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. (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.

Keywords: Airway smooth muscle, length adaptation, bronchi, hyperresponsiveness

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 et al. 2004, Bosse 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. 2014). 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 (Bosse 2014). 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 strip 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 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.

Methods

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

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

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, 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 with timescale σ such that

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

This timescale 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 2014) 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 the data of (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 timescale γ so that

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

(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. 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 this 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. 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. These points are considered further in the Discussion. 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.

Simulations

The first goal of this study was to mathematically replicate the protocol of Ansell et al. (2014) 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 hour. 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. 2014), 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 persistant 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). For more information, please see the discussion.

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 overlayed with experimental data, the data are drawn from Fig. 3 in (Ansell et al. 2014) and are presented as mean ± standard error.

Results

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 began with the simplest question: mimicking the protocol of Ansell *et al.* (2014), does the model exhibit significant evidence of length adaptation in intact airways? To this end we match the airway wall compliance and degree of ASM activation to the experimental data as closely as possible, fit the timescales to the experimental data (see Appendix A), and simulate the change from +5 cmH_2O P_{tm} to +25 cmH_2O P_{tm}; the data are shown in Fig. 1. Two sets of simulations are shown; column A (panels A1-A3) are results with the linearly compliant airway wall, and column B contains equivalent figures for the nonlinear airway wall model. Row 1 (panels A1 and B1) show the model simulations as time series with data from Ansell et al. 2014 for comparison; row 2 (panels A2 and B2) present the same data in terms of relative airway narrowing. In row 3 (panels A3 and B3) the same data are shown on radius-force axes, and overlaid on the governing length-tension curve at the starting length. Annotations are provided in A3 to illustrate these figures -- this method of displaying the data illustrates the role of the classic length-tension curve in organising the behavior of the model airway. Without length adaptation, the original length-tension curve is followed exactly; by contrast, adaptation allows recovery ‘above’ this curve, eventually returning to reference force.

The two sets of data (columns A and B) illustrate the role of airway wall nonlinearity. Though the nonlinearly compliant airway wall model is a widely used representation, the airways used by Ansell *et al.* appear to be closer to linearly compliant over this pressure range (demonstrated by the inability of the nonliner airway wall model to accurately fit the data). Thus in order to match the relative degrees of contraction and expansion more closely, we also include the linearly compliant airway wall model (for which the fit is very good). However, in neither case is there any significant time-dependent increase in the contractile response, in the sense that there is no significant increase in narrowing of the airway after the expansion of the airway in response to the change in P_{tm} – even though the ASM does adapt to the new length and eventually re-exerts maximal isometric force. Thus it is clear that no significant increase in narrowing is evident in the intact system, at least for a relatively central airway, even though the ASM is following the classic length-tension curve and undergoing length adaptation. This is not to say that length adaptation has no effect at all, but rather that it serves to arrest the decline in narrowing, rather than driving an increase in narrowing.

The model output is consistent with the results of Ansell et al. 2014 where an increase in P_{tm} to 25 cmH_2O produced a decrease in airway narrowing capacity, with no recovery that may reflect adaptation. The model also allows a breakdown in the relative contributions to the reduction in airway narrowing capacity seen upon pressure increase,

with roles for both airway wall compliance and the reduction in ASM tension. In the case of the linearly compliant airway wall, the entire reduction in narrowing is due to reduced ASM tension. With the non-linearly compliant airway wall, the reduction in narrowing is broken down as roughly one third due to the reduction in ASM tension, and the remaining part is attributable to the decreased airway wall compliance.

2. Adaptation to deflation

We also consider the case of deflation to -5 cmH_2O, as in Ansell et al. 2014; the model is unchanged, except for the driving pressure change. The results are given in Fig. 2, both the model results and comparison with the experimental data. In the left panel of Fig. 2 we give the changes in airway calibre over time. Here adaptation does generate fractionally more narrowing than the non-adapting case, though the change is much smaller than the experimental error. Similarly we explicitly quantify the narrowing in the right panel of Fig. 2. As with the inflation case discussed at length previously, adaptation does not lead to an increase in narrowing, but rather halts the decline in narrowing.

3. Factors regulating length adpation and sensitivity analysis

We explored the reasons for the apparent failure of length adaptation to produce an increase in narrowing in the intact system. Results are presented for the scenario of inflation to +25 cmH_2O P_{tm} however findings are broadly similar when modelled for a

deflationary P_{tm} of -5 cmH_2O. We find that there are two key parameters which govern the appearance of length adaptation in the intact airway: airway wall compliance and the timescale on which the airway adapts to changes in radius (σ). To illustrate, we consider changes to these parameters (high and low airway wall compliance, fast and slow airway adaptation timescale) and their combinations. We plot the results relative to the length-tension curve in Fig. 3 (recall that Fig. 1 panel A1 contains representative annotations for this type of figure). With the slow passive expansion timescale (small σ), the airway expands slowly in response to the pressure increase, and so the ASM is already adapting to longer lengths as the airway expands. Thus the maximal decrease in force seen is relatively modest. With this slow adaptation timescale, there is no increase in narrowing for either high or low airway wall compliance. On the other hand, when the passive expansion is fast (large σ), the airway dilates much faster than the ASM adapts, and so there is a significant reduction in force following the length-tension curve. Only once the expansion is complete does the ASM adapt significantly to the new length, with the resulting increase in force driving an increase in narrowing. However, even in this case the increases are modest: with the fast adaptation timescale there is an 0.18% increase in narrowing for the low airway wall compliance and a 1.1% increase in narrowing for the high compliance airway. Note that these are extreme cases, used to illustrate the role of each parameter. Thus it is clear that for length adaptation to be evident as an increase in narrowing in the intact airway, a combination of high airway wall compliance and fast

airway adaptation timescale is required, and even then the increase in narrowing is modest. This exploration also serves as a sensitivity analysis for these key parameters.

4. Alternate protocols

We also considered simulation protocols at pressures corresponding to more moderate lung volumes, so that the airways remain in the more compliant part of the pressure-volume curve. Because this may reduce the passive tension, we also allowed for an increased σ at the same time in order to make the conditions for an increase in narrowing as advantageous as possible. However, in all such cases considered, we found no more than a 3.0% increase in narrowing in any such configuration.

Discussion

The central question this study was designed to answer is: can the behavior of the airway wall itself account for the failure to see length adaptation in the intact airway? By reproducing the protocol of Ansell et al. 2014, we show with our model that in central, intact airways, no significant increase in narrowing should be expected following physiological changes in ASM length, even when the ASM is following the classic length-tension curve and undergoing length adaptation. The lack of an effect of length adaptation in the intact airway contrasts with results in ASM strips, and discussed below are several explainations for the discrepancy that have been revelaed from the model.

Airway compliance is predicted to be a signficant influence in how adapative properties of the ASM impact airway narrowing. All other things being equal, higher airway wall compliance results in both a greater initial change in radius (hence reduction in ASM tension by moving futher down the classic length-tension curve), and also greater potential for additional narrowing as tension redevelops during adaptation. Essentially, a more compliant airway wall allows for a greater ASM length change in response to an imposed pressure change, such that the ASM initially descends further ‘down’ the classic length tension curve, providing more scope for adaptation. Moreover, when the force does redevelop during adaptation, if the airway is more compliant, then this results in a greater change in radius. Thus, airway wall compliance has two

mechanisms of influence, and the relatively low compliance of cartilaginous airways impedes the appearance of length adaptation in large intact airways. The low compliance of the airway wall is also thought to partly explain the reduced response of the airway wall to oscillatory strain compared with isolated ASM (Hiorns et al. 2014).

In order to further address the issue of airway wall compliance, we have considered not only the nonlinearly compliant airway wall model of (Thorpe and Bates 1997), but also a linearly compliant airway wall. These two cases allow us to consider a range of airway wall behaviours. Though the nonlinear relationship is widely used, and the airway is certainly not linear beyond a narrow range, it appears that the pig airways used by Ansell et al. (2014) are closer to linearly compliant over the 5-25 cmH_2O P_{tm} range than similar generation airways used by Thorpe and Bates (1997), even though the pig airway is most compliant between -5 and 5 cmH_2O P_{tm} and stiffens at higher pressures (Noble et al. 2002). Of course, construction of a full pressure-volume curve would be ideal, but because the experimental protocol did not allow for this we must use existing data (Ansell et al. 2014). In the absence of sufficient information to parameterize an entirely new airway model, we consider these two extremes. However, in all cases, small airway behaviour is largely extrapolated from central airways, as little direct evidence is available. Alternatively the Lambert model (Lambert et al. 1982) could be used, (in fact,

the results are essentially identical) though at the cost of additional complexity, or perhaps a new model based on other existing data sources (Tiddens et al. 1999).

In terms of potential species differences, the model for large airways is porcine by virtue of the fit to the data of (Ansell et al. 2014). For small airways, the parameters of (Thorpe and Bates 1997) which we use here were fitted to canine data. More recent data (Harvey et al. 2015) on smaller airways also indicates that these theoretical estimates for small airway compliance are reasonably accurate, at least for bovine airways.

We also explore changes to both airway wall compliance and timescale parameters in order to test the sensitivity of the analysis, and to understand the ways in which length adaptation might produce an increase in narrowing which is functionally meaningful. There are two timescales in the problem. One is the timescale of length adaptation, denoted γ. The other one, denoted σ, is the timescale of expansion for a pressure change on a relaxed airway, and it is the ratio of these timescales that is the key quantity. We show that a combination of high airway wall compliance, and a fast passive expansion timescale, are required to see significant evidence of adaptation in the intact airway. Using our best available data for an order 1 airway, we estimate that only a negligible (0.18%) increase in narrowing would occur, even if experimental techniques could be adapted to the very smallest airways. Similarly, we explored the possibility that length

adaptation might be evident in a protocol at more moderate pressures, in which the airway does not leave the highly compliant part of the presure-volume curve, and the passive tension of the stretch is simultaneously reduced (Gunst and Stropp 1988). Indeed the airway wall response to oscillatory strain is more siginficant when pressures are applied at compliant regions of the pressure-volume curve (Harvey et al. 2013). However, we found that even with a simulated protocol optimised for these conditions, no more than 3.0% increase in narrowing could be obtained. Thus it is not clear that a significant increase in narrowing due to length adaptation would be evident in any intact airway no matter what the distending pressure. Of course, higher airway wall compliance results in more evidence of length adaptation, and because of the uncertainties regarding the compliance of the smallest airways, it remains possible that length adaptation could be of relevance to small airway function, particularly at more moderate volumes in which the airway is confined to the highly compliant part of the pressure-volume curve.

Whether the ASM in situ (whole airway) expresses adaptation to a reduced or increased length -- the two scenarios simulated in the present study -- has implications to physiological and pathophysiological airway behaviour. For instance, ASM length adaptation is thought to play a role in the development of AHR. It has been proposed that in asthma, as the ASM adapts to a progressively shorter length during episodes of bronchoconstriction, ASM force production is optimised which increases airway

narrowing capacity (Wang et al, 2001). A more recent study in isolated ASM also demonstrated a role of increased ASM length accompanying lung hyperinflation (Lee-Gosselin et al. 2013) suggesting that the ASM in situ may actually operate at a length below its optimal force capacity and that distension of the ASM length with hyperinflation increases force production[1]. The capacity of ASM to adapt to an increased ASM length is relevant to the above scenario and may serve to exacerbate the deliterious effects of hyperinflation. Nevertheless, our findings suggest at most a limited role for ASM length adaptation in the pathogenesis of AHR as a result of either an increase or decrease in ASM length.

The biological significance of ASM length adaptation also theoretically extends to the mechanism underlying the beneficial response to deep inspiration, which in healthy humans reverses existing bronchoconstriction (bronchodilation) and attenuates bronchoconstriction induced subsquent to the deep inspiration (Skloot and Togias 2003). Two plausible mechanisms may underpin bronchodilation and bronchoprotection to deep inspiration, namely perturbation of cross-bridge binding (Fredberg et al. 1999), and adaptive remodelling of the ASM in response to length change (Wang and Pare 2003). That little to no adaptation is predicted (by either our mathemaical or biological models)

[1] If one assumes that the in situ length of ASM is significantly shorter than the optimal length, then the model results for the inflation case would change markedly because of the rise, rather than fall, in force at longer lengths. However, the deflation case would remain qualitatively the same.

even when the ASM is held in a persistent distended state at pressures likely to occur at the peak of deep inspiration (25 cmH_2O), suggests that mechanisms other than length adaptation contribute significantly to the effect of deep inspiration on airway calibre.

The model assumes no intrinsic change to the behaviour of the ASM when coupled to the airway, via epithelial mediators or complex cell-cell interactions. Contributions from non-muscle tissue could well explain the deviation of the model data from the physiological data. We also assume that the modality through which ASM contraction is induced, for example neural stimulation as opposed to application of exogenous agents such as acetylcholine, does not influence the expression of length adaptaion at the airway level. Indeed, the vast bulk of previous studies demonstrating length adaptation using isolated ASM stips have induced contraction via neural stimulation (Chin et al. 2010, Chin et al. 2012, Kuo et al. 2001, Pratusevich et al. 1995 and Wang et al. 2001). The failure of length adaptation to manifest is simply a consequence of the mechanical coupling between airway and ASM. Thus we see that length adaptation in ASM is not necessarily sufficient for the phenomenon to be evident in intact airways, without recourse to modifications of the ASM behaviour. Rather, we suggest that it is simply a result of the mechanical and dynamic behaviour of the airway wall.

It remains possible that in an oscillatory or dynamic protocol, which takes account of the short-term behaviour of ASM (e.g. fluidization (Krishnan et al. 2008)), length adaptation would play a more important role. Our simulation protocols are designed to broadly mimic the experimental approach of Ansell *et al.* (2014) without introducing undue complexity. Thus we have used static pressures rather than oscillations, and instead of periodic stimulation (contraction) we simply have two cases, one contracted and the other relaxed. The former is easily justified by the fact that both static and oscillatory protocols are considered in the experiments, and the latter is a convenience based on the fact that the muscle model does not fatigue. Simulations were also performed with periodic stimulus for comparison, and away from the transient change the results presented here are unchanged. Previous studies have demonstrated length adaptation in isolated ASM strips under static (Pratusevich et al, 1995) and oscillatory (Pascoe at al, 2012), as well relaxed (Pratusevich et al, 1995) and contracted (McParland et al, 2005) conditions. A model of ASM adaptation under the dynamic conditions of breathing could be constructed by following prior methods (Donovan 2013), but at the expense of significantly complicating both the model, and limiting the possible analysis.

One observation made in the Ansell *et al.* (2014) study that the present model cannot resolve relates to the active pressure measurements, and subsequent calculation of ASM active tension. There was little, if any, regeneration of ASM tension after inflation to +25

cmH_2O P_{tm}, while the model predictions would indicate 5-10% increase (depending on the use of the nonlinear or linearly compliant airway wall model). An effect size of 5% may be beyond the detection levels of the intact airway model, where contributions from the heterogeneity amplify experimental noise. Indeed, a trend towards an increase in tension was observed by Ansell et al, (2015) following inflation to 25 cmH_2O, although this did not reach statisitcal significance.

As with any modelling study, there are a number of assumptions and limitations which must be carefully considered. Here we have opted for a minimal model which includes only the essential phenomena, and allows for relatively simple model formulation and analysis. In particular, we employ an extremely simple model of ASM which is concerned only with the length-tension curve and how it changes in response to persistant chagnges in length on a relatively long time scale. The first order kinetics imposed on this adaptation process, while convenient mathematically, are also in good agreement with the available experimental data (Wang et al. 2001). Many more complex phenomena of ASM, for example power law stress relaxation (Lenormand et al. 2004, Syyong et al. 2011) or fluidization (Krishnan et al. 2008) are neglected on this scale. Several other important assumptions require discussion. The passive expansion timescale σ is fitted to inflation data as a simple exponential; however, the limited data available suggest that it may be multi-exponential, or another more complex form (e.g. power

law). Further, no parenchymal tethering term is included (e.g. Lai-Fook 1979). This present model is designed to mimic the behaviour of an excised airway segment; of course, *in vivo*, parenchymal tethering would play a role.

Finally, it remains possible that some behaviour of the intact system is lost by the use of such a simple model, where there are more complex models available that could be used. However, the mechanisms by which length adaptation fails to manifest in the model – namely, compliance and adaptation timescale – provide a clear understanding of the mechanisms at work, and a more complex model would only cloud this picture. In summary, the present study, through use of a minimal mathematical model, provides an explanation for recent findings that length adaptation does not clearly manifest in intact airways. We suggest that airway wall stiffness and the time scales of adaptation reduce the impact of ASM length adaptation at the level of the large bronchus. The role of ASM length adaptation in health and disease remains uncertain.

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Conflicts of Interest: None

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Appendix A

This appendix includes details of the model which are inappropriate for inclusion in the main text, but nonetheless are important for reproducing these results. Several technical points are also discussed in greater depth.

One important point is that length adaptation may influence the behaviour of the airway on a relatively short timescale, but in the end the final radius is always the same. This is because both the equilibiria and the Jacobian are independent of the parameter β which controls the "width" of the length-tension curve. If $\beta=0$, then there would be no adaptation, just maximal tension exerted at any length – and the long-term airway behaviour would be unaltered.

The failure of the intact system to exhibit length adaptation can be understood by examining the phase portrait and nullclines of the system (e.g. Blanchard et al. 2004), given in Fig. A1. Here we see that the airway compliance determines the shape of the R nullcline; only by "bending" this curve higher can length adaptation become apparent. More compliant airways could thus result in ever more increase in narrowing. However, the relative timescales are also important, as expressed by the ratio σ/γ. Only when this ratio is large does the trajectory move quickly onto the R nullcline – for small σ/γ the

approach follows an intermediate trajectory. Thus length adaptation will only be apparent with a combination of both high compliance, and large σ/γ.

Parameters

The length-tension parameter β is obtained by roughly fitting the quadratic decrease to the length-tension data in (Wang et al. 2001) and the value is 4. Likewise γ is a parameter that controls the rate of the length adaptation of the ASM, and the value for γ is fit to the same data set and is equal to $0.00183\ s^{-1}$.

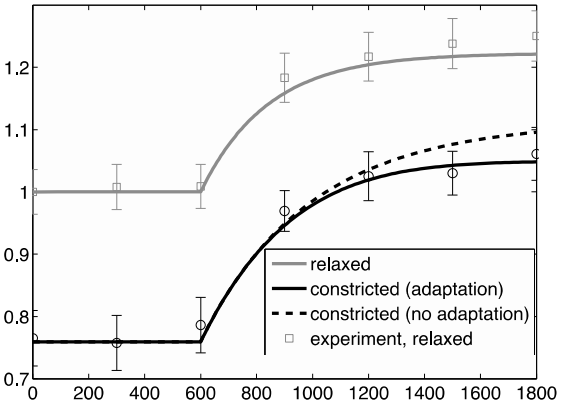
In order to model the kind of airway used in (Ansell et al. 2014) we require the physiological values for σ. The value for σ was found by fitting the passive expansion and relaxation curves of the airway in that study to the analytical solution for passive expansion in the above model. Passive expansion means the ASM is inactive and this is represented by setting κ, our maximum ASM force coefficient to 0. This function was fit to the passive radius inflation and deflation data from (Ansell et al. 2014), and the obtained physiological value for σ was $0.00415\ s^{-1}$. Other parameters used are: $\kappa = 3.284$ and $a_0 = 0.694$ (fit to (Ansell et al. 2014)).

In addition to the nonlinear airway wall model presented in the main text, we also linearize the airway model, which requires replacing Eq. 1 with

$$\bar{R} = a_0 P_p / P_{TLC} + a_1 \tag{9}$$

and subsequently substituted through the rest of the model derivation. For the main stem bronchus we have $a_0 = 0.2275$ and $a_1 = 0.772$. with $\kappa = 13.42$. Pressures are given in cmH_2O, but appear everywhere in the equations normalized to $P_{TLC} = 25$ cmH_2O. The variables R, R_f and $\bar{R}$ are given in dimensionless units, normalized to the relaxed radius at P_{TLC}.

Figures


1.2
1.1
1
0.9
0.8
0.7
0
200
400
600
800
1000
1200
1400
1600
1800
relaxed
constricted (adaptation)
constricted (no adaptation)
experiment, relaxed

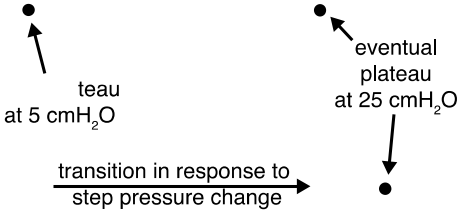

teau
at 5 cmH2O
eventual
plateau
at 25 cmH2O
transition in response to
step pressure change

Figure 1: Model simulations mimicking the protocol of (Ansell et al. 2014) of a step change from +5 cmH_2O P_{tm} to +25 cmH_2O P_{tm} at 600 s. Column A (panels A1-3) give the results for a linearly compliant airway, while column B (panels B1-3) give the same information for the nonlinear airway wall model. Row 1 (panels A1 and B1) give the change in airway in response to the change in pressure overlaid with the experimental data of (Ansell et al. 2014). Model simulations are shown both with and without length adaptation of the ASM, and the change in constricted radius between the two cases is clear. In all cases the radii are normalized to the relaxed radius at 5 cmH_2O. In row 2, the same data are given in terms of relative airway narrowing, both with and without adaptation. Row 3: the data from row 1 are shown on radius-force axes, (as opposed to time-radius) which demonstrates the effect of the initial length-tension curve on force production with and without adaptation. Explainatory annotations are given in A3; essentially the ASM follows the length-tension curve strictly when there is no adaptation, and when length adaptation is present the tension fully recovers with a timescale governed by σ and γ.

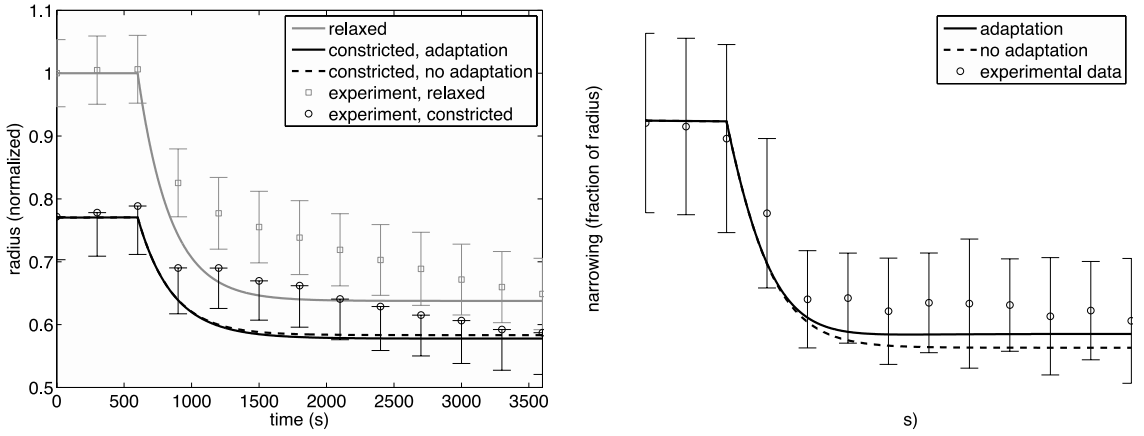


Figure 2: Deflation case, nonlinear airway model. Left panel: resposnse in airway calibre to a sustained deflation to -5 cmH_2O, model results and comparison to experimental data. The lines are model simulations, with grey the relaxed airway, solid black the constricted airway with adaptation, and dashed black the constricted airway without adaptation. Corresponding relaxed and constricted experimental data are given by the grey squares and black circles, respectively, with error bars denoting standard errors. (Note some error tails have been suppessed on one side for visual clarity.) Right panel: explicit quantification of narrowing for the calibre data given in the left panel.

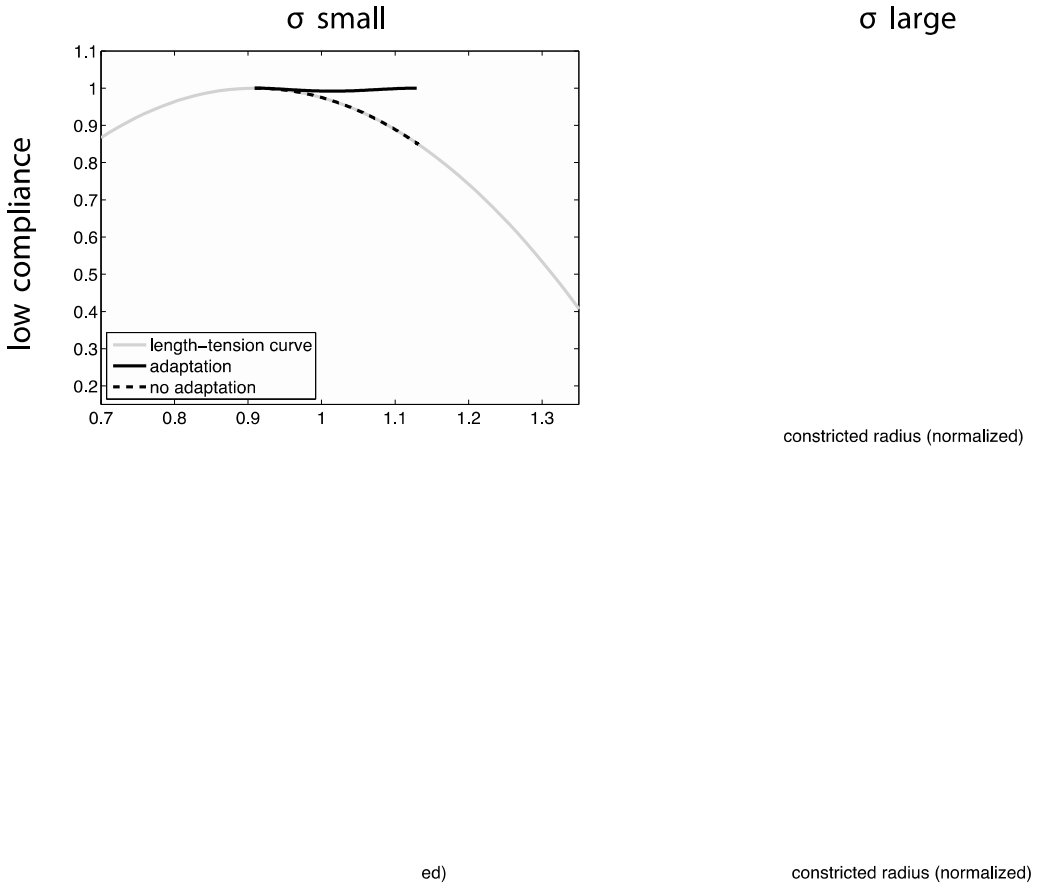


Figure 3: Trajectories of airway radii when pressure is increased to +25 cmH_2O P_{tm}, in both adaptation (solid black) and no adaptation (dashed black) cases, overlaid with the length-tension curves at the equilibrated length which govern ASM behavior (grey). Rows and columns are labeled with airway wall compliance (high or low) and airway time constant (small or large) respectively. Note that these are extreme cases, used to illustrate the role of each change, and not physiological values.

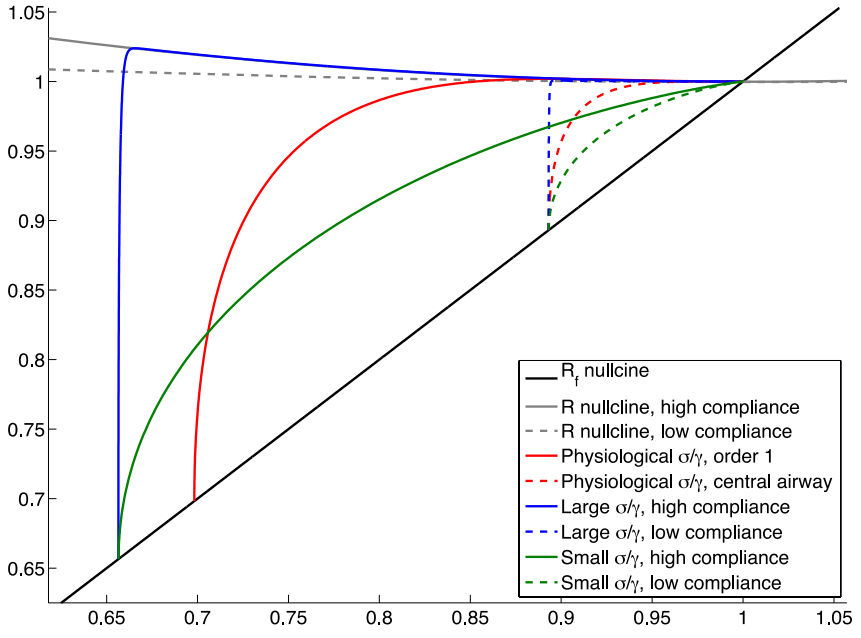


Figure A1: Phase portrait illustrating the structure which organizes the approach to equilibrium, and hence any appearance of length adaptation. Changes to both the timescales and the airway compliance are shown, with linestyle coding provided in the legend. Here the radii are normalized to the constricted equilibrium at 25 cmH_2O. [ed: black and white version available for print]