A Model of Tracer Transport in Airway Surface Liquid

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Abstract This study is concerned with reconciling theoretical modelling of the fluid flow in the airway surface liquid with experimental visualisation of tracer transport in human airway epithelial cultures. The airways are covered by a dense mat of cilia of length $\sim 6 \mu m$ beating in a watery periciliary liquid (PCL). Above this there is a layer of viscoelastic mucus which traps inhaled pathogens. Cilia propel mucus along the airway towards the trachea and mouth. Theoretical analyses of the beat cycle (Smith et al., 2006b; Fulford and Blake, 1986) predict small transport of PCL compared with mucus, based on the assumption that the epithelium is impermeable to fluid. However, an experimental study (Matsui et al., 1998) indicates nearly equal transport of PCL and mucus. Building on existing understanding of steady advection-diffusion in the ASL (Blake and Gaffney, 2001; Mitran, 2004), numerical simulation of an advection-diffusion model of tracer transport is used to test several proposed flow profiles and to test the importance of oscillatory shearing caused by the beating cilia. A mechanically derived oscillatory flow with very low mean transport of PCL results in relatively little ‘smearing’ of the tracer pulses. Other effects such as mixing between the PCL and mucus, and significant transport in the upper part of the PCL above the cilia tips are tested and result in still closer transport, with separation between the tracer pulses in the two layers being less than 9%. Furthermore, experimental results may be replicated to a very high degree of accuracy if mean transport of PCL is only 50% of mucus transport, significantly less than the mean PCL transport first inferred on the basis of experimental results.

Keywords Mucus · Cilia · Tonicity · Advection · Diffusion · Dispersion

1. Introduction

The airways of the lung are lined with a thin ($\sim 5$–$20 \mu m$) protective layer of liquid which is secreted by the airway epithelium, then propelled towards the trachea and mouth by the action of cilia. The cilia beat in a watery periciliary liquid (PCL),
above which lies a viscoelastic mucous layer consisting of water and glycosylated mucin proteins. There has been considerable doubt regarding the mean axial transport of PCL, since theoretical studies (Smith et al., 2006b; Fulford and Blake, 1986) have predicted that transport is small compared with transport of mucus, whereas experimental studies using tracer particles in cilia cultures (Matsui et al., 1998) appeared to show equal transport (cotransport) of mucus and PCL. This paper is concerned with reconciling theoretical results and experimental observations, and in particular we seek to discover what mean transport profiles may be consistent with the observed tracer transport results. The modelling approach has applications to similar problems, for instance morphogen transport causing symmetry breaking in the embryonic ventral node (see for example Okada et al., 2005).

In this study we briefly describe the characteristics of the muco-ciliary system in the lungs, then discuss the question regarding the normal tonicity of airway surface liquid (ASL) and the related issue of the mean transport of periciliary liquid (PCL). We describe the contradictory conclusions arising from in vitro experiments of Matsui et al. (1998) and the theoretical modelling work of Smith et al. (2006b) and Fulford and Blake (1986). An existing physically-based phenomenological model of the time dependent fluid flow in the ASL (Smith et al., 2006b) based on the assumption that the epithelium is impermeable to fluid is briefly reviewed. Tracer transport and dispersion under this, and other suggested velocity profiles, are modelled as an advection-diffusion process similar to that of Blake and Gaffney (2001). The resulting equations are solved using an alternating direction implicit (ADI) method, together with the QUICK scheme of Leonard (1979) for advective discretisation. Numerical results are interpreted quantitatively, leading to insight into the apparent conflict between experimental results and theoretical modelling.

1.1. Muco-ciliary clearance

The airway epithelium is covered with a dense mat of cilia, of length \( \sim 5–7 \mu m \), radius \( \sim 0.1 \mu m \) and spaced around \( 0.3–0.4 \mu m \) apart (data from Sleigh et al., 1988; Toskala, 1994). The cilia beat in coordinated waves with a frequency of around 6–15 Hz. The ciliary beat is asymmetric, consisting of an ‘effective’ or propulsive stroke, and a ‘recovery stroke’, the effective stroke lasting about a fifth as long as the entire beat (Sanderson and Sleigh, 1981). During the effective stroke the cilium is fully extended so that it penetrates the overlying mucous layer, propelling it along the airway towards the trachea and mouth. During the recovery stroke, the cilium bends slightly so that it does not engage the mucous layer.

Detailed modelling of the fluid dynamics of muco-ciliary flow (Smith et al., 2006b; Fulford and Blake, 1986) predicts that the mean transport of PCL is very small in comparison to transport of mucus. Such studies assume that the epithelium is impermeable to fluid, consistent with the hypotonic ASL hypothesis described below, and indeed due to the converging geometry of the airways, if no fluid is absorbed by the epithelium, the PCL thickness would not be maintained at the depth of \( \sim 5 \mu m \) that is essential for efficient coupling of the cilia and mucus. A typical mean profile reproduced from Smith et al. (2006b) is given in Fig. 6.