Monaldi Arch Chest Dis
2004; 61: 4, 222-225

The mechanics of the lung parenchyma and airway responsiveness to metacholine

F.G. Salerno[1], O. Resta[2], M.P. Foschino-Barbaro[3], A. Spanevello[1]

ABSTRACT: ***The mechanics of the lung parenchyma and airway responsiveness to metacholine. F.G. Salerno, O. Resta, M.P. Foschino-Barbaro, A. Spanevello.***

The lung parenchyma is anatomically and mechanically connected to the intraparenchymal airways. Due to forces of interdependence the lung parenchyma represents a mechanical load that opposes bronchial narrowing during airway smooth muscle activation. The mechanical load caused by the parenchyma is a function of the number of the alveolar attachments to the airways, and of the mechanical properties of the parenchyma. The extracellular matrix is a major component of the lung parenchyma responsible of most of its mechanical properties. The excessive airway narrowing observed in the asthmatic population may be the consequence of the altered mechanical properties of the extracellular matrix reducing the mechanical load that opposes airway smooth muscle contraction. ***Monaldi Arch Chest Dis 2004; 61: 4, 222-225.***

Keywords: Interdependence, extracellular matrix, asthma, lung mechanics.

[1] Divisione di Pneumologia, Fondazione Salvatore Maugeri, Istituto Scientifico di Cassano delle Murge,
[2] Istituto di Fisiopatologia Respiratoria, Dipartimento di Metodologia Clinica e Tecnologie Medico-Chirurgiche, Università di Bari,
[3] Istituto di Malattie Respiratorie, Università di Foggia; Italy.

Correspondence: Dr. Francesco G. Salerno; Divisione di Pneumologia, Fondazione Salvatore Maugeri; Via per Mercadante Km 2, 70020 Cassano Murge, Bari, Italy; e-mail: fsalerno@fsm.it

Excessive airway narrowing is the crucial abnormality in bronchial asthma and in chronic obstructive pulmonary disease. The mechanisms underlying this abnormality are still poorly understood. Under physiological conditions, the extent to which airways can narrow is dependent on the force generated by the airway smooth muscle, the load it works against, and the geometry of the airway wall. The load the smooth muscle within the intrapulmonary airways must overcome in order to shorten is provided by the mechanical deformation of the bronchial wall itself, and by the tethering of the surrounding lung parenchyma. Indeed, the lung parenchyma and the intraparenchymal airways are mechanically interdependent and under normal conditions, the airway-parenchyma attachments pull the intraparenchymal airways contributing to the maintenance of their patency [1]. The tethering effect of the lung parenchyma on the airways is dependent on lung volume, the mechanical properties of the parenchyma and the number and quality of the alveolar attachments to the airways. An alteration of any of these factors may affect airway caliber and airway reactivity [2]. In addition, the transmission of the lung parenchyma tethering on the airway smooth muscle is a function of the structural composition of the interposed airway wall, and may be reduced as a consequence of the remodeling of the airway wall characteristic of different pulmonary diseases [3, 4].

Lung Volume

A decrease in lung volume causes bronchoconstriction and increased airway responsiveness to methacholine. Nagase *et al* [5] have shown, in open-chest and mechanically ventilated rats, that when lung volume is manipulated by modifying transpulmonary pressure (through a modification of end expiratory pressure) lung resistance varies accordingly. Ding *et al* [6] have shown, on normal humans challenged with an aerosol of methacholine, that the degree of bronchial responsiveness is enhanced when end expiratory volume is decreased under the physiological level. Macklem [7] in his theoretical analysis on the effect of smooth muscle load on airway narrowing predicts the importance of the lung distending pressure on the load the airway smooth muscle must overcome in order to shorten. In his analysis he predicts also that peribronchial inflammation, uncoupling the parenchyma from the airways may reduce the effect of lung volume on airway caliber. The decrease in lung volume and transpulmonary pressure affect airway caliber because it decreases the lung recoil and the subsequent pulling effect on the intraparenchymal airways.

Alveolar attachments

The number and quality of the alveolar attachments to the airways may affect airway responsiveness to smooth muscle agonists. If the alveolar attachments are altered, the tethering of the lung parenchyma on the airways may be reduced. Centrolobular lung emphysema, a disease characterised by the destruction of the lung parenchyma especially around the airways, is indeed associated to increased airway reactivity [8]. The effect of the reduced mechanical interdependence between the airways and the parenchyma may be important under static conditions, or even more under dynamic conditions by reducing the effect of tidal stretch and deep inspirations on the airways.

Lung parenchyma mechanical properties

It has been proposed that, during induced bronchoconstriction, the lung parenchyma mechanical properties are important in determining the amount of the mechanical load exerted on the airway smooth muscle and therefore airway calibre [2]. It has also been suggested that the different mechanical properties of the lung parenchyma observed between species may, at least in part, cause differences in the degree of airway responsiveness to methacholine [9]. Guinea pigs, similar to asthmatics, show excessive bronchoconstriction when challenged with a smooth muscle agonist without reaching a clear plateau response [10]. Not surprisingly, *in vivo*, the constricted lungs of guinea pigs bronchodilate less when transpulmonary pressure is raised compared to the rat, a "non hyperresponsive" species of similar size [5]. When the mechanical properties of the lung parenchyma are compared in the two species *in vitro*, the guinea pig show a smaller dependence of lung stiffness on applied stress [9] (figure 1). In so far as lung stiffness represents the load against which airways must constrict, this data suggests the importance of the parenchyma in the observed different level of airway responsiveness between the two species and in the different effect of transpulmonary pressure on lung resistance. The intrinsic mechanical properties of the lung parenchyma affect airway caliber through the tethering effect of the lung parenchyma on the airways.

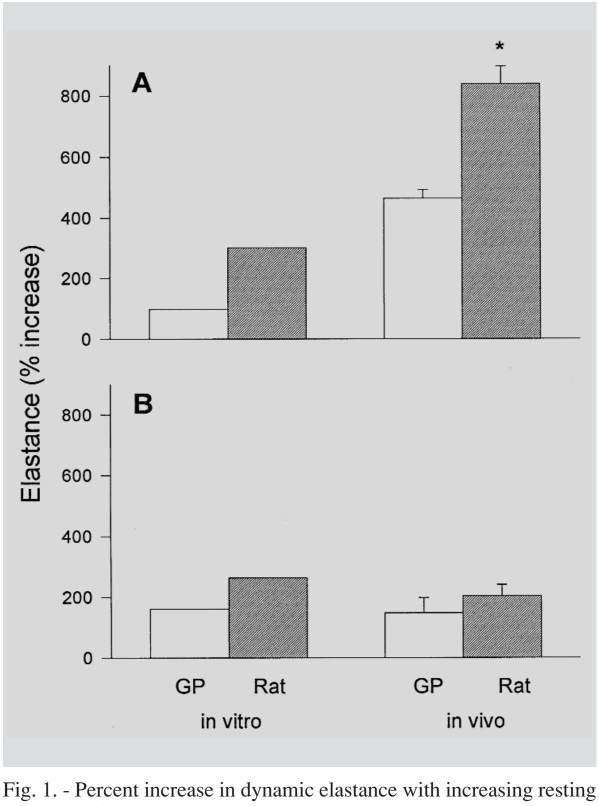

Fig. 1. - Percent increase in dynamic elastance with increasing resting tension (0.5 to 1.0 g) (in vitro) and transpulmonary pressure (3 to 11 cm H_2O) (in vivo) in rats and guinea pigs (GP) under baseline conditions (A) and after induced constriction (B). *$p < 0.05$ versus guinea pig. The percent increase in elastance in rat versus guinea pig parenchymal strips was different under both baseline and constricted conditions (from reference 9 with permission).

An additional potential source of mechanical load during bronchoconstriction is the stretch and distortion of the lung parenchyma in close proximity to the airways when airway diameter decreases [11]. The additional elastic load because of this "local" tissue distortion is function of the capability of the lung parenchyma to oppose isovolumetric changes in shape [12].

There are a number of determinants in the intrinsic mechanical properties of the lung parenchyma. The lung parenchyma includes small airways, small vessels, non smooth muscle contractile elements and the alveolar walls. All these components contribute to the mechanical properties of the lung parenchyma. The extracellular matrix, the major component of the lung parenchymal tissue in both the fiber and interfiber compartment, is likely responsible for the majority of the lung mechanical properties [13, 14]. An altered extracellular matrix may alter the mechanical behaviour of the parenchyma, affect the load the lung parenchyma exerts on the airways and therefore cause hyperrsponsiveness. *In vitro,* on isolated lung parenchyma, elastase and collagenase (enzymes that degrade proteins among which elastin and collagen, major constituent of the extracellular matrix) modify the elastic and hysteretic properties of the lung parenchyma [15, 16]. The same pattern has been observed, *in vivo*, on animal models, where lungs treated with elastase (endotracheal instillation) display altered mechanical properties [17] and increased airway responsiveness to methacholine [18]. Other reports demonstrate that the interfiber compartment is an important determinant of the mechanical behaviour of the lung. Proteoglycans, a major component of extracellular matrix, are increased in asthmatic airways, and show a positive correlation with airway responsiveness suggesting the implication of the extracellular matrix in airway wall remodeling and asthma [19]. Regarding the parenchyma, conditions characterized by a change in proteoglycans composition in the parenchyma, as it happens in the bleomycin induced lung injury model where in the early phase only an increase in proteoglycans is detectable, are associated with alterations in lung parenchymal mechanics [20]. Recently, Al-Jamal *et al* [21] have shown that specific degradative enzymes of matrix glycosaminoglycans, in rats, affect the mechanical behaviour of lung parenchyma suggesting that the ground substance is responsible of at least part of the viscoelastic behaviour of the lung tissue. These observations, taken together, pinpoint the importance of the extracellular matrix, in both the fiber and the interfiber compartment, in determining the mechanical behavior of the lung tissue, the subsequent load on the airway smooth muscle and, possibly, the degree of induced bronchoconstriction. There is no clear evidence, however, that the extracellular matrix of asthmatics, at the level of parenchyma, is qualitatively and quantitatively different from that of normal subjects.

Dynamic of breathing

The lungs, as a result of breathing, normally function under dynamic conditions. Under dynamic conditions, the load the parenchyma exerts on the intrapulmonary airways depends not only on pure elastic properties but also on viscous properties (tissue resistance). Lung tissue resistance increases during the activation of the contractile machinery induced by airway smooth muscle agonists. Several studies, both *in vivo* and *in vitro*, have confirmed the capability of the lung parenchyma to contract, and change its elastic and hysteretic properties in response to airway smooth muscle agonists [22-24]. Kapanci *et al* [25] have described in rats, through an immunofluorescence study of the lung parenchyma, the presence of many interstitial cells binding antiactin antibodies defined as "contractile interstitial cells". These cells, likely play a role in the local regulation of the ventilation/perfusion ratio and, when activated, may modify the lung parenchymal mechanics being responsible of the observed increased in tissue resistance. The parenchymal contractile apparatus surely contributes to the mechanical properties of the lung parenchyma in the constricted state, but it does not seem to affect substantially the mechanics of the parenchyma in the non-constricted state. Indeed, isolated preparation of lung parenchyma show similar mechanical behaviour regardless of the viability of the cellular components, suggesting that the major determinant of the mechanical behaviour of the lung parenchyma, in the non-constricted state, is extracellular [26]. The increase in lung tissue elastance and resistance during lung constriction may be accounted for by different mechanisms. It may come from within the contractile apparatus (isolated airway smooth muscle increases its viscous behavior substantially when activated) or it may be due to the stretch and distortion of the adjacent fiber network [11]. If for some reason the effect of lung constriction on tissue mechanics is altered, airway hyperresponsiveness may develop.

The lung parenchyma may be involved in the broncodilator effect of deep inspirations. Deep inspirations cause temporary dilation of bronchoconstricted airways in normal subjects but not in asthmatics [27, 28]. The differential effect of deep inspirations in asthmatic versus normal subjects may be involved in the pathogenesis of asthma. Deep inspirations may have a differential effect on airway smooth muscle contractility [29] because of an airway smooth muscle altered response to stretch. An alternative hypothesis suggests the implication of the airway and lung parenchyma mechanics. Indeed, large mechanical stretches, reproducing the effect of deep inspirations *in vivo*, profoundly affect lung parenchymal mechanics *in vitro* [30]. Airways and lung parenchyma, display hysteretic behaviour [31-34], a property by which, at any absolute lung volume, the elastic recoil is higher in inspiration than in expiration. If airway hysteresis exceeds lung hysteresis, a deep breath would cause the lung recoil to decrease less then that of the airways with a final transient bronchodilatory effect. Therefore, if asthmatic lungs have altered hysteretic properties, deep inspirations could result in less bronchodilation, or even bronchoconstriction [35, 36]. To date, however, there is no conclusive data on differences in the viscoelastic properties of the lung parenchyma in asthmatics vs. normals.

In conclusion, the lung parenchyma mechanical properties may be important in determining the amount of mechanical load that opposes airway narrowing during airway smooth muscle activation. In hyperresponsiveness subjects the mechanical properties of the lung parenchyma may be altered in such a way that excessive airway narrowing results. The extracellular matrix in both the fiber and interfiber compartment is a major candidate of these alterations. Further studies are necessary to better define the role of the lung parenchyma in the pathogenesis of airway hyperresponsiveness and asthma in humans.

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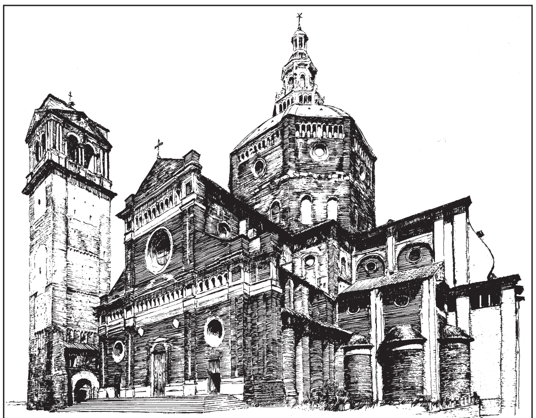

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