A multi-scale model to study airway hyper-responsiveness

MH Tawhai[1], GM Donovan[2], K Murphy[1], MA Sanderson[3], JHT Bates[4], A-M Lauzon[5], J Sneyd[2]

[1]Auckland Bioengineering Institute and [2]Dept Mathematics, University of Auckland, Auckland, New Zealand; [3]Dept Physiology, University of Massachusetts; [4]Dept Medicine, and Dept Molecular Physiology & Biophysics, University of Vermont; [5]Dept Medicine, Meakins-Christie Laboratories, McGill University, Montreal, Canada

Asthma is a widespread and surprisingly serious disease, with more than 180,000 attributed annual deaths. Fundamentally it is a disease of airway constriction and obstruction. Recently much attention has focused on so called deep inspirations and strain-induced fluidisation, which are widely thought to produce significant dilation in constricted airways in normal subjects, but not in asthmatic patients; wherein lies the difference is the critical question. In an effort to better understand these complex phenomena, we have constructed a multi-scale mathematical model of the human lung, accounting for important behaviour at spatial scales ranging from intracellular ion concentrations to the mechanics of the entire organ. The model considers four coupled spatial scales: organ, tissue, cell and molecule. At the largest scale, the lung parenchyma is modelled as a 3D continuum, subject to both gravity and the mechanical deformation of breathing. Embedded in this continuum is the conducting airway tree, which bifurcates asymmetrically from the trachea into approximately 30,000 conducting airways per lung. Each airway in the tree is modelled as an embedded cylinder under plane strain assumptions, and contains a layer of airway smooth muscle (ASM) cells. ASM contraction leads to airway constriction. Each ASM cell contains sliding filaments which generate muscle force, and these are in turn stimulated by intracellular Ca^{2+} and agonist levels within the cell. At the molecular scale, applied agonist (such as MCh or ACh) triggers a response in the form of elevated intracellular Ca^{2+}, typically short-period oscillations. Force generated by the ASM is obtained from the cellular level model, a sliding-filament crossbridge model with rate functions depending on both agonist and Ca^{2+} concentrations. Force generated by the muscle then contributes to the pressures acting on the airway. Tethering pressures are obtained from the mechanical deformation of the organ-level parenchymal continuum, and local parenchymal deformation around the airway due to airway constriction. All forces then must be balanced to obtain the correct airway radius, for each airway, at each time step. To compute force balance in the entire lung, we have adopted a random sampling and interpolation approach whereby the organ scale is calculated for the full lung at all times, but only a small but representative fraction of the airways are directly calculated under the full multi-scale model, and those results are then extended to the remaining airways. The model results suggest that deep inspirations during airway constriction do result in potent, transient bronchodilation, in line with expectations for normal subjects. Thus we are currently using the model to explore the possible differences between normal and asthmatic lungs which compromise this response.

Supported by: NHLBI R33-HL87789