Topical Review

Hysteresis of airways and lung parenchyma

V. BRUSAICO* AND R. PELLEGRINO

Cattedra di Fisiopatologia Respiratoria, Dipartimento di Scienze Motorie, Università di Genova, 16132 Genova; and Servizio di Fisiopatologia Respiratoria, Ospedale A. Carle, 12100 Cuneo, Italy

Introduction

Like elastic materials, mammalian lungs may change shape according to the force applied to their surface. When the force is released, the pressure stored in the elastic components brings the lungs back to their original status. Unlike elastic materials however, the pressure-volume (PV) relationship of the lung is nonlinear, in that greater pressure is necessary to distend the lungs at high volumes than at low volumes. In addition, more pressure is necessary to increase than to decrease lung volume. This latter characteristic embodies the failure of the system to maintain the energy stored during the cycle. This means that any time the lung expands and then recovers to the previous volume, some energy is dissipated in its internal structures. The area inscribed in the PV loop is called hysteresis and it is due to the viscoelastic and plastoelastic components of the lung (1-3).

Mechanical Models

The viscoelastic behaviour of the lung can be simply modelled by an elastic spring and a dashpot arranged in parallel (Fig. 1, Voigt body). If the body is stretched out, part of the energy is stored in the spring and part is lost in the dashpot. If the rate of stretching increases, further energy is dissipated in the dashpot. Therefore, the width of the PV loop becomes larger when the frequency of cycling is increased. Hildebrandt (2) and Stamenovic et al. (4) estimated that about 67-75% of lung hysteresis is explained by viscoelasticity. Energy is also dissipated when the amplitude of stress is increased, suggesting that the viscous component does not account entirely for the mechanical responses of the lung to stress.

The plastoelastic behaviour of the lung can be simply modelled as an elastic spring and a dry friction element arranged in parallel (Fig. 1, Prandtl body). An external force causes a step-like expansion of the body when it exceeds the frictional forces. After removing the external force, the energy stored in the springs is equal to the frictional forces, and the body cannot reach its original position (plastic deformation). Such an irreversible process is dependent on the magnitude and not the rate of deformation. Evidence for this mechanism occurring in the respiratory system has been extensively reported (1,2,5).

Combining these mechanisms, Stamenovic et al. (4) demonstrated a good fit between the observed and the predicted oscillatory responses at low frequencies in excised cat lungs and human chest wall in vivo. This suggests the existence in the respiratory system of visco-plastoelastic elements that contribute to the dynamic hysteretic response to stress.

In paralysed open-chest dogs, Robatto et al. (6) demonstrated that dynamic tissue hysteresis (which is due to both viscoelastic and elastic components) during tidal breathing is much greater than quasi-static hysteresis (mainly due to the plastic deformation of lung tissue). Similar results have been confirmed in vivo in dog lungs by Shardonofsky et al. (7). These

*Author to whom correspondence should be addressed at: Dipartimento di Scienze Motorie, Facoltà di Medicina e Chirurgia, Viale Benedetto XV, 16132 Genova, Italy.
data suggest that over the range of tidal breathing, the energy dissipation is mostly due to the viscoelastic properties of the lung. On the other hand, at higher volume ventilation, the static PV area increases relatively more than the dynamic one, suggesting that the plastic components of the lung operate at high lung volumes.

Sites and Mechanisms of Hysteresis

Since the early studies of Von Neergaard (8), the lung parenchyma has been deemed to be the most important contributor to hysteresis. By measuring the PV area in isolated lungs, Von Neergaard (8) demonstrated that the width of the PV area decreases after filling the lungs with saline instead of air, in addition to the absolute distending pressures at any volume. This experiment suggested that the origin of hysteresis could reside in the air–liquid interface of the alveolar spaces. Nowadays, there is a body of evidence that lung parenchyma is a source of energy dissipation during stress. This has been recently confirmed by using the alveolar capsule technique (9) that allows the tissue hysteresis to be directly measured in animals in vivo and in vitro during quasi-static and dynamic conditions. However, lung tissue is not the sole contributor of hysteresis.

By measuring the PV curves of isolated airways, Martin and Proctor (10) demonstrated more than three decades ago that airways also exhibit a hysteretic behaviour. Apparently, hysteresis is greater in the small airways than in the larger ones or the trachea. In addition, the bronchial PV area is less during quasi-static than dynamic conditions. Such findings have been confirmed subsequently by other investigators in isolated airway segments (11,12).

What are the anatomical structures of the lung where energy is dissipated during stress? In an anelastic expandable body the only way to dissipate energy during cycling (i.e. to increase the PV area) is to increase the frictional force (--- ---), whereas in (b) it can also be increased as a consequence of an increase in elastance (---) (dP/dV).

CONTRACTILE TISSUES

The elastic force generated by the contractile tissues is related to the number of cross-bridges between actin and myosin. However, during cyclic stretching, some cross-bridges may rupture engendering plastic deformation and thus irreversible loss of energy. As the major part of contractile tissues of the lung is distributed in the airways, and the vagal activity keeps them constantly, slightly contracted (13), it is reasonable to assume that most of the airway hysteresis relies on this mechanism (12). However, as contractile elements also reside in the entrance rings of the alveolar ducts and probably in the interstitium (14), they also account, in part, directly or indirectly for the lung tissue hysteresis.

SURFACE FILM

During inflation, the film of active molecules becomes tiny and the molecules are absorbed to the surface. This movement is associated with energy store. However, during deflation, the film may buckle as some molecules cannot gain their initial position, thus leading to plastic deformation of the film and loss of energy.

CONNECTIVE TISSUE

Even if the single connective fibres have no virtual hysteresis, their network disposition makes the hysteresis increase as plastic deformation occurs during stretching.

ALVEOLAR RECRUITMENT AND DERECRUITMENT

As the alveoli and small airways have critical distending pressures greater than closing pressures, energy is lost in the process of recruitment and derecruitment of alveolar units (15).
Fig. 3 Plots of tracheal pressure (Ptr) and alveolar capsule pressure (Palv) in an isolated canine lung at two breathing frequencies and fixed tidal volume (c. 245 ml). Note that in isolated lungs, Ptr equals transpulmonary pressure. At low frequency [7 min$^{-1}$, (a)], parenchymal hysteresis (■) accounts for most of the total hysteresis, thus the contribution of tissue resistance ($R_{TI}$) to lung resistance ($R_{L}$) is large. At high frequencies [46 min$^{-1}$, (b)] dynamic hysteresis (□) increases greatly, whereas parenchymal hysteresis changes little, thus the contribution of $R_{TI}$ to $R_{L}$ is small.

Altogether, these findings demonstrate that both airways and lung parenchyma are imperfect elastic tissues as they dissipate energy during volume changes. On the other hand, one may imagine that further energy would be lost if they were poorly coupled or not coupled at all. According to Mead et al. (16), the matching occurs via the interdependence forces that allow the airways to synchronously follow the movements of the lung. If the magnitude of airway and parenchymal hystereses is the same, and the interdependence forces promptly transmit the mechanical stimulus to the external airway wall, then no more energy is dissipated during the whole cycling. On the other hand, if one hysteresis prevails over the other one, or if the mechanical inflating stimulus is poorly transmitted to the airways, then further pressure is required to drive the same flow through the airways to the alveoli and back to the mouth.

**Hysteresis and Pulmonary Flow Resistance**

Pulmonary flow resistance ($R_{L}$) is generally calculated as the ratio of transpulmonary pressure minus elastic pressure to flow, over the tidal volume range. Therefore, the greater the dynamic hysteretic loop, the greater the $R_{L}$. Because of lung pressure-volume hysteresis, the total dynamic hysteretic loop is determined by the sum of pressure differences across the airways and lung tissue. As a consequence, $R_{L}$ is the sum of tissue ($R_{TI}$) and airway ($R_{AW}$) resistances. Partitioning of $R_{L}$ into its components, $R_{TI}$ and $R_{AW}$, can be obtained by relating flow to changes of transpulmonary and alveolar pressures (Fig. 3).

The contribution of $R_{TI}$ to $R_{L}$ is highly-dependent on lung volume and breathing frequency. $R_{TI}$ increases with lung volume because parenchymal hysteresis is larger at high lung volumes (2,6,7). Conversely, $R_{TI}$ decreases at high breathing frequencies (17,18) because parenchymal hysteresis does not increase proportionally with flow (Fig. 3).

**Clinical Implications**

During bronchoconstriction, lung tissue or airway hysteresis, or both increase (3,11,12,19–21). Thus, $R_{L}$ increases and flow decreases. However, both hystereses tend to decrease after a deep inhalation (DI) (3,19–21), which implies that both $R_{TI}$ and $R_{AW}$ decrease after DI. Assuming that both parenchymal and airway hystereses respond to the inflating stimulus similarly, and that elastic recoil is unaffected by DI (which is not completely true), then the new conditions depend on the relative magnitude of each hysteresis. According to the theoretical analysis of Froeb and Mead (22), the airway calibre after DI is larger if bronchial hysteresis exceeds parenchymal hysteresis than in the opposite case (this mechanism is depicted in Fig. 4). However, two other factors should be taken into account when flows or resistance are considered, before and after DI. First, DI
generally causes a transient but consistent decrease of elastic recoil (23), thus blunting the DI-induced increase of flows. Second, a peripheral bronchoconstriction (to a greater extent than a central bronchoconstriction) may reduce the forces of interdependence between lung parenchyma and airways. Therefore, the dilator response of DI may be further blunted when parenchymal hysteresis prevails over bronchial hysteresis.

On this theoretical scenario, one could infer the magnitude and the relationship between airway and parenchymal hystereses. This can be done by analysing the effects of DI on airflow and resistance. In control conditions, DI generally causes a small increase of flow or decrease of resistance in healthy individuals (23-26). This is consistent with there being a slightly greater bronchial than parenchymal hysteresis in such conditions. In asymptomatic asthmatics the dilator effect may be similar or slightly greater than in normal subjects, due to an increased bronchomotor tone (23,24,27).

During methacholine (MCh)-induced bronchoconstriction, DI systematically increases expiratory flow and decreases $R_t$. However, this response is markedly blunted in asthmatics compared to normal subjects (24,28). In addition, the dilator effect of DI tends to decrease in asthmatics when the decrement of FEV$_1$ exceeds about 30% of control. The quasi-static PV area always remains constant in normal subjects after inhaling MCh, but almost doubles in asthmatics (24,26,27). According to the analysis of relative hysteresis (22), these findings can be interpreted to suggest that bronchoconstriction is probably located in the more central airways in healthy humans, thus increasing airway hysteresis, but also in the peripheral lung in asthmatics, thus increasing both airway and tissue hystereses.

Bronchospasm, induced by chemical agents with different effects on airways and lung parenchyma, is associated with different effects of DI. We have recently shown that inhaling histamine (supposed to constrict the peripheral airways), after a plateau response to MCh (supposed to constrict preferentially the central airways), decreases the forced expiratory flow after, but not before, DI. This was associated with a significant increase of the quasi-static PV area after histamine but not after MCh (26). Altogether these findings suggest that if the constriction is limited in the central airways, then the bronchial hysteresis increases and DI partially restores the airway calibre. However, when the constriction is extended to the peripheral structures of the lung, the increase of bronchial hysteresis is balanced by the increase of parenchymal hysteresis.

The early-phase bronchospastic response to allergens in asthmatics is also reversed by a DI, but not to the extent as with MCh. However, during the late-phase response, the dilator response to a DI further decreases (29), suggesting that peripheral structures of the lung may be involved with a consequent increase of parenchymal hysteresis. Alternatively, bronchial hysteresis may decrease as a result of a progressive stiffening of airway walls.

Spontaneous or chronic bronchospasm is generally associated with a reduction of forced expiratory flow after a DI. This generally occurs in both asthmatics (30,31) and subjects with chronic bronchitis (23). The magnitude of the bronchoconstrictor effect of DI is proportional to the severity of obstruction (30). These findings seem to be consistent with a prevalent peripheral airway obstruction, and a consequent increase of parenchymal hysteresis and/or reduction of the decrease in bronchial hysteresis.

Beta-agonists reduce airway hysteresis as they relax bronchial smooth muscle (12). However, at high doses they also may reduce the quasi-static PV area. Wang et al. (32) demonstrated that low doses of inhaled albuterol increased partial, more than maximal, forced expiratory flow both in normal subjects and asymptomatic asthmatics. However, at higher doses, PV area was reduced and maximal flow increased more than partial flow. These findings are consistent with albuterol inducing an initial decrease of the airway to parenchymal hysteresis ratio, due to the relaxation of bronchial smooth muscle, followed
by an increase of this ratio when high doses of albuterol also reduces the parenchymal hysteresis.

Conclusion

Constrictor reactions occurring in the lungs may target either airways or lung parenchyma, thus changing their relative hystereses. This may alter the volume-dependent effects of the mechanical interdependence of the airway calibre. Even though it is not possible to assess the separate changes of airway resistance and parenchymal hysteresis in clinical settings, the effect of DI on airflow and resistance appears to provide information regarding the site of underlying events. In general, a remarkable bronchodilator response to a DI is thought to be associated with constriction of the large airways. On the other hand, a blunted or paradoxical response to a DI is consistent with either an involvement of the peripheral airway and parenchyma, or a stiffening of the large airways.

References
