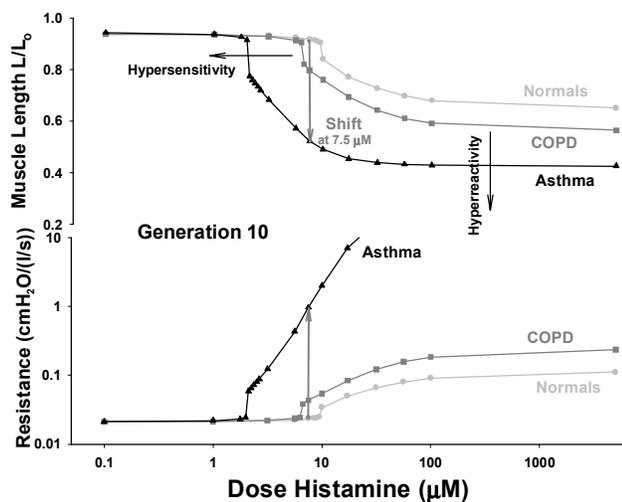


## Molecular Origins of Critical Phenomena Associated With Abrupt Airway Closure in Normals and Asthmatics

Mijailovich, Srbojub M.

Harvard School of Public Health, Boston, MA, USA

Asthmatics subjects lack the bronchodilating response and bronchoprotective effects of deep inspirations (DI). However, the underlying mechanisms are not causally linked at the contractile protein or tissue levels. We developed a theoretical model of airway narrowing to quantitatively assess how and in what degree the observed alternations in airway smooth muscle (ASM) cross-bridge kinetics and airway wall remodeling in asthma and chronic obstructive pulmonary disease (COPD) can account for the above clinical observations. In the model, the ASM length is determined by the balance between the ASM contractile force and the airway wall reaction force (AWRF). The ASM contractile force is determined based on the theory of perturbed equilibria of myosin binding (HHM theory; Mijailovich et al., *Biophys. J.* 79: 2667-81, 2000). The airway wall reaction force (AWRF) was set by the elasticity and geometry of the airway wall, tethering of the airway to the lung parenchyma, and the state of lung inflation (Lambert et al., *J. Appl. Physiol.* 74(6): 2771-2781, 1993). Thus, the smooth muscle experiences a dynamic load by a virtual AWRF that corresponds to the transpulmonary pressure variations during normal breathing. Once the ASM length is determined, the airway luminal area is calculated from the geometry of the airway wall and the calculation takes into account the thickness of submucosal layer. From the luminal area the airway resistance is calculated for each generation of Weibel's symmetrical bronchial tree. In the calculations we included the effect of DI superimposed over quiet tidal breathing for normal, COPD, and asthmatic subjects. The theoretical predictions of the model revealed a **critical phenomenon**: above particular level of ASM activation, the ASM drastically shortens and becomes very stiff. The Figure shows the change of smooth muscle length and airway resistance for a human airway (generation 10) as a function of histamine dose, i.e., ASM activation level. At low histamine doses, the ASM of normal subjects equilibrates at long muscle lengths indicating that the normal airways are almost completely open and compliant. However, at histamine doses above a critical value ( $\sim 11 \mu\text{M}$ ), the ASM drastically shortens causing the airway to severely constrict. In both COPD and asthma, the critical histamine dose is lower than in normals, and the degree of abrupt ASM shortening is greater. Thus, airways in COPD and asthmatic patients become severely constricted at lower levels of ASM activation than in the normal subjects. In this case, DI may not be sufficient to open constricted asthmatic airways. For example, at dose of  $7.5 \mu\text{M}$  histamine normal airways are completely open while at the same dose asthmatic airways are severely constricted. The airway resistance in an



asthmatic subject is more than 50 times larger than in a normal subject, and deep inspirations indeed cannot enhance bronchodilation. We also demonstrated that both hyperreactivity and hypersensitivity observed in asthmatic and COPD airways exposed to contractile agent or allergin can be explained by a single mechanism – perturbed equilibria of myosin binding. The fragile dynamic equilibrium that defines the critical activation level depends on many factors – at the contractile protein level: increased cross-bridge cycling rates, myosin isoform, thin filament regulation, cytoskeletal remodeling, and, – at the airway tissue level: airway and lung tissue remodeling.

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