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Airway compliance and dynamics explain the apparent discrepancy in length adaptation between intact airways and smooth muscle strips

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ABSTRACT

Length adaptation is a phenomenon observed in airway smooth muscle (ASM) wherein over time there is a shift in the length-tension curve. There is potential for length adaptation to play an important role in airway constriction and airway hyper-responsiveness in asthma. Recent results by Ansell et al., 2015 (JAP 2014 10.1152/japplphysiol.00724.2014) have cast doubt on this role by testing for length adaptation using an intact airway preparation, rather than strips of ASM. Using this technique they found no evidence for length adaptation in intact airways. Here we attempt to resolve this apparent discrepancy by constructing a minimal mathematical model of the intact airway, including ASM which follows the classic length-tension curve and undergoes length adaptation. This allows us to show that (1) no evidence of length adaptation should be expected in large, cartilaginous, intact airways; (2) even in highly compliant peripheral airways, or at more compliant regions of the pressure-volume curve of large airways, the effect of length adaptation would be modest and at best marginally detectable in intact airways; (3) the key parameters which control the appearance of length adaptation in intact airways are airway compliance and the relaxation timescale. The results of this mathematical simulation suggest that length adaptation observed at the level of the isolated ASM may not clearly manifest in the normal intact airway.

1. Introduction

Length adaptation has been studied extensively in airway smooth muscle (ASM) strips, and has been thought to play a potentially important role in airway hyper-responsiveness (AHR) in asthma (Bai and Bates, 2004; Bossé et al., 2008; Wang et al., 2001). The central idea is that ASM has a so-called optimal length at which it can generate maximal force, and altering this length produces an immediate reduction in force production. However, ASM can adapt to the new length (hence the term length adaptation) and the same profile of force generation will then be seen relative to the new adapted length. Length adaptation theoretically predicts that airway narrowing capacity, similar to force, can be maintained under a wide range of mechanical conditions including lung inflation, deflation and bronchoconstriction.

Recently, translation to the intact airway, rather than ASM strips, has revealed the seemingly counterintuitive result that intact airways do not express 'adaptive-like' properties (Ansell et al., 2015). One might have expected that the presence (or absence) of the airway wall would neither enhance nor attenuate ASM length adaptation, and that intact airways would display length adaptation in much the same way as isolated ASM strips (Bossé, 2015). The reason for the disparity between the isolated ASM strip and intact airway wall requires further investigation in order to advance our understanding of how the airway wall responds to physiological and pathophysiological changes in ASM length.

To that end we constructed a minimal mathematical model which couples the behaviour of the airway wall with that of length adaptation in isolated ASM strips, and used this model to understand ways in which ASM length adaptation might be attenuated within the in situ environment. We find that indeed the coupling between the airway wall and ASM layer can explain the apparent failure of length adaptation to alter function in the intact airway, and that there are two key factors: the compliance of the airway wall, and the timescale on which the passive elements of the airway adjust to changes in airway radius. Thus, central airways with

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low compliance are not expected to exhibit any significant length adaptation; and while it is possible that more compliant peripheral airways may be impacted by length adaptation, our estimates suggest that the effects on airway function are likely to be small.

2. Methods

2.1. Model construction

More extensive details of the model, including parameter values and solution techniques, are provided in the Appendix. For our minimal model we are interested in changes in two quantities: the airway radius (R), and the radius (length) at which the ASM is adapted (R_f). We formulate ordinary differential equations which govern the time evolution of each, based on existing models already in the literature.

In order to describe the behaviour of the airway wall, we begin with the model of Thorpe and Bates (1997) which gives the passive pressure-radius characteristics of the airway as

$$\bar{R} = a_0 + (1 - a_0)\left(\frac{P_p}{P_{TLC}}\right)^{\frac{1}{3}} \tag{1}$$

where the parameter a_0 is determined by the compliance of the airway wall, P_{TLC} is a parameter which sets the total lung capacity, P_p is the effective pressure across the airway wall, and we use the symbol $\bar{R}$ for the radius at which static pressures are in balance. We assume that this equation holds at equilibrium (that is, $R = \bar{R}$), and that the approach to equilibrium is given by simple first-order kinetics[1] with time constant σ such that

$$\frac{dR}{dt} = \sigma\left(\bar{R} - R\right). \tag{2}$$

This time constant σ incorporates several phenomena which govern the passive expansion, perhaps most imporantly the passive tension of ASM (e.g. Gunst and Stropp, 1988). The effective pressure across the airway wall, P_p, is calculated in the conventional manner (e.g. Affonce and Lutchen, 2006; Donovan and Kritter, 2015) as

$$P_p = P_{tm} - \kappa\frac{F}{R} \tag{3}$$

where F is the normalized force-length relationship (see below), the parameter κ sets the maximal ASM isometric tension, and P_{tm} is the imposed transmural pressure. Thus Eq. (2) becomes

$$\frac{dR}{dt} = \sigma\left(a_0 + (1 - a_0)\left(P_{tm} - \frac{\kappa F}{R}\right)^{\frac{1}{3}}(P_{TLC})^{-\frac{1}{3}} - R\right). \tag{4}$$

We model the ASM, and its length adaptation, with similar simplicity. We assume a quadratic force-length relationship, about the adapted length R_f, based on existing data on ASM strips (Wang et al., 2001), as

$$F = 1 - \beta\left(R_f - R\right)^2 \tag{5}$$

and that the adapted length adjusts toward the current length with time constant γ so that

$$\frac{dR_f}{dt} = \gamma\left(R - R_f\right). \tag{6}$$

This formulation assumes that the muscle generates optimal force at the adapted length (e.g. initially equilibrated at 5 cmH_2O), and decreases above or below this length. Then in fully explicit form we have the final equations for R and R_f as

$$\frac{dR}{dt} = \sigma\left(a_0 + (1 - a_0)\left(P_{tm} - \kappa\frac{1 - \beta\left(R_f - R\right)^2}{R}\right)^{\frac{1}{3}}(P_{TLC})^{-\frac{1}{3}} - R\right)$$

$$\frac{dR_f}{dt} = \gamma\left(R - R_f\right).$$

Note that the model is a highly simplified representation of ASM behaviour designed only to capture length adaptation, and neglects many complex behaviours of ASM which are important in other contexts, for instance when modelling the transient bronchodilatory effects of deep inspiration (e.g. Bates, 2015). We have modelled both time-dependent processes with first order kinetics for simplicity, and refer to the resulting time constants as the "timescales". It is possible that power law or multi-exponential dynamics might be important—for more detail, please see Section 4. It is also important to note that neither radius nor force are prescribed, but rather the model requires that both radius and force balance and co-evolve according to their mutual dependencies. Pressures are given in cmH_2O, but appear everywhere in the equations normalized to pressure at total lung capacity (P_{TLC}) which we define to be 25 cmH_2O. The variables R, R_f and $\bar{R}$ are given in dimensionless units, normalized to the relaxed radius at P_{TLC}. We also use a linearly compliant airway wall model for comparison; details of this modification to the model are given in the Appendix.

2.2. Simulations

The first goal of this study was to mathematically replicate the protocol of Ansell et al. (2015) where the intact airway, from a baseline P_{tm} of 5 cmH_2O, was 'adapted' to a distending P_{tm} of 25 cmH_2O, and also a deflationary P_{tm} of −5 cmH_2O, for ∼1 h. The model was equilibrated at P_{tm} = +5 cmH_2O before a step change to +25 cmH_2O or −5 cmH_2O was imposed, depending on the protocol. We also are able to consider several configurations not tested experimentally in Ansell et al. (2015) either through design or resource limitations. In particular, we are able to model the simulated protocols in more peripheral (i.e. highly compliant) airways, and also at a range of pressures corresponding to more moderate lung volumes (and hence more compliant parts of the pressure-volume curve). Because of the relative simplicity of the model, the simulation was held under static conditions and no oscillations simulating breathing were included. For the model simulations we treat the airway as either relaxed ($\kappa = 0$) or contracted ($\kappa > 0$) throughout the simulation protocol, rather than imposing periodic stimulation as in the original experiments. We employ this simplification principally because we are interested in the effects of persistent changes in length and the resulting adaptation, rather than effects produced by transient/dynamic changes in ASM length (for which such a simple model is not suited).

2.3. Analysis and outcomes

Numerical solutions were obtained using MATLAB's built in ODE solver ODE45 (Mathworks Inc., Natick MA). The primary output of the model was the increase in airway narrowing produced by an adapting ASM. In figures where model data is overlaid with experimental data, the data are drawn from Fig. 3 in (Ansell et al., 2015) and are presented as mean ± standard error.

3. Results

3.1. Adaption to inflation

Adaptation is expected to produce a time-dependent increase in narrowing following sustained inflation to +25 cmH_2O P_{tm}. We

[1] The implications of assuming first-order kinetics, rather than a more complex form (e.g. multi-exponential, or power law), are discussed later in this section and also in Section 4.