

Asthma: pathophysiology of the bronchial obstruction

From a pathophysiologic perspective, the changes that occur in asthma are multiple, diverse, and complex. Assessment of the mechanical properties of the ventilatory apparatus provides several different types of information, depending on the gravity of the bronchial obstruction. During asthma, or induced bronchial obstruction, the function of the muscles is altered, causing changes in respiratory timing. Expiratory duration decreases more than inspiratory duration, and the functional residual capacity (FRC) increases, due to mechanical changes within the airways that lead to air trapping. The related hypoventilation is responsible for hypoxemia and hypercapnia, but it does not severely affect the diffusion capacity of the alveolocapillary membrane. We describe the pathophysiology of the bronchial obstruction in asthmatic patients, underlining the critical function of the respiratory muscles. Moreover, we clarify the relations between the ventilatory changes and gas-exchange alteration.

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Static and dynamic mechanical properties of the respiratory system

The function of the respiratory muscles is critical in the mechanism of pumping air in and out in the gas-exchange portion of the lungs. Therefore, the respiratory muscles serve as a vital link between the different components of the pump: the central nervous respiratory centers (source of the impulses), the conducting nerves, and the lung parenchyma itself (1).

The most important muscles in normal ventilation are the diaphragm and the intercostal muscles. These muscles exert their force through the underlying structures (pleura, lung parenchyma, and bronchus), generating a negative pressure in the thorax, with production of an airflow.

The work of the muscles during ventilation is normally produced during inspiration, and all the muscle strength is used to overcome the airway flow resistance, wasting energy through heat. Almost half of the inspiratory energy is wasted during inspiration, while the remainder is temporarily stored and expended during expiration. Therefore, the quality of elasticity allows the inspiratory muscles to perform the work of expiration.

All the above structures make up a mechanical complex that may be divided into two components:

- 1) an external component, represented by the rib cage, thoracic muscles, and diaphragm, making up the *external mechanic ventilation*
- 2) a visceral component (conducting, distribution, and gas-exchange systems) consisting of the visceral pleura, the anatomic underlay of the *internal mechanic ventilation*.

In the expiratory phase of ventilation, the presence of retractable forces is due to the tension of the alveolar surface and to the elastic recoil of the mesenchymal structures of the lung parenchyma. These forces are correlated with the release of stored energy during the previous inspiratory phase, through kinetic energy.

The physiomechanical balance of the thoracopulmonary complex is the result of two different mechanical balances: the *external ventilation* (expressed by the relation $C_{th} = \Delta V / P_{pl} - P_{atm}$) and the *internal ventilation* (expressed by the relation $C_L = \Delta V / P_A - P_{pl}$). The endopleural pressure is determined by the following formula: $P_{pl} = P_A - P_{el L} = P_{mus} - P_{el th}$; when the muscle strength is lost at the end of the expiration, the pleural pressure represents a neutral or opposing force to the elastic recoil of the thoracic wall. Therefore, the thoracopulmonary balance is expressed by the combined formula $C_{rs} = \Delta V / P_A - P_{atm}$.

The thoracopulmonary systems develop three different balance levels:

- 1) the thoracic system, with a balance level at 55% of the total lung capacity (TLC) (upper limit of the current volume [CV])
- 2) the pulmonary system, with a balance level a little lower than the residual volume (RV)
- 3) the thoracopulmonary system with a balance level at the volume where the opposite forces of the first two systems are equal (inferior limit of the CV, FRC level).

In static conditions, the endobronchial pressure is generated by the elastic recoil of the lung parenchyma, while, in dynamic conditions, it is related to all the forces that determine the air volume inside the lungs: muscle force, tissue qualities, flow resistance,

and inertia of the ventilatory system. At the end of a maximal inspiration, the lung parenchyma is totally stretched and the elastic recoil force of the lung is at its highest level. Therefore, during a forced expiration, there is a gradient in pressure between the alveoli and the mouth.

The alveolar pressure is related to the elastic recoil and to the pleural pressure. This pressure forms the pushing force to guarantee an expiratory flow through the canalicular bronchioli, where the pleural pressure (peribronchial pressure) acts on the bronchial walls.

Airway obstruction

The obstruction of the pulmonary airways, independently of its reversibility, is present when the smooth-muscle section of the bronchial tree is affected by an inflammatory process, either in a diffuse or localized way. Correlation between markers of inflammation and pathophysiologic indices of the severity of asthma has been reported in several studies (2, 3).

Pathophysiologically, the bronchial obstruction requires an increment of the P_A , according to the relation $P_A = V_{Raw}$. The alveolar pressure is related to the incomplete emptying of the alveoli, which increases the elastic tension of the interstitial fibers, intensifying P_{el} and, indirectly, P_{pl} ($P_A = P_{pl} + P_{el}$). However, the pleural pressure increases for other mechanisms: increase of the closing volume of the pulmonary airways, and toxic activation of the inspiratory muscles.

In asthma, the balance of pulmonary and thoracic systems moves on the left part of the volume-pressure diagram, according to the variability of pleuritic pressure. Consequently, the balance curve of the thoracopulmonary system displaces on the left, too. For this reason, in asthmatic subjects, the volume-pressure curve shows the following changes:

- 1) reduction of the DV/DP slope in the expiratory stress portion
- 2) reduction of the peak respiratory flow
- 3) reduction of the maximal pressure, at the level of which the airways start to close.

The new bronchopulmonary mechanical balance is reached at a higher percentage of the lung-volume level, compared with the physiologic balance. In these cases, the ventilation is performed at the expense of the inspiratory reserve volume (4).

The increase of the CV keeps constant the ventilation per minute, preventing the increase of the ventilatory rate ($V_E = V_t/T_i \times T_i/T_{tot}$). This mechanism minimizes the airflow turbulence through the bronchial airways, worsening the ventilatory workload.

As described above, the bronchopulmonary balance develops a new rest level at a higher lung volume, which is the FRC level. The increase of the FRC widens the

airway caliber and restores a new air gradient, supporting air distribution through less stretched lung basal segments (5). The lung stretching, due to the increase of the FRC, causes a persistent positive elastic recoil pressure at the end of the expiration (iPEEP) (6); even if this positive pressure could represent a compensatory mechanism for the increase of the airflow resistance, it is an added pressure which must be overcome by the inspiratory muscles to reverse the gradient of pressure between alveoli and mouth (7).

The presence of an iPEEP is a sign of alveolar hyperdistension only with the absence of an expiratory muscle contraction. In fact, in patients with severe bronchial obstruction, the abdominal muscles are phasically active during the expiration (8). Their activity could overestimate the iPEEP because part of the pressure gradient generated by the above muscles is not used to produce an airway flow but rather to overcome the iPEEP. Moreover, the decrease in muscle strength is as high as the increase in lung-volume capacity, which constitutes the new rest level of the thoracopulmonary system (FRC). In fact, the capacity of the inspiratory muscles to produce pressure is reduced because of the increase of the FRC, due to the unfavorable relation between tension and length of the muscle fibers present at high lung volumes (9).

The increment of the FRC increases the resistance (iPEEP); therefore, the workload of the inspiratory muscles is increased (4). To prevent worsening of the muscle efficiency, the thoracopulmonary system keeps the normal ventilation per minute with an increase of the CV without changing the respiratory rate. This compensatory method is not mechanically valid, but it could become significant when the bronchial obstruction persists, developing an increase of the muscle resistance.

Gas tension changes in asthma

In asthmatic patients, the alveolar ventilation falls if it is not followed by a compensatory increment of the volume per minute, independently of an increase in the physiologic dead space, due to the anatomic or alveolar component (10). This reduction of the alveolar ventilation causes changes in the "ideal" alveolar tension, similar to the changes produced by a decrease of the respiratory volume per minute.

The alveolar Pa_{CO_2} increases, whereas the Pa_{O_2} decreases, keeping a constant ratio, exclusively influenced by the inspiratory air composition and, slightly, by the respiratory rate (11). The stable hypercapnia of patients affected by chronic asthma is not due to an inadequate response of the neuromuscular drive to the hypercapnia stimulus, but does represent an epiphenomenon of the uncommon respiratory pattern of this group of patients, who breathe with a short T_i , a reduced V_t , and a correlated increase of the V_o/V_t ratio.

For the reasons described above, the exchange function of chronic asthmatic patients could be more or less compromised, developing various aspects of the disease (healthy subjects to chronic pulmonary insufficiency). These aspects are also related to the changed V/Q ratio, to the altered transmembrane gradient of the gas, and to the defect of the alveolocapillary diffusion (DLCO).

The valuation of the DLCO is important because it can be used in these cases for the different diagnosis of asthma and chronic obstructive pulmonary disease (COPD): the diffusion is usually normal in the asthmatic group.

The altered gas-exchange function is responsible for the hemodynamic changes of the pulmonary vasculature, causing mild-to-moderate pulmonary hypertension. However, the pulmonary pressure could increase during hypoxemia, hypercapnia, and mild exercise, a common situation in asthmatic patients, worsening the pulmonary pressure (12).

Conclusions

Our understanding of the pathophysiology of asthma has greatly advanced in the last decade, and the mechanisms of airway inflammation have also been reviewed. Despite these advances, many important questions still remain unanswered. With acute flares of asthma, marked decreases in flow rates, together with hyperinflation of the lungs, are observed in tests of lung mechanics. Hypoxemia is an additional common finding in subjects with wheezing, hypercapnia developing in the most severe circumstances. Frequently, even with the resolution of the clinical signs and symptoms of the airway obstruction, tests of lung function still show impairment and may no longer become normal. In this group of patients, the major risk factor for severe episodes of airway obstruction appears to be the loss of elastic recoil.

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