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SERIES 'LUNG HYPERINFLATION IN AIRWAY OBSTRUCTION'
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On the causes of lung hyperinflation during bronchoconstriction

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ABSTRACT: Airway obstruction in asthma and chronic obstructive pulmonary disease (COPD) is often associated with lung hyperinflation. In this review, we examine the mechanisms that may cause functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC) to increase during acute and chronic airway obstruction.

Normally, FRC at rest is determined by the static characteristics of the lung and chest wall. When airways narrow, FRC may be also be determined by dynamic factors. There are data suggesting that expiratory flow limitation during tidal breathing represents the starting trigger for FRC to increase, in order to allow breathing at higher flows. Indeed, the increase in FRC during induced bronchoconstriction in asthma is closely associated with the occurrence of flow limitation, *i.e.* the achievement of maximum flow during tidal breathing. Conversely, the decrease in FRC following bronchodilatation in COPD is closely associated with flow limitation disappearing or occurring at lower lung volumes.

In normal young people, RV is determined by the static characteristics of the chest wall. During bronchoconstriction RV may also be determined by dynamic factors; therefore, changes in flow or airway calibre at low lung volumes may modulate RV during bronchoconstriction. During acutely induced bronchoconstriction, RV achieved with an expiration from TLC is less than with an expiration from tidal breathing, and this effect appears to be linked to the bronchodilator effect of the deep inhalation.

The reasons for the increase in TLC during airway narrowing are not clear, but the duration of the bronchoconstriction by itself may play a role.
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In healthy humans, lung volumes are determined by the static properties both of lung parenchyma and chest wall, and reflect the balance between the forces that pull the lung inwards and outwards [1]. When the airways narrow, residual volume (RV), functional residual capacity (FRC), and, to some extent, total lung capacity (TLC) tend to increase. As there is no clear definition for lung hyperinflation, we will include under this term the increments of any of these lung volumes. Under diseased conditions, the altered properties of airways and lung parenchyma are deemed to represent the main cause of lung hyperinflation [2]. In clinical practice, it can be observed that some volumes increase before others. For example, RV is generally the first to increase, followed by FRC and then by TLC, which suggests that bronchoconstriction probably causes lung hyperinflation through different mechanisms. The aim of this review is to present and discuss a series of potential factors that may increase the lung volume during airway narrowing.

Increase of functional residual capacity

In normal individuals at rest, FRC is set at the volume at which the inward recoil of the lung and the outward recoil of the chest wall are of equal magnitude (relaxation volume). This volume is normally reached at the end of a quiet breath, even though expiration is slower than inspiration due to the gradual reduction of inspiratory muscle activity and the narrowing of the glottic aperture [1]. In individuals with airway obstruction, FRC may be increased to varying extent depending both on type and severity of the underlying disease. There are different mechanisms that may account for the increase in FRC under conditions of airway obstruction.

A reduction of the elastic recoil of the lung can increase FRC [1, 2] by two mechanisms. Firstly, if the elastic recoil of the chest wall does not change, then the relaxation volume of the respiratory system will necessarily increase above normal (fig. 1). Secondly, a reduction of the recoil of the respiratory system may cause

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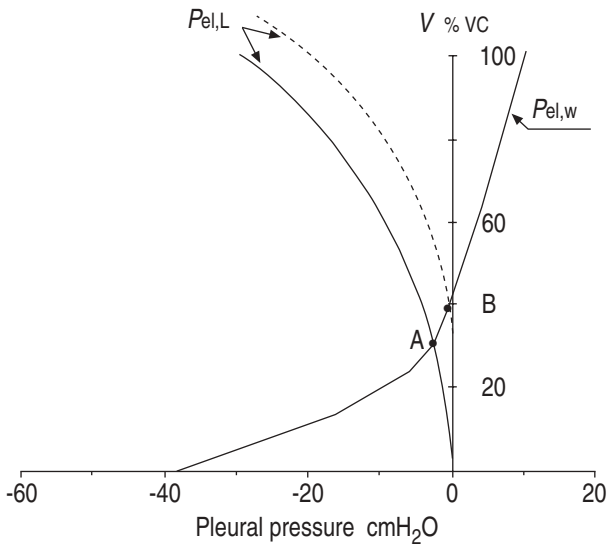

Fig. 1. – Elastic recoil pressure of the lung ($P_{el,L}$) and chest wall ($P_{el,w}$) plotted against lung volume (V) during normal conditions (——). Point A (at the intersection of the two lines) defines the level of functional residual capacity (FRC). If $P_{el,L}$ at any given lung volume decreases (– – –) whilst $P_{el,w}$ remains constant, then tidal breathing is passively set at a higher FRC, indicated by the point B at new intersection between the $P_{el,w}$ line and the $P_{el,L}$ dashed line. VC: vital capacity.

the passive expiratory flow to decrease, such that the relaxation volume cannot be reached within the expiratory time allowed, unless expiration becomes active. There is little doubt that these mechanisms may be responsible by themselves for the increased FRC in patients with pulmonary emphysema. This, however, does not seem to be the case in other circumstances. For example, in healthy subjects and some asthmatics, the bronchoconstriction induced by chemical stimuli, *e.g*. histamine or methacholine, may be associated with an increase in FRC with no shift of the expiratory limb of the pressure-volume curve of the lung [3–6]. This suggests that mechanisms other than loss of lung elastic recoil are responsible for the increase of FRC in these individuals. In other asthmatic subjects during acutely induced airway narrowing [4–6], or natural asthma attack [7, 8], and during chronic bronchoconstriction, the lung elastic recoil is low near FRC [2]. In these individuals, both loss of elastic recoil and other mechanisms (see below) may contribute to the increase of FRC at rest.

Bronchoconstriction causes the airway resistance to increase. If the increase in expiratory resistance is such that the time constant of the respiratory system increases beyond the maximum expiratory time, then the relaxation volume cannot be reached [9]. In order to compensate for the increase in lower airway resistance, subjects with chronic bronchoconstriction decrease the inspiratory muscle braking during expiration [10]. If this compensation is not sufficient, the next breath will occur before reaching relaxation volume, and FRC will be greater than relaxation volume. During both natural and induced asthma, sustained postinspiratory activity of the inspiratory muscles and glottic narrowing have been observed [11–14]. These two factors would further reduce expiratory flow, thus impeding passive expiration to reach the relaxation volume. However, it seems paradoxical that an increased airway resistance triggers changes resulting in a further reduction of expiratory flow. In this scenario, the increased postinspiratory activity of the inspiratory muscles during induced airway narrowing could be interpreted as a result rather than a cause of hyperinflation [13].

We have recently advanced a new hypothesis on the causes of the increase in FRC during bronchoconstriction, *i.e*. the attainment of expiratory flow limitation during tidal breathing could represent the trigger for the initiation of inspiration. If flow limitation occurs, it must be above the relaxation volume, and initiating inspiration at the onset of flow limitation increases FRC. In the rest of this section, we will present and discuss data that support, even if they cannot fully prove, this hypothesis.

Changes of FRC during exercise

Young normal individuals during incremental work progressively reduce FRC as they increase tidal volume, so that at high workloads the relaxation point is near mid-tidal volume [15]. In contrast, patients with mild chronic obstructive pulmonary disease (COPD) and older normals with high levels of cardiovascular fitness may progressively increase FRC with increasing ventilatory demands [16]. The increase in FRC is generally associated with the attainment of maximal expiratory flow near end-expiration [16]. Once this occurs, further increases

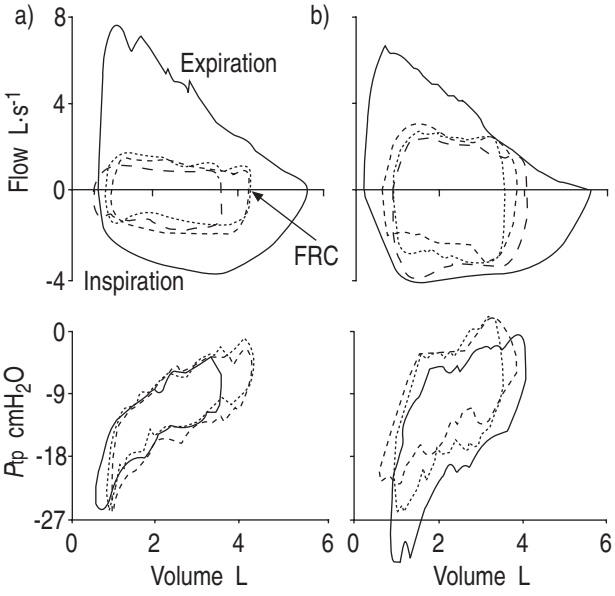

Fig. 2. – Effects of an expiratory threshold load (ETL) of 5 cmH_2O on the expiratory flow-volume and pressure-volume curves in moderately obstructed individuals during exercise. In the upper panels, the external loops represent the maximal flow-volume curves, whereas the internal loops represent the flow-volume curves during tidal breathing. In the lower panels the tidal pressure-volume curves are shown. a) Under conditions of no flow limitation, applying ETL decreases expiratory flow and increases FRC (— —) relative to the control (·····). Removing ETL restores the control conditions (- - -). b) Under conditions of flow limitation, applying ETL decreases flows (— —) compared to control (·····), but expiration consistently terminates at lower FRC. Removing ETL restores the control conditions (- - -). (From [18], with permission). FRC: functional residual capacity; P_{tp}: transpulmonary pressure.

in ventilation are achieved by increasing FRC rather than using maximal flow throughout the expiration or increasing inspiratory flow. Similar responses have also been reported in an exceptionally fit group of elderly males [17]. A link between the increment of FRC and flow limitation during tidal breathing has been demonstrated by applying an external expiratory threshold load during steady-state exercise [18]. In individuals who do not achieve flow limitation at end-expiration, expiring against a threshold load causes small decrements in expiratory flow and proportionally smaller increments in expiratory time, such that FRC increases slightly (fig. 2a). In marked contrast, subjects who achieve maximal expiratory flow at end-expiration respond to the expiratory threshold load with an increase in expiratory time proportionally larger than the decrease in flow, such that FRC consistently decreases (fig. 2b). The inspection of flow-volume curves in these individuals shows that expiration stops when tidal expiratory flow impinges on forced expiratory flow, suggesting that flow limitation may represent a signal for expiration to be prematurely interrupted, thus increasing FRC.

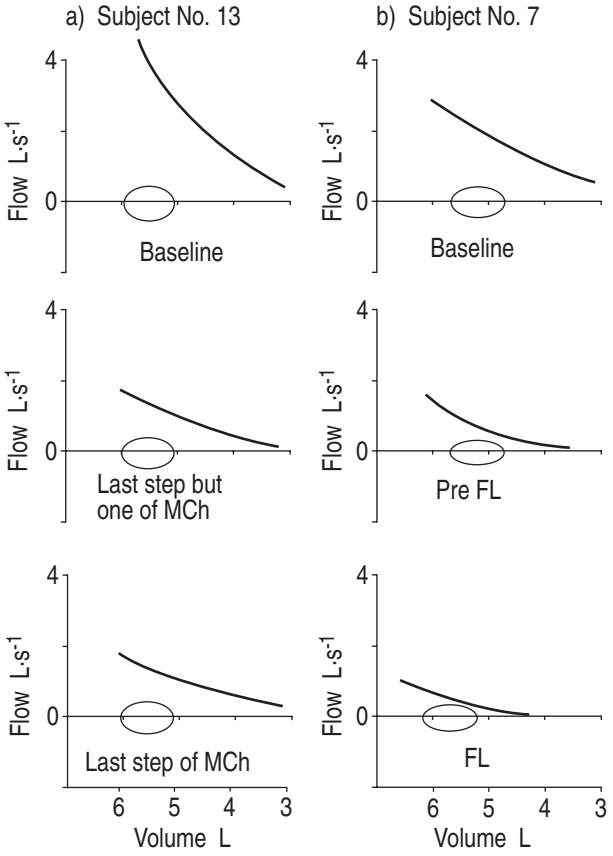

Fig. 3. – Tidal and partial (*i.e.* started from a lung volume below total lung capacity) forced expiratory flow-volume loops in two typical individuals in whom inhaling methacholine (MCh): a) did not increase FRC; and b) did increase FRC. Upper panels are baseline conditions. b) In subject No. 7, FRC increased only when the tidal flow-volume loop at a given dose of methacholine (central panel) would have impinged on the partial loop of the next step (lower panel) (flow limitation (FL) conditions). a) In contrast, in subject No. 13, FRC did not increase after methacholine, and the conditions of flow limitation never occurred, as inferred from the presence of expiratory flow reserve near end-expiration. FRC: functional residual capacity. (From [13], with permission).

Changes of FRC during bronchoconstriction and bronchodilatation

When bronchoconstriction is acutely induced by inhaling methacholine, some individuals (generally normals) do not increase FRC despite a significant decrement of forced expiratory flows (fig. 3a). In these subjects, the forced expiratory flow never decreases to an extent sufficient to make it equal to the end-tidal expiratory flow at control FRC, suggesting that expiratory flow limitation does not occur during tidal resting breathing [13]. Other individuals (most asthmatics, but also some normals) consistently increase FRC during bronchoconstriction when the forced expiratory flow is reduced such that it equals the tidal expiratory flow at control FRC (fig. 3b). This suggests that FRC increases in these subjects when it would be impossible for them to keep tidal volume at the relaxation volume without expiring under conditions of flow limitation. The reduction of forced expiratory volume in one second (FEV_1) in subjects who do increase FRC is not greater than in those who do not, and generally, no consistent changes of breathing pattern are observed either in individuals who do or do not increase FRC after inhaling the bronchoconstricting agent. Thus, the increase in FRC appears to be due to tidal flow impinging on maximal flow rather than to the degree of bronchoconstriction [13].

The hypothesis that the kind of bronchoconstricting agent, by itself, could be the cause of the increment of FRC has been ruled out in a study where the same phenomenon was reproduced by using a variety of bronchoconstricting agents [19]. This indicates that the increment of FRC is not a pharmacological effect of a given agent but rather a mechanical event associated with the attainment of maximal expiratory flow during tidal breathing.

Individuals with mild-to-moderate bronchoconstriction may or may not decrease their FRC after inhaling bronchodilating agents. In general, the subjects who do not achieve flow limitation during tidal breathing at control conditions do not decrease FRC even when expiratory flows are markedly increased. Conversely, the individuals with tidal expiratory flow impinging on forced expiratory flow under control conditions generally decrease FRC, unless expiration already ends at the relaxation volume. Furthermore, these data are consistent with the hypothesis that attainment of maximal expiratory flows during tidal breathing regulates the level of FRC during bronchoconstriction.

Altogether, these findings consistently indicate that expiration terminates any time flow limitation occurs during tidal breathing. A sustained postinspiratory activity of the inspiratory muscles does not seem to be a prerequisite for FRC to increase, as it is totally absent, for example, during chronic bronchoconstriction [10]. The same interpretation may be extended to the possible role of breathing pattern in generating hyperinflation during tidal breathing.

The mechanism by which flow limitation may regulate the level of FRC is open to speculation. Maximal expiratory flow is reached when the velocity of air matches the speed of wave propagation [20] at some point in the intrathoracic airways, the so-called choke point. Once this occurs, the expiratory driving pressure in excess is dissipated in collapsed airways and violent vortices

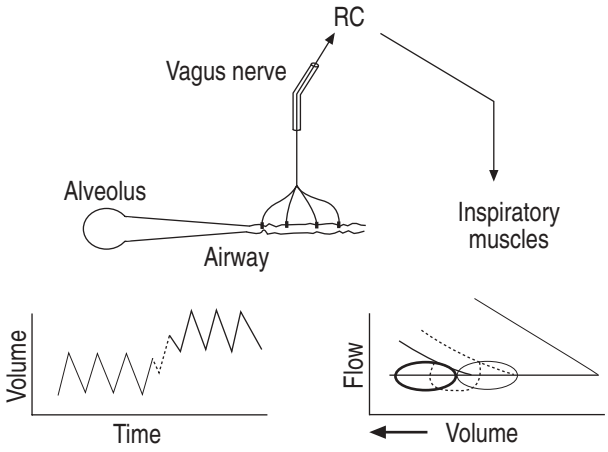

Fig. 4. – Hypothetical mechanism through which flow limitation may increase functional residual capacity (FRC). When the airways collapse downstream from the flow-limiting point, mechanoreceptors could be triggered and send a signal to the respiratory centres (RC) (through the vagus nerve?), which in turn could be reflected to the inspiratory muscles for premature activation. In the example, the thin continuous lines on the tidal spirogram correspond to the thin flow-volume loops (control conditions). Under these conditions, there is no flow limitation, as the partial flow-volume curve is distant. When the partial flow decreases (dashed line) due to sudden airway narrowing, the tidal flow-volume loop would hit the new partial curve, unless expiration terminates immediately due to premature activation of inspiratory muscles. The same happens again when the partial curve further decreases (thick continuous line). Note that the increment of FRC in the example is associated with a transient decrement of expiratory time (see the spirogram).

develop in the airways downstream from the choke point [21]. Although subjects breathing under conditions of flow limitation do not necessarily generate pressure in excess of that required to achieve maximal flow, it is possible that there is sufficient stress applied to the airway walls to stimulate afferent mechanoreceptors, which could prematurely initiate inspiration by reflexly activating the inspiratory muscles. In agreement with VINEGAR *et al*. [9], such a mechanism would imply transient decrements of expiratory time, as schematically represented in figure 4.

Increase of residual volume

In normal young individuals, RV is primarily determined by the elastic properties of the chest wall [22]. However, in the elderly and in the presence of airway obstruction, the reduction of lung elastic recoil and the increased airway resistance, respectively, may be the major determinants of RV. This is because the expiratory flow at a given lung volume is low and expiration is switched off before reaching the volume at which the chest wall cannot be squeezed further [22]. Another mechanism that has been invoked to explain the increase of RV in these individuals is airway closure, which may be the result either of reduced lung elastic recoil or airway narrowing [23–25]. If airway calibre is a determinant of RV during bronchoconstriction, then factors affecting airway calibre should also regulate RV. We will present, hereafter, a detailed analysis of the mechanisms that may increase RV by decreasing airway calibre.

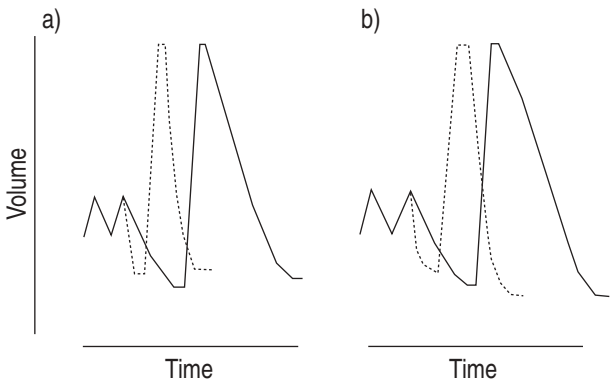

Fig. 5. – Slow maximal and partial expiratory spirograms (continuous lines) and forced maximal and partial expiratory spirograms (dashed lines) in two typical individuals with: a) chronic bronchoconstriction; and b) induced bronchoconstriction.

Effect of expiratory flow

In individuals with chronic or acutely induced bronchoconstriction, RV reached with a forced expiratory manoeuvre initiated from a given lung volume is always greater than the RV reached with a slow expiratory manoeuvre [26, 27] (fig. 5). This suggests that expiratory flow has an important effect on RV under these conditions. There are, at least, two mechanisms that can explain this finding.

Firstly, increasing the expiratory effort increases pleural pressure, which in turn easily attains and exceeds the minimum (critical) pressure necessary for generating maximal flows in individuals who are already bronchoconstricted. Therefore, flow limitation occurs soon after initiating expiration, as the wave-speed of constricted airways is low [28]. Under these circumstances, RV would depend on the breathholding capacity of the subject [22]. This mechanism is also likely to be operative when expiration is slow, but pleural pressure may exceed the critical pressure only at a lower lung volume, when the latter is near zero. This would explain why, even during slow expiratory manoeuvres, RV is always reached at higher volume during bronchoconstriction than during normal conditions.

Secondly, forced expiration may induce some airways to close. Under these circumstances, the increment of RV could be due to the exclusion of alveolar units from emptying. Whether and how this occurs in humans during bronchoconstriction is unknown, but animal models have shown that closure of airways may occur near end-expiration. For instance, excised dog lobes and excised canine airways close at low lung volumes when airways are contracted with methacholine [24, 25], suggesting that similar events may likewise occur in humans during airway narrowing. Alternatively, some airways may close soon after starting expiration at a lung volume just below TLC, as proposed by OLIVE and HYATT [23]. This hypothetical mechanism could be operative when bronchoconstriction is unevenly distributed in the lungs and located in the most peripheral airways.

In summary, even though we do not know whether and how the above mechanisms are active in humans, these data emphasize the remarkable effects of increasing expiratory flow on RV, probably due to the reduction of airway calibre occurring during expiration.

Effect of volume history

A deep inhalation to TLC has profound effects both on airway calibre and RV. For example, during acutely induced bronchoconstriction, greater expiratory flows and smaller RV are achieved with a forced expiratory manoeuvre started from TLC (maximal manoeuvre) than from a lower lung volume (partial manoeuvre). The increase in flows and the decrease in RV after taking a deep breath are greater in healthy than in asthmatic subjects [3, 4, 29–37]. On the contrary, a deep inhalation to TLC consistently decreases expiratory flow and increases RV in individuals with chronic airway narrowing [38]. The changes in RV due to the effect of volume history are represented in figure 5. This suggests that the mechanisms by which volume history modulates airway calibre may also modulate RV.

When the inspiratory muscles contract maximally, the inflating stimulus is not only transmitted to the parenchyma but also to the airways. Therefore, both the calibre and length of airways tend to increase. The inflating stimulus is transmitted from the pleural space to the airway walls through the connective and elastic network of lung parenchyma. There are some potential mechanisms that may modulate the magnitude of the inflating stimulus on the airway calibre under pathological conditions. Firstly, the inflating stimulus may be blunted or even abolished in the anatomical zone between the airways and the surrounding parenchyma, where the so-called bronchial-to-parenchymal interdependence originates [39]. Thereafter, when the stimulus reaches the airway wall, the change in internal calibre will depend on the thickness, as well as on the mechanical properties, of the wall. The latter mostly embodies the energy losses occurring when biological tissues are stretched, and is called hysteresis [40]. Therefore, any time the airways are stretched outwards, the changes of airway calibre will depend on the mechanical properties of the airway wall. Not only airways but also lung parenchyma show hysteretic behaviour [41], in that for a given lung volume the transpulmonary pressure is less during expiration than inspiration. Thus, the final change of airway calibre after stretching will depend both on airway and parenchymal characteristics [42]. Why do airways and lung tissue increase their hysteretic behaviour under bronchoconstricting conditions? Basically, the width of the pressure-volume loop increases when the contractile elements of the airways and parenchyma increase the tone generated by the coupling between actin and myosin [25, 43, 44]. Under these conditions, more energy may be dissipated after stretching due to the high number of cross-bridges which are the site of stored energy [45].

Let us consider first the hypothesis that the decrement of expiratory flows and the increase of RV during bronchoconstriction are uniquely due to the loss of the forces of bronchial-to-parenchymal interdependence. The extreme case would be that the inflating stimulus is not transmitted at all to the airways. If there were no parenchymal hysteresis, the expiratory flows and RV recorded after a deep inhalation should be identical to those recorded before it. However, individuals with spontaneous or chronic airway narrowing very often show lower flows and higher RV after a maximal compared to a partial expiratory manoeuvre [32, 38]. Therefore, parenchymal hysteresis is a potential mechanism for this phenomenon.

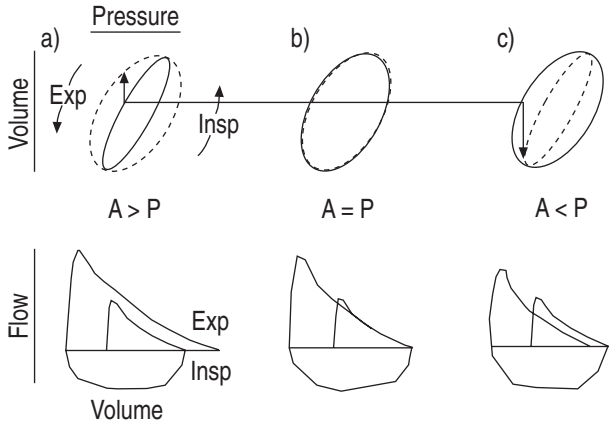

Fig. 6. – Changes of expiratory flow according to the hypothesis of FROEB and MEAD [41]. In the upper panels the pressure-volume (*P-V*) loops are represented (dashed loops are airway *P-V* curves and continuous loops are parenchymal *P-V* curves). In the lower loops partial and maximal flow-volume curves are depicted. a) For a given partial expiratory flow, the maximal flow is greater than partial flow when the airway (A) hysteresis prevails over the parenchymal (P) hysteresis because the expiratory airway calibre is greater (lower panels). b) When the airway and parenchymal hystereses are equal, the flows before and after a deep breath are supposed to be the same. c) On the contrary, when parenchymal hysteresis is relatively greater than airway hysteresis, the flows after a maximal manoeuvre are less than before. Exp: expiratory; Insp: inspiratory.

The hysteretic properties of the bronchial and parenchymal tissues can affect expiratory flows and RV. Under conditions of airway narrowing, the relationship between airway and parenchymal hysteresis may change. According to the theoretical analysis provided by FROEB and MEAD [42], the effects of volume history on airway calibre may differ substantially depending on the relative magnitudes of airway and parenchymal hysteresis. When airway hysteresis exceeds parenchymal hysteresis (fig. 6a), for a given lung volume the airway volume will be greater during expiration than inspiration. This usually happens when constriction is confined to conducting airways, as during methacholine-induced bronchoconstriction in healthy or mildly asthmatic subjects [3]. As shown by the relative partial (*i.e.* started from a lung volume below TLC) and maximal flow-volume curves, the expiratory flows will be greater and RV will be less after than before the deep inhalation to TLC. In moderate and severe asthmatics, inhalation of a bronchoconstricting agent may cause parenchymal hysteresis to increase, as the most peripheral airways and possibly lung structure are involved [4, 31]. If airway and parenchymal hystereses increase to the same extent (fig. 6b), then there will be no difference in airway calibre between inspiration and expiration, and expiratory flows and RV on partial and maximal expiratory manoeuvres will be equal. However, if parenchymal hysteresis exceeds bronchial hysteresis (fig. 6c), for a given lung volume the airway calibre will be less after than before deep inhalation [32, 38]. Therefore, flow will decrease and RV will increase after a maximal compared to a partial expiratory manoeuvre.

Altogether, these data suggest that the close relationship between the increment of RV and the effects of volume history during bronchoconstriction may rely on losses of interdependence between airways and surrounding

parenchyma and, more likely, on the anatomical and functional characteristics of airway and parenchymal tissues.

Increase of total lung capacity

TLC is the volume of the lung at which the maximum elastic pressures of the lung and the chest wall counterbalance the pressure exerted by the inspiratory muscles [1] during a maximal inflating manoeuvre.

During acutely induced bronchoconstriction, TLC does not systematically change [6, 46], even though occasional increments after inhaling allergens [23], histamine [47], and methacholine [13], or after exercise [5, 48, 49] have been reported. Possible errors overestimating lung volumes in such cases could have been due to the plethysmographic technique, because of poor transmission of the alveolar pressure signal to the mouth [50], or inequality of changes of alveolar pressure in inhomogeneous lungs during panting manoeuvres [51], even though a panting frequency <1 Hz can minimize such errors [52]. However, due to the decrements of the elastic recoil of the lung [4, 5, 49] and the chest wall [49] observed in some patients during acutely induced bronchoconstriction, it is reasonable to accept that TLC may occasionally increase under these circumstances. What is not known is why the elastic pressures of the respiratory system should change so suddenly after exposure to constricting agents. Changes in surface forces, stress relaxation, or elastic and connective fibres of the lung, and increment of trapped gas at TLC have been suggested but not proven [5, 49]. More studies are necessary to understand and discover what potential mechanisms may occasionally increase TLC during induced airway narrowing.

More is known about the increment of TLC in individuals affected by chronic or spontaneous bronchoconstriction. During natural attacks of asthma, for example, TLC systematically increases [7, 8, 53, 54], as demonstrated by radiographic measurements of lung volumes. The same happens in individuals affected by COPD [54]. What is surprising is that, even for similar impairments of lung function, TLC consistently increases during spontaneous, but not during induced, bronchoconstriction. The reasons for this are still unknown. It could be due to the different time course required for bronchoconstriction and hyperinflation to develop. For example, when a resistive valve is implanted in dog trachea, it takes some time for TLC to increase. Then, hyperinflation persists for 2–4 weeks after removing the resistance [55]. Therefore, reversible relaxation and remodelling of the lung tissues, which may occur when patients breathe for long periods of time at very high FRC, could be the causes of increment of TLC [2]. In addition, chronic distortion of the chest wall and activation of the abdominal expiratory muscles during expiration could favour and optimize the length-tension relationship of the diaphragm in order to generate more pressure necessary for overexpanding the lungs [11].

Clinical implications

The knowledge of the above-mentioned mechanisms of lung hyperinflation during bronchoconstriction gives rise to some practical considerations for the diagnosis and the therapy of asthma and COPD. Firstly, recognizing the presence of high lung volumes in a bronchoconstricted patient gives insight into the disrupted regulatory mechanisms of airway calibre, and/or static properties of the lung parenchyma. Secondly, there is a body of evidence that breathlessness occurs in asthmatics and subjects with chronic airflow limitation when tidal breathing moves to high lung volumes [56–58]. That is to say, that lung hyperinflation may represent one of the most important causes of dyspnoea, which is the symptom prompting most patients to ask for treatment. Whenever this is the case, bronchodilator therapy, to be effective, should increase airway calibre to an extent sufficient to allow the patient to breathe at a lower lung volume. The patients may then feel much better even in the extreme and paradoxical case that expiratory flows do not apparently increase, probably due to decrement of absolute lung volume after relief from bronchoconstriction [7]. It appears, therefore, important to recognize the changes of lung volumes when evaluating the effectiveness of bronchodilator treatments and the symptoms reported by the patients. Conversely, when bronchodilators are ineffective or inadequate and the disease deteriorates, the increment of airway resistance will cause further increase of lung volumes, with potentially life-threatening burden on the inspiratory muscles.

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