and airway area at choke point. Forced vital capacity is reduced, because small airways tend to close at increased lung volume.

Also parallel ventilation inhomogeneities tend to reduce forced expiratory flow, but this effect appears to be less important compared to the above discussed in series heterogeneities. The idea is that they may be somewhat counterbalanced by compensatory mechanisms. This was investigated by Solway *et al*[32] with the use of an electrical analogue. By introducing different types of parallel inhomogeneities, the Authors produced multiple axial choke points. Surprisingly however, flow-volume loops exhibited near normal configurations. The interpretation was that lung regions with higher driving pressure emptied faster, thus contributing to maintaining overall ventilation near normal. Wilson *et al*[33] examined flow at the junction of two tubes emptying with different driving pressures upstream from the flow-limiting segment. Flow from the region with higher driving pressure was higher than flow from the region with lower driving pressure, thus suggesting a sort of mechanical compensatory mechanism keeping ventilation near normal during forced emptying. McNamara *et al*[34] measured alveolar pressure in excised dog lungs with the help of alveolar capsules. Despite appreciable pressure differences between regions, expiratory flow-volume loops were normal or near normal. All this provides evidence of different kinds of flow interdependence between and within lobes that mask the effect of parallel heterogeneity on lung emptying.

In conclusion, serial heterogeneities appear to affect the main spirometric parameters more than parallel heterogeneities. This might help explain why in the early stages of obstructive or restrictive lung diseases that are characterized by heterogeneous ventilation, spirometry is still normal or near normal despite the presence of initial structural damage.

LUNG ELASTIC RECOIL

Lung elastic recoil is one of the major determinants of maximum flow as anticipated in the introductory section of this review. If in emphysema the decrease in Pel is reflected by a decrease in FEV_1, the increase in Pel in interstitial lung diseases is not associated with an increase in FEV_1. This is because of a reduction in lung volume. However, examining maximum flow as a function of absolute lung volume will show that for any given lung volume, flow is higher than predicted value because of the increase in Pel[35] (Figure 4). In patients with combined emphysema and pulmonary fibrosis[36] the decrease in flow and thus FEV_1 due to emphysema is usually well compensated by the increase in lung recoil due to pulmonary fibrosis. As a result, the FEV_1 is still normal. Under these conditions, TLC will also be normal because the loss of alveolar units due to pulmonary fibrosis is compensated by the increased enlarged emphysematous airspaces.

DYSANAPTIC LUNG GROWTH

In childhood, the airways and lung parenchyma usually grow proportionally so that in adulthood the FEV_1 will be about 80% of VC. In a small number of healthy young adults however, the FEV_1 is normal, but the ratio of FEV_1 to VC is surprisingly below normal range. In a recent study[37], it was reported that about 20% of these

cases had a history free of any respiratory symptoms or diseases and no abnormalities could be detected even with additional pulmonary function tests. The pattern is consistent with asynchronous development of airways and air spaces during the early stages of life[38], with some individuals having lung parenchyma disproportionally growing faster and to a greater extent than airways. Among the hypothetical mechanisms, natural events such as intense physical activity or disease conditions occurring before definite maturation of the respiratory system have been reported. Under these conditions, it is suggested that the subjects undergo further functional evaluation to exclude a disease condition.

CONCLUSION

Spirometry is one of the most used tests in medicine and research because of its good sensitivity to detect pulmonary function defects, easiness and noninvasiveness of the manoeuvre, standardisation of the technique, and low cost of the instruments. Yet, it must be acknowledged that many factors significantly contribute to amplify or blunt its changes in disease conditions. As the FEV_1 and VC are the classical parameters used by current guidelines for the diagnosis of pulmonary defects and severity grading, spirometry should always be included within a panel of functional tests capable of thoroughly examining lung function within its whole volume and time domains.

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