Varying the duration of aerosol delivery: a means to probe the kinetics of methacholine transport to the airway smooth muscle

Understanding and treating lung disease involves the mechanics as well as the physiology of the respiratory system. One such disease, whose mechanics is poorly understood is asthma. Asthma patients have a tendency to suffer from bronchoconstriction more than non-asthma patients do; this symptom is known as airway hyperresponsiveness. Methacholine (MCh) dose-response relationships constitute the experimental basis for the diagnosis of airway hyperresponsiveness. Such relationships are determined by measuring the changes in lung function induced by delivery of increasing concentrations of MCh aerosol, assuming that the dose of MCh delivered into the lung is an accurate reflection of that reaching the airway smooth muscle. This is not necessarily the case; some of the MCh is removed via circulation and degraded by enzymes as it diffuses through the airway wall. In order to better understand the transport kinetics of MCh we assessed the mechanical response of normal BALB/c mouse lung to various durations of MCh aerosol of a fixed concentration. MCh was nebulized into the airways for periods of 20, 40, 60 and 80s during which airway resistance (Raw) was monitored using a forced oscillation technique. Raw increased progressively throughout each period of aerosolization, reaching levels of 29.5%, 83.9%, 145.4%, and 377.4% above baseline by the end of the nebulization periods, respectively. However, following the 20, 40 and 60 s deliveries, Raw continued to increase for 10-30s past the point of cessation of nebulization to reach peak values of 47.9%, 132.8%, 275.4% and 421.0% of baseline. Contrastingly, the peak value of Raw following the 80s MCh delivery occurred at the end of nebulization. This demonstrates that delivering a fixed concentration of MCh for increasing periods of time not only produces a MCh dose-response relationship, but it also reveals the kinetics of MCh transport to the smooth muscle. The overshoot in Raw of the shorter delivery durations shows that MCh accumulated in the airway wall tissue from where it diffused to the smooth muscle with a time-constant in the order of 30s. Pathologic processes that affect the diffusivity of MCh would be expected to affect the magnitude of the subsequent response in Raw. Alterations in the delivery kinetics of MCh may thus have an important influence on the assessment of airways responsiveness.