

**New Perspectives on the Mechanical Basis for Airway Hyperreactivity and Airway
Hypersensitivity in Asthma**

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Abstract:

We revisit the airway wall model of Lambert et. al. (JAP 1993:2771). We examine in detail the notion of a general airway bi-stability such that the airway lumen can suddenly decrease from a relative open to a relatively closed condition without needing additional increase in active airway smooth muscle (ASM) tension during the stimulation. The onset of this bi-stability is an emergent consequence of the balance of forces associated with airway wall properties, parenchymal tissue properties, maximum lung elastic recoil, and the maximum stress that the ASM can generate. In healthy lungs we find that all these properties reside in conditions that largely prevent the emergence of the bi-stability even during maximum ASM stimulation. In asthmatic airways, however the airway wall and ASM remodeling conditions can tip the balance so as to promote the onset of the bi-stability at a lower dose of ASM stimulation (enhanced sensitivity) and then work to amplify the maximum constriction reached by each airway (enhanced reactivity). Hence, a larger fraction of asthmatic airways can display overall airway hyperreactivity (AHR). Simulations studies examine the role of increasing ASM maximum tension, airway wall stiffening, reduced lung volume, and decreased parenchymal tethering. Results predict that the single most important factor causing this AHR is amplified maximum ASM tension, and not a thickening of the airway wall per se.

Introduction

The principal functional defect in asthmatics is that they display airway hyperreactivity (AHR). For the purposes of this paper, AHR is a combination of amplified airway *reactivity*, resulting in a greater luminal reduction to a given dose of airway smooth muscle (ASM) constrictor, and airway *sensitivity*, corresponding to luminal reductions occurring at a lower dose of ASM constrictor. Several mechanisms have been proposed for AHR. Three leading ones include: 1) inflammation and remodeling in the airway wall, causing decoupling of the ASM from surrounding lung parenchyma and thus a decrease in the load against which the ASM must constrict (18, 21, 22); 2) thickening of the ASM itself in a manner that could result in increased force generating capabilities (7, 8, 16); and 3) remodeling the contractile apparatus of the asthmatic ASM so that it becomes stiffer and more contractile (i.e., able to generate more force) (9, 10, 13, 23, 29). The feasibility of such mechanisms can be examined via computational models. A foundational such model by Lambert et. al. predicted the impact of thickening of all three airway wall layers (19). The primary prediction of the Lambert study was that thickening of the ASM was the primary cause of amplified narrowing in the asthmatic airway (19). However, a primary misconception is that such a result is due to the geometric impact of a thickened ASM layer. This is not the case. The preponderance of amplified reactivity in the Lambert model derived from the underlying model assumption that maximum tension generating capacity of ASM increased in proportion to increased thickness of the ASM layer. Hence, the real

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conclusion of this study was that the primary cause of AHR is the presence of ASM capable of generating greater maximal tension.

In the current study, we re-visit the Lambert model to exploit its inherent potential paradigm in which the interplay between the non-linear passive pressure-area relationship of the airway wall and ASM tension can cause an intriguing form of airway bi-stability, one that in principle with certain remodeling conditions can be invoked throughout the entire airway tree (19). This bi-stability is completely distinct from the bi-stability of the recent Anafi and Wilson study, which studied AHR only at the level of terminal airway without considering airway pressure-area (P-A) relationships (1). We will show that as a consequence of its fundamental assumptions, airway bi-stabilities within the Lambert model simply require an ASM capable of generating more maximum tension. During constriction, such an airway can then “flip” from a relatively large diameter to a small diameter at a lower percentage of the maximal ASM tension (i.e., a lower “dose” of airway agonist). Hence, these bi-stabilities can explain hypersensitivity and hyperreactivity seen in asthmatics. We point out that the conditions necessary for this bi-stability were alluded to in the original Lambert paper, but they were not fully exploited in the context of explaining the enhanced sensitivity and reactivity of asthmatic airways..

The primary goal of this study is to investigate how airway wall thickening with and without concomitant increases in ASM maximum tension impact airway reactivity and sensitivity. We further investigate how, stiffening of the airway wall,

unloading of the ASM by decreasing lung volume, and decoupling of the ASM from the surrounding lung parenchyma could influence airway hyperreactivity via enhancing the likelihood of invoking this airway bi-stability during provocation.

Airway Model

We first briefly review the model developed by Lambert et. al., and then describe a new perspective regarding the bi-stability (19). The model assumes each airway is a thin-walled compliant tube and then determines the load against which ASM must shorten (Fig.1). This load includes bulk forces generated by transpulmonary pressure (P_{tp}), the local shearing of lung parenchyma (ΔP), and passive pressure-area characteristics of the airway wall (P_p). From Fig. 2, we call the radius to the interior wall of the ASM as r_{asm} and consider this the independent variable. All other radii (luminal radius (r) and outer radius (r_{out})) can be calculated relative to this, assuming that the cross sectional area of the airway wall is constant. The thickness of each individual airway wall layer as a function of airway size is based on the histological data from asthmatic and healthy airways from Kuwano et. al. (16). Table I contains the thickness of each airway layer for the healthy and diseased cases. For a specified percent muscle shortening (PMS):

$$r_{ASM_C} = r_{ASM_r}^{PMS} \quad (1)$$

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where r_{ASM_c} is the radius of the constricted ASM, and r_{ASM_r} is the ASM radius when the ASM is relaxed. Once luminal radius (r), ASM radius (r_{ASM}), and outer radius (r_{out}) for a given PMS are known, two pressures work to distend the airway. One is the bulk pressure across the airway wall (P_L) defined as the difference between the pleural pressure (P_{pl}) and the intraluminal pressure (P_{in}) at any time (eq.2). The other is the pressure due to parenchymal shearing (ΔP) (i.e., local tethering of an airway to parenchyma which was modeled based on the original analysis of Lai Fook (17)). According to Lambert (19):

$$P_L = P_{in} - P_{pl} \quad (2)$$

$$\Delta P = 2\mu \frac{r_{out} - r_{out_{TLC}}}{r_{out_{TLC}}} \quad (3)$$

where μ is the shear modulus of lung parenchyma, r_{out} is the airway outer airway radius at any ASM constriction, and $r_{out_{TLC}}$ is the outer radius of the airway at total lung capacity (TLC). (Note: under static condition P_L is transpulmonary pressure). With this notation the transmural pressure (P_{tm}) would be equivalent to the peribronchial such that $P_{tm} = P_L + \Delta P$.

The material properties of the airway wall result in its own P-A characteristics. This relationship is non-linear, can work to distend or constrict the airway lumen, and has been modeled in various forms (12, 20). A commonly used equation, based on the data of Gunst and Stropp, was proposed by Thorpe and Bates (11, 12, 32):

$$P_p = P_{TLC} \left(\frac{r/r_{TLC} - \alpha_0}{1 - \alpha_0} \right)^3 \quad (4)$$

Here, P_p is the passive pressure due to P-A characteristics of the airway wall, P_{TLC} is the P_L at TLC, r is the constricted radius of the airway lumen, and r_{TLC} is the radius of the airway lumen at TLC,. The α_0 is a constant that depends on airway generation in accordance with data from Gunst and Stropp so that small airways are generally more compliant (12). The equations for α_0 are given by Gillis and Lutchen (11).

During airway constriction it is possible to calculate the separate tensions arising from each of the three pressures using the law of Laplace :

$$T_{P_L} = P_L r_{ASM} \quad (5)$$

$$T_{\Delta P} = \Delta P r_{ASM} \quad (6)$$

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$$T_{Pp} = P_p r_{ASM} \quad (7)$$

where T_{PL} is the tension due to P_L , $T_{\Delta P}$ is the tension due to shearing of the lung parenchyma, and T_{Pp} is the tension due to the passive P-A relationship of the airway wall. Equations 5-7 presumes r_{asm} as the driving parameter for tensions such that the model invokes a thin walled tube assumption (an issue addressed in the discussion). The tension that the ASM must generate to shorten to any given r_{asm} is the negative of the sum of these three tensions:

$$T_{ASM} = -(T_{PL} + T_{\Delta P} + T_{Pp}) \quad (8)$$

Eqs. 5-7 were used in the original Lambert model and will be used here. The tension from eq. 8 at any particular ASM length needs to be reconciled with the maximum tension an ASM can generate at that length. This maximum tension has been derived empirically (Lambert) using ASM length-stress curves and its thickness (11, 19).

As the ASM is shortened, new radii, thicknesses, and active tensions are calculated for the new ASM length (as per eqs. 3-7). The new ASM active tension is compared to the maximal tension that ASM at that given length can generate which is derived via the sigmoidal relation described in the original Lambert paper and which derived from isolated ASM data. This relation depends on airway wall thickness which is airway generation dependent. If maximal

tension has not been reached the muscle is further shortened until maximal tension is reached or the airway closes. For example, similar to (11, 19), Figure 3 shows the response of actively stimulating ASM for four distinct airway generations, each with airway wall areas consistent with a healthy person. We plot percent maximal stress ($\% \sigma_{\max}$) as a function of constricted ASM length normalized by the length at which the ASM develops maximal stress ($L_c/L_{\max}$). The dashed line represents the maximal stress that ASM can develop at any constricted length. During active tension development, the ASM shortens. In a 3.8 mm, 1.8 mm, and 0.7 mm airway ASM shortens until the maximal stress curve is reached. At this point, no additional shortening is possible. The degree of shortening in each case was not sufficient to close the airway, although the maximum constriction possible was greater for the higher generations (i.e., smaller airways). In contrast, a 0.3 mm airway will close (i.e., its luminal radius becomes zero) before the maximal ASM stress is reached.

Figure 4 shows the individual tensions of the three loads during active ASM shortening as a function of percent muscle shortening (PMS) of a 3.8 mm severe asthmatic airway. The tension in the airway wall that is generated due to pressure across the airway (P_L) decreases linearly with PMS. The tension generated by local shearing of the surrounding parenchyma is nearly constant over a wide range of PMS. Most important is that at low values of PMS the load generated by the passive P-A characteristics (P_p in figure 4), is negative and works to constrict the airway, while at large values of PMS this load becomes positive and works to distend the airway. However, over a wide range of PMS (10-40%), this passive P-A load is nearly constant and very small. Hence, for the ASM to shorten from 90% to 60% of its unperturbed

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length, the muscle itself needs to generate very little additional tension. This means that as the ASM actively shortens there is the potential for airway bi-stability, where the airway lumen can go from nearly open to nearly closed with virtually no additional active ASM tension being developed. It is this form of airway bi-stability that we focus on as a possible fundamental mechanism driving AHR in the asthmatic airway.

Simulation Studies:

Four simulation Case studies were designed. The first Case focuses on the phenomena of ASM thickening relative to how airway bi-stabilities can influence AHR. Case 2 addresses the original Lambert model assumption that the thickened airway wall of the asthmatic has the same pressure-area (P-A) characteristics as the non-thickened airway wall. However, the thickened airway wall of the asthmatic is more fibrotic (4). and it has been shown that at least the central airways of asthmatics are stiffer (4). Moreover, as the ASM thickens in asthmatics, it may do so in a manner so as to stiffen the airway wall. Thus, our second set of simulations focus on the impact of wall stiffening on the bi-stability. Case 3 predicts the impact of airway provocation initiated at a lower lung volume. Ding et. al. (6) have suggested that the lung is more reactive at lower lung volumes and suggested this was due to the reduced loading on the ASM. Finally, Case 4 addresses the explicit role of local parenchymal tethering. In all cases the intent is to investigate how these phenomena may or may not lead to enhanced airway reactivity and sensitivity by facilitating an airway's transition to a bi-stable state.

Case 1: Airway Wall Thickening with and without Proportional Increased ASM Strength: Here ASM shortening was imposed pre and post ASM thickening. All three airway layers were thickened as described by Kuwano et. al. (16). In the original Lambert model, whenever the ASM layer was thickened there was always a proportional increase in ASM maximum tension, implying that the thicker ASM in asthmatics occur by with increased force generating capabilities. We contrast this with the situation where the ASM was geometrically thickened but without increasing its maximal tension generating capabilities. This condition would represent ASM growth via increases in connective tissue, or via cell swelling and thus without altering its contractile apparatus. Any amplification of luminal narrowing that occurs during the thickening without strengthening would therefore be due purely to geometric impact of thickening of the airway wall from a thicker ASM and the corresponding preservation of wall mass condition imposed by Wiggs et al. (37).

Case 2: Impact of airway wall stiffening on AHR. The original Lambertr (19)study employed the same P-A characteristics for the healthy and asthmatic airways, even though the asthmatic airway wall is thicker and more fibrotic (4). In Case 2 we contrast the impact of ASM stimulation occurring around an airway with its baseline P-A relationship (eq. 4) versus an airway with a stiffened P-A relationship. For the latter, we changed α_0 in eq. 4 from 12.5 to 12.0 for the 3.8 mm airway shown in figure 4 so that the stiffened airway dilated less from FRC to TLC (i.e. less compliant), and there is an increase

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in constricted diameter at which the airway wall starts to generate a distending force. Figure 5 contrasts the two P-A relationships for a 3.8 mm airway. While the stiffened airway curve is not explicitly data-driven, it is consistent with the phenomenological impact of ASM stimulation on isolated airway pressure-area relationships as reported by Noble et. al. (27).

Case 3: Impact of decreasing FRC: Ding et. al. has shown that lowering lung volume results in enhanced reactivity (6) and proposed that this occurs because of a reduced load on the ASM during stimulation. In the Lambert model, initiating ASM stimulation at lower lung volumes was achieved by lowering the baseline transpulmonary pressure from 5 cm H₂O to 2.5 cm H₂O. This effectively starts the ASM shortening from a shorter baseline length which alters its pre-stimulation tension, and the shortening is imposed from a point on the airway wall P-A curve closer to the lower inflection point (Fig. 5). Also, according to eq. 3, there is less effective parenchymal tethering because the lower lung volume is created via a decrease in P_{tp} and lung shear modulus (μ) is proportional to transpulmonary pressure ($\mu = 0.7 P_{tp}$).

Case 4: Impact of decreased parenchymal tethering: It has been hypothesized that airway thickening and inflammation can decrease local tethering forces associated with shearing of the parenchyma, which work to distend the airways. These forces represent an additional local load against which the ASM must constrict (18, 21, 22). In this case we

contrasted the baseline simulations from a case where we set the pressure load due to shearing of lung parenchyma (ΔP in eq. 3) to zero (i.e., to a case in which the local shearing forces associated with parenchymal tethering play no role in modulating ASM shortening).

In all simulations we express airway responses in as normalized diameter vs. normalized ASM tension. We contrast the results for a midsized airway (3.8 mm diameter at FRC) and a peripheral airway (0.7 mm diameter at FRC). Constricted airway diameter (D_c) is normalized by the airway diameter at baseline, D_b (i.e., no ASM shortening). We plotted D_c/D_b versus the ASM tension at D_c normalized by the maximum tension achievable by the ASM at the shortest length it can possibly reach during constriction. This normalized ASM tension has been shown to be a surrogate of “dose” of a constricting agent (28). If the shortest length occurs because of closure (eg., 0.3 mm airway in Fig. 3), the max tension is found from the dashed empirical curve at the L_c/L_{max} of closure. The rationale for this is that even though the airway closed, in principle with additional dose the ASM can develop more (now isometric) tension but due to closure this tension cannot further reduce diameter. Another interesting consequence of this approach is that during active constriction the ASM tension first rises and then can actually decrease with further ASM shortening (eg., 0.3 mm airway of Fig. 3) prior to maximum shortening. This occurs because of the unique interplay between the tension derived from the airways inherent P-A curve and the tension from the P_L . For example, in Fig. 4 at 20% ASM shortening, the tension from the P-A relationship becomes nearly constant with further shortening while that due to P_L decreases. Hence, when we

present simulation results normalized in this fashion at some D_c/D_b , the normalized ASM tension could exceed the maximum achievable at the eventual minimum diameter.

Results

Airway Wall Thickening with and without Proportional Increased ASM Strength. Figure 6 shows the impact of geometrically thickening the asthmatic airway wall with and without a concomitant increase in maximal ASM tension and compares this to a healthy airway of similar size. The healthy larger airway can only reduce luminal diameter by 13%. At that point the ASM reaches its maximal tension. The severe asthmatic airway, with the same luminal diameter but with thicker walls in which maximal ASM tension is increased in proportion to thickness (i.e., airway wall thickening with increased ASM strength), behaves dramatically different. Specifically, the interplay between passive tensions and active tension triggers a bi-stable state such that this asthmatic airway flips from nearly maximum diameter to nearly closed at about 50% of maximal tension. The leftward shift for the onset of airway constriction represents an increase in airway sensitivity while the amplified minimal diameter corresponds to increased airway reactivity. Also shown is the impact of a thicker ASM without a concomitant increase in maximal tension (airway wall thickening without increased ASM strength). Here, the bi-stable state is not triggered and there is no enhancement in airway reactivity or sensitivity over that predicted for the healthy airway.

In the peripheral case (0.7 mm diameter), the healthy airway shows evidence of triggering this bi-stability as does the thicker asthmatic airway even if the thickening does not also increase ASM maximum tension. In this case the maximum airway constriction is 60% of baseline for the healthy airway and 80% for the asthmatic. If, however, thickening of the peripheral airway wall occurs concurrently with increasing maximal tension, the airway bi-stability occurs well before maximal stimulation is reached, thereby substantially enhancing peripheral airway sensitivity to a ASM provocation. Here, as the ASM shortens it develops more tension which works to reduce airway diameter. At approximately a 20% diameter reduction, any further increase in tension (eg., due to higher dosage), dramatically and rapidly causes the airway diameter to flip from 80% open to 90% constricted.

Case 2: Impact of airway wall stiffening on AHR. In the central airways, with mild or severe-like asthmatic wall thickening as prescribed by Kuwono et al. (16), concomitant airway wall stiffening causes the onset of airway bi-stability to occur at a lower percentage of maximal ASM tension. For all simulations of this case, we assumed that the maximum ASM tension increased in proportion to its increased thickness as in the original Lambert model. While the bi-stability occurred at lower ASM tension, the eventual maximum constriction was less for the stiffened airways. For example, the thicker but unstiffened severe asthmatic airway will flip from nearly open to near closed when the ASM reaches about 55% of its maximum tension, and will eventually constrict by 85% of its original diameter. If this same airway had a stiffened wall as described by Fig. 5, the bi-stable flip occurs at only 40% of maximum ASM tension (lower dose), but the

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eventual maximum constriction is only 50% of the original diameter. Stiffening of the healthy central airway leads to a small increase in both airway sensitivity and reactivity, but to a much smaller degree than does alteration in ASM. In contrast, stiffening of the peripheral airway walls does not alter the point at which airway bi-stability occurs (i.e. does not alter airway sensitivity), and it also does not alter the maximal possible constriction. However, wall stiffening did allow the ASM to eventually achieve a higher maximum tension. For example, for the severe asthma peripheral airway, the maximum constriction achievable is a 90% reduction in diameter and this occurred when the ASM achieves only 39% of its maximum tension. But, after wall stiffening, this maximum constriction occurred when the ASM reached 74% of its maximum tension. Stiffening of the healthy airway did not alter airway sensitivity or reactivity for peripheral airways.

In summary, for larger airways, wall stiffening enhances sensitivity so that constriction and the airway bi-stability would begin at a lower “dose”, but the stiffening limits the maximal constriction possible thus attenuating reactivity. The impact of similar stiffening on very small airways is less substantial and less definitive regarding airway sensitivity or reactivity.

Case 3: Impact of decreasing FRC. We can simulate ASM shortening when stimulated from baseline P_{tp} of 2.5 cm H₂O (below FRC) as compared to 5 cm H₂O (Fig.8) thus mimicking airway provocation with less ASM load. The decreased load occurs directly because the P_{tp} is lower (eq. 2) and indirectly because of reduced local tethering at lower lung volumes (i.e., eq. 3 and assuming that $\mu = 0.7P_{tp}$ as per Lambert). For larger airways, initiating constriction from a

lower lung volume amplified net constriction, even in healthy airways. Here, the net constriction was 35% for the case where the P_{tp} was 2.5 cm H₂O as compared to just 13% when P_{tp} was 5 cm H₂O. For the asthmatic larger airway, the impact of beginning ASM stimulation at a reduced FRC was more dramatic and caused a leftward shift in the onset of airway bi-stability (i.e., an increased sensitivity). The net diameter reduction was similar since in both cases eventually the ASM can nearly close the airway. The results for peripheral airways were more intriguing, particularly for healthy airways. Here, the reduction in lung volume caused the maximum constriction in airway diameter for healthy subjects to increase from only 60% if stimulation began at FRC, to essentially completely closed (90%) if the stimulation began at the lower lung volume. Also, the bi-stability and preponderance of this closure occurred at only 40% of the normalized ASM max tension as opposed to 100% for the FRC case. Thus, decreasing lung volume has a dramatic impact on healthy airway sensitivity and reactivity. In the asthmatic airway, decreasing FRC also amplified sensitivity (leftward shift of bi-stability), but could not amplify net diameter reduction because the airway lumen is already nearly completely closed.

Case 4: Impact of decreased parenchymal tethering In the absence of any parenchymal shear tension, there is a slight increase in maximum airway constriction possible in large sized healthy airways (Fig. 9). In the asthmatic airway, this decoupling from the parenchyma results in a small shift to the left in the onset of airway bi-stability, (i.e., a slight increase in airway sensitivity, but no amplification of net maximum constriction). In the lung periphery decoupling the airway from the parenchyma has a substantial effect on airway sensitivity in the healthy and milder asthmatic airway. This

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decoupling also causes an amplification of maximal constriction possible in the healthy airway. For example, this decoupling resulted in the onset of airway bi-stability in a healthy person at 60% of maximal tension versus 100% and a maximum airway constriction of 95% as compared to 50% in the tethered airway. The implication is that local tethering is an important inhibitor of airway reactivity and sensitivity in the healthy peripheral airways, a moderate inhibitor of hypersensitivity in milder asthmatics, but only a small factor in severe asthmatics.

Discussion

The primary dysfunction in asthma is AHR. This study revisited the Lambert model to investigate how airway wall thickening might or might not be able to impact AHR. We convey a novel perspective embedded in the model in that the interplay between airway wall properties, parenchymal tethering, and ASM length-tension properties can conspire to produce a phenomenon of airway bi-stability in principle for any airway. This perspective was eluded to in Lambert's original paper, but its impact and implications were not fully exploited. Indeed, the bi-stability provides a remarkable scaffold for explaining the mechanical basis for both enhanced sensitivity and reactivity of asthmatic airways. Specifically, during activation the ASM attempts to contract and in doing so its active tension increases in a fashion governed by the balance of forces associated with the airway wall's inherent P-A material properties, the bulk force due to the transpulmonary pressure acting to distend the airway, the local shearing pressure, and the ASM's isolated inherent

length-stress relation. As the ASM shortens, the airway diameter decreases, and the active ASM tension increases. But, under certain conditions, the ASM length and airway lumen can dramatically and suddenly decrease with very little corresponding increase in ASM active tension (in fact, a decrease is possible). This phenomenon is the result of the passive pressure-area characteristics having a rapid increase in area for small increases in pressure. In other words, at this point of its pressure-airway curve the airway wall offers very little resistance to reduction in diameter for a wide range of muscle shortening. We call this phenomena an airway bi-stability in that for a very narrow range of ASM tensions the airway can “flip” from being mostly open and stable to being nearly closed but stable again. In this paper, we convey airway response as normalized diameter versus ASM tension normalized to its maximum attainable value. This is done to show the impact of effective *dose* of ASM contractile stimulant on the occurrence and eventual impact of the bi-stability. The maximum dose is always that which would create maximum ASM tension. Thus, conditions resulting in shifts in these curves to the left are those that enhanced an airway’s sensitivity to a contractile stimulant in that the ASM can tip the occurrence of the airway system bi-stability and achieve enhanced maximum constriction at a lower dose.

Presented in this fashion, we first predict (Case 1) that healthy larger airways at FRC do not reside in a state that can provoke the bi-stability. Healthy peripheral airways may, but only at the very maximum “dose” or tension that the healthy ASM is able to achieve (eg., Fig. 6). Even here, maximum constriction reached is still 60% (Fig. 6). We also show that conditions that simply increase the thickness of the ASM without increasing the maximum tension the ASM can

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generate will not be sufficient to trigger the airway bi-stability in a fashion that enhanced airway sensitivity or reactivity. However, conditions that do enhance the maximum achievable stress (eg., asthmatic like ASM thickening with concomitant enhanced maximum stress) dramatically enhance the likelihood of the bi-stability occurring for all sized airways. Also, the bi-stability now occurs at levels of ASM tension significantly lower than the maximum tension that the ASM can achieve (i.e., at lower doses) (Fig. 6).

It is important to recognize the critical role played by the maximum stress-bearing properties of the ASM. In Fig. 6, the absolute tension necessary to trigger the bi-stability is nearly the same for the healthy airway as it is for the thicker asthmatic airway. However, because the thicker airway has an increase in maximum stress, the bi-stability occurs at a lower percentage of this maximum stress (i.e., lower dose). The details of the bi-stability shape and eventual maximum constriction can be different as they depend on the full balance of forces governed by eqs. 5-7. Our analysis describes the phenomena of the airway bi-stability, and more important that its occurrence and resulting impact of severe airway constriction are far more likely at lower doses if and only the ASM should remodel in a fashion that amplifies its maximum stress generating capacity.

This model predicted that a fully stimulated ASM surrounding healthy larger airways will not invoke the bi-stability and that the maximum these airways will constrict will be small (eg, 13% in Fig. 6 for a 3.8 mm diameter airway). This prediction is in conflict with results of Brown and Mitzner who showed that they could cause a rather large canine airway

to close by exposing a concentrated part of the airway to a large dose of methacholine (5). One possibility is that the ASM *in situ* operates with a significantly stronger maximum tension versus length relation than was presumed by Lambert. However, the Lambert relation was already based on isolated ASM for which periodic length oscillations had been avoided for some time. Hence, it is unclear how the *in situ* ASM could generate even more tension. Moreover, we are aware of no evidence that large airways can be made to close in a healthy human even when exposed to rather large doses of methacholine (24, 25). We speculate that rather than a fundamental flaw in the Lambert analyses, this discrepancy reflects an inherent distinction between dogs and humans perhaps associated with dogs having less cartilage or that the airway of dogs have an greater proportion of ASM than that of humans.

We further examined how the enhanced airway bi-stability that occurs with thickening and increased maximum tension could be modulated by changes in airway wall stiffness (Case 2), reductions in lung volume (Case 3), and parenchymal tethering (Case 4). Stiffening of the thickened asthmatic airway wall increases airway sensitivity in both central and peripheral airways, while causing a reduction in reactivity in central airways and having no effect on reactivity in the lung periphery. This increased sensitivity is the result of an increased constricting force of the passive airway wall structures due to airway wall stiffening. The reduced reactivity seen in the central airways is the result of the thickened airway wall being stiffer and hence harder to constrict. Decreasing lung volume results in a huge increase in reactivity and sensitivity in healthy and asthmatic airways. This is the result of directly lowering the both the bulk pressure

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difference across the airway wall, and the forces associated with parenchymal tethering (by lowering the shear modulus of the lung tissue). Also, eliminating the load due to local shearing of the parenchyma effectively reduces the distending force presented to the ASM. As a consequence, there is an increase in airway sensitivity and reactivity in both the central and peripheral airways of healthy and asthmatic airways. Any or all of these conditions may further amplify the impact of an increase in the maximum tension capabilities of the ASM. Most provocative and unexpected was the substantial impact on healthy peripheral airway sensitivity and reactivity simply by removing the distending force due to parenchymal shear modulus. The implication is that chronic inflammation can enhance airway reactivity by such mechanical decoupling and not necessarily by amplified levels of bronchoconstrictor mediators or by inducing remodeling of the ASM contractile apparatus.

Taken together, this means that enhanced sensitivity and reactivity can occur via a combination of any ASM remodeling that amplifies its maximum tension generating ability, a decreased lung volume, or a removal of local parenchymal tethering. This summation in itself is certainly not new, but our analysis clarifies that the manner in which they cause such changes may be manifest via an airway bi-stability. We further show how and when that stability is likely to be invoked. Moreover, airway wall stiffening (which has been reported in asthmatics (4)) can actually enhance airway sensitivity (although it will also act to limit the maximum constriction). Almost surely the remodeling in the airway wall and ASM in asthmatics results in such stiffening (9, 10, 13, 23, 35, 36).

Whether amplified maximum tension capacity of the ASM results from thickening of the ASM or simply remodeling of the contractile apparatus is irrelevant from our model predictions point of view. For example, the ASM cytoskeleton could remodel in a fashion that does not increase its thickness but does allow it to generate more tension (9, 10, 13, 29, 30, 35, 36). This cytoskeleton remodeling could be caused by lack of stretch (34), or by local inflammatory mediators causing an increase in ASM tone, which leads to stiffening of the ASM and increased force generating capabilities (36). Stiffening of the airway wall can also lead to alterations in length cycling of the ASM, because a stiffened airway wall will dilate less during tidal ventilation and also dilate less with a deep inspiration (2, 3, 15). These alterations could possibly lead to remodeling of the cytoskeleton of the ASM in a fashion that increases the muscle's ability to generate tension. It has also been shown that when ASM is allowed to adapt to shorter lengths, it can regain its maximal force generating capabilities (23, 26, 29, 35). This adaptability to short length could allow the ASM of the asthmatic to generate larger forces, as the asthmatic airways start at a reduced diameter. Again, only the maximum active tension capacity of the ASM need be enhanced to invoke airway bi-stabilities inherent in the Lambert model so as to increase both airway reactivity and sensitivity. How this increase evolves is beyond the scope of this study.

Relation to Other Forms of Airway Bi-stability: It is important to note that the bi-stability shown in this report is not the same as that predicted by Anafi and Wilson (1), in that it is not limited to terminal airways and does not require dynamic flow events. Specifically, the Anafi and Wilson bi-stability occurs because of loss of the interplay between

tethering in the terminal airway and airway constriction leading to reduced luminal pressures in the periphery during dynamic flow. The higher resistances during constriction, even if the constriction occurs higher in the airway tree, creates transmural pressure conditions that result in terminal airways that either collapse or stay open. The Anafi and Wilson form of bi-stability may occur as well, but the need to conclude that severe airway constriction in asthma is limited to only the terminal airways is a wholly unsatisfying result. Our model suggests severe constriction need not be limited to peripheral airways, and in fact any and all airways are capable of rapid constriction without necessarily additional increases in ASM tension (i.e., a bi-stability).

Recently Venegas and Winkler et. al. exploited the Anafi and Wilson form of bi-stability in a branching airway system to predict that airway constriction heterogeneity might be a necessary consequence of lung provocation, and further that the resulting ventilation heterogeneity would necessarily form in clusters (33). However, again all ventilation defects in their model must occur due to closures only in the terminal airways. It may be that our form of bi-stability is perfectly compatible with such clustering of ventilation defects as well, but would allow for severe airway constrictions higher up in the airway tree. Indeed, a recent study by Tgavalekos et. al. (31), predicted that while functional airway closures are likely occurring in very small airways only, constriction of these airways alone are insufficient to explain the simultaneous measured mechanical and ventilation heterogeneities in asthmatics. Substantial constriction was required in non closed airways as well.

Implications to Deep Inspiration Response: Several studies (2, 3, 15) have indicated that compared to healthy subjects, asthmatics have a reduced ability to maximally dilate their airways at total lung capacity (TLC) even if they generate 30 cm H₂O during the deep inhalation to TLC. To some degree, our analysis can explain this. Specifically, if the ASM of asthmatics is simply stronger, then after provocation the bi-stability permits it to reach substantially shorter length with more absolute tension at the same dose compared to that of healthy subjects. Such an airway should be more difficult to subsequently stretch with deep inspiration. Moreover, subsequent dynamic forces of tidal breathing would also result in less ASM length oscillations per breath. As mentioned, isolated ASM studies (26) show that if sustained chronically the shorter length combined with reduced length oscillations can cause the ASM to shift its force-length curve so as that its maximum force can now occur at a shorter length. The model in this paper does not impose this particular ASM remodeling phenomenon, but provides a potential enabling explanation which would only work to even further enhance the impact of the airway bi-stability relative to asthma.

Model Limitations: This model assumes that the airways are idealized cylinders; this is not the case *in vivo* where airway wall thickness is not constant, the airway wall is not perfectly cylindrical, and there are epithelial folds. Also, the calculations of hoop stress are based on the assumption that the airway is a thin walled pressure vessel (radius $\gg$ thickness). If the thin walled assumption holds, then from eq. 5 the total tension is the total pressure drop times the radius at the midwall (r_{asm}). When the thin walled assumption is not valid, the tension is best calculated as the average

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circumferential stress times thickness, an analysis that would better account for nonlinear relations. We only include the thin-walled case because to retain symmetry with the original Lambert model. However the thin-walled assumption likely breaks down when the airway lumen is severely constricted because during constriction, wall area is preserved via thickening of the wall layers. We anticipate that the transition to a thick-walled vessel should have little effect on the end result, as it would generally increase the stresses due to each load in a similar fashion.

The model used for parenchymal interdependence in this study was a linear model, Lai-Fook has shown that when there parenchymal distortion are large the relationship between force and diameter is non linear (17). We anticipate that this would not alter our results as the non-linearities would only become valid once the airway was severely constricted and had already traversed the bi-stable state. It was also shown by Lai-Fook that the linear and non-linear models were convergent at low values of P_{tp} , such as is the case in our model. Gunst et. al. (14) have shown that parenchymal interdependence was insufficient to prevent airway closures below 10 cm H₂O, providing further proof that under the conditions presented here the non-linear model was not essential.

Another limitation of the model is that it presents the consequence of quasi-static pressures and tensions where as in reality airway walls are viscoelastic and subject to dynamic conditions. We negate any effects of flow and fluctuations in transpulmonary pressure which are associated with breathing. These variations in transpulmonary pressure could also work to attenuate the constriction due to the dynamic properties of ASM and hysteresis of the airway wall as a whole.

A recent study by Noble et. al. (27) in isolated pig airways indicated that the airway wall is likely not isotropic, and that the ASM layer can in fact decouple itself from the adventitial layer of the airway. They found that the thickness of the airway wall in some cases may not be constant. If this phenomenon does in fact occur in airways it could alter both the airway P-A relationship, and the forces associated with parenchymal tethering. We suggest that the implications on the P-A relationship are not crucial because our P-A relationship was based on data of Gunst and Stropp (12) acquired via a volume controlled system which directly quantifies changes in luminal area regardless of any airway wall decoupling that may occur. However, the decoupling could significantly impact the predicted impact of parenchymal tethering forces. Specifically, decoupling the ASM from the adventitial layer should serve to reduce the load against which the ASM must constrict which would serve to increase ASM sensitivity and reactivity (as seen in case 4 figure 9). Moreover, this may explain why experimentally observed maximum constriction of non-asthmatic larger animal airways (5) exceeds that predicted by our model with its isotropic wall.

Summary: We have introduced the notion of a general airway bi-stability such that the airway lumen can suddenly decrease from a relative open to a relatively closed condition without needing additional increase in active ASM tension during the stimulation. The onset of this bi-stability is an emergent consequence of the balance of forces associated with airway wall properties, parenchymal tissue properties, maximum lung elastic recoil, and the ASM. This could not be

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predicted by any one of these in isolation. It appears that healthy lungs are “lucky” in that all these properties reside in conditions that prevent the bi-stability to emerge except under the most maximally stimulated conditions and then only in the lung periphery. Unfortunately, however, in asthmatics, airway wall and ASM remodeling tip the balance of conditions so as to promote the onset of the bi-stability at a lower level of ASM stimulation and usually to amplify the maximum constriction reached by each airway as well. Thus, a larger fraction of asthmatic airways are now able to display airway hyperreactivity. Moreover, this paper fuels the controversy as to which airways are most responsible for functional degradation during an asthma attack.

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Acknowledgements

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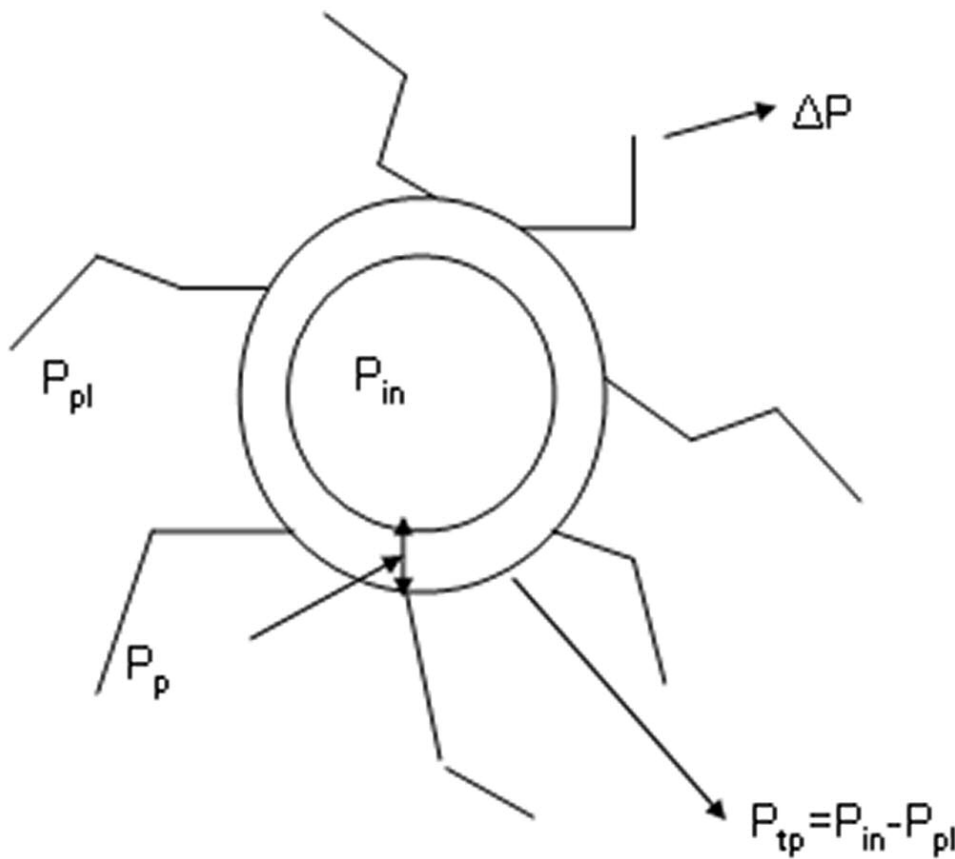


Figure 1: Passive forces working to dilate or constrict the airway wall.

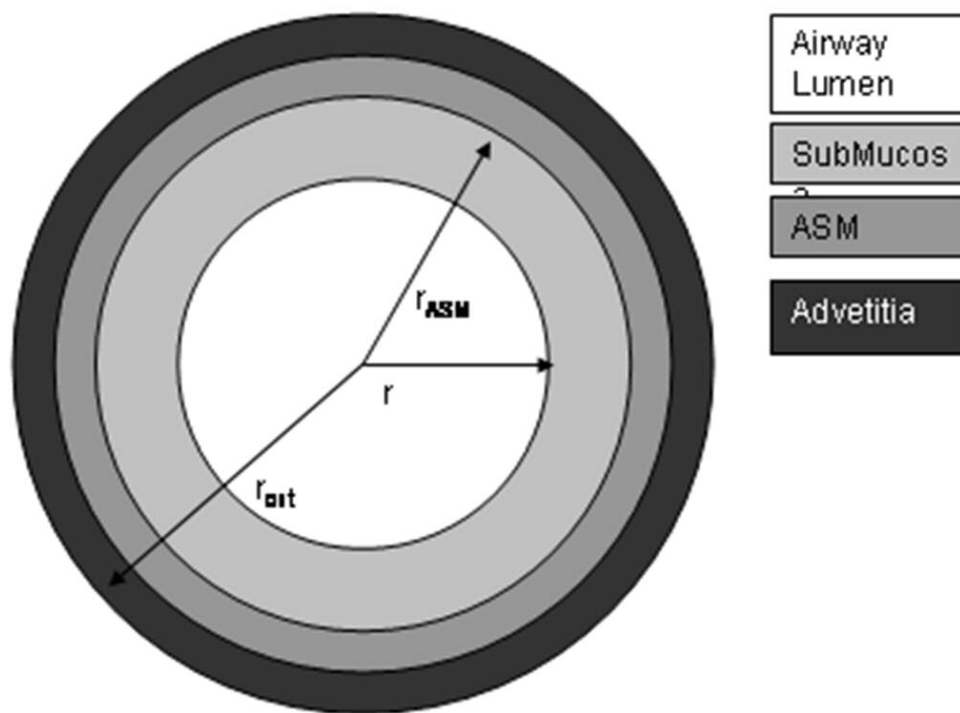


Figure 2: Schematic of an airway wall with relevant airway radii defined.

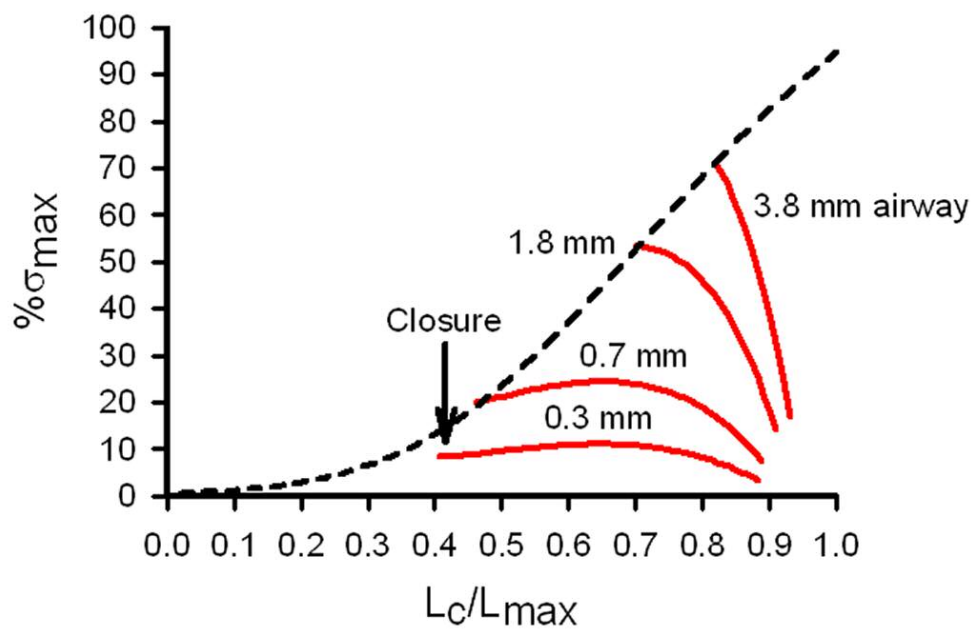


Figure 3: Relation of passive stress-length curve for ASM to stress-length developed during active constriction in four distinct airway generations. The black line represents the limiting stress as a function of $L_c/L_{\max}$, and the red lines represent model results of active airway constriction for 3.8, 1.8, 0.7, and 0.3 mm airway.

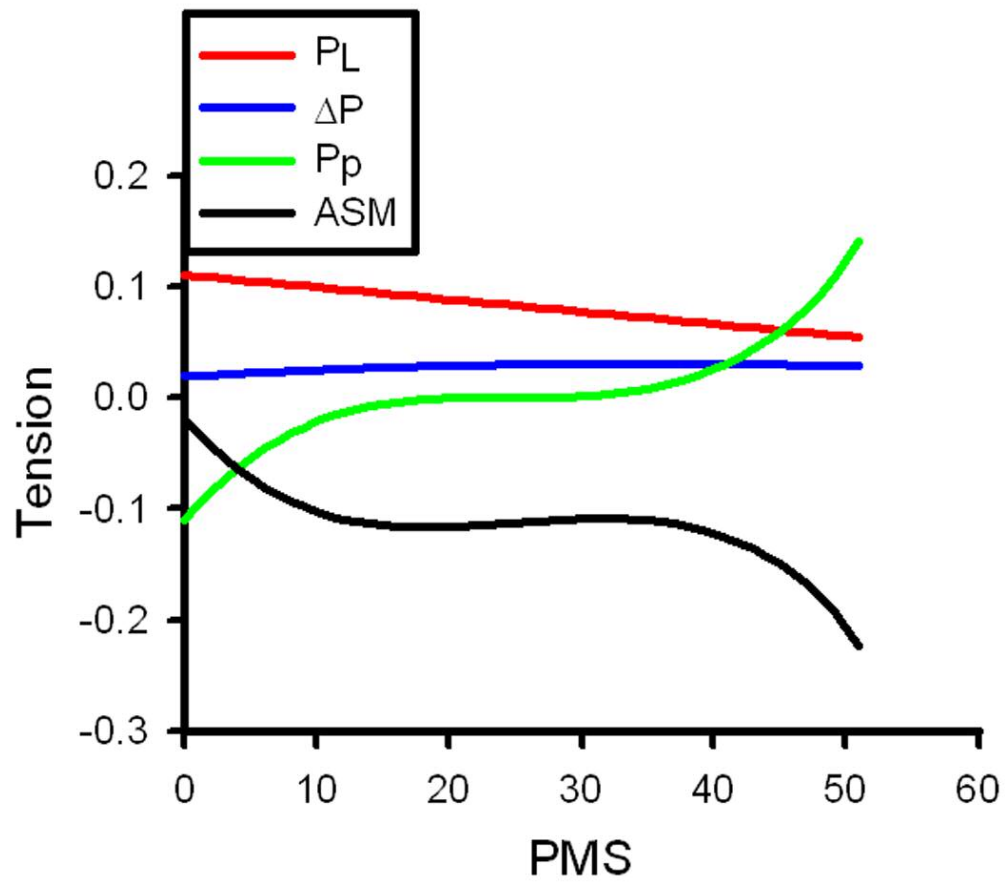


Figure 4: Individual tensions developed by pleural pressure, shearing of lung parenchyma, passive P-A characteristics of the airway wall, and ASM shortening as a function of PMS for a 3.8 mm airway.

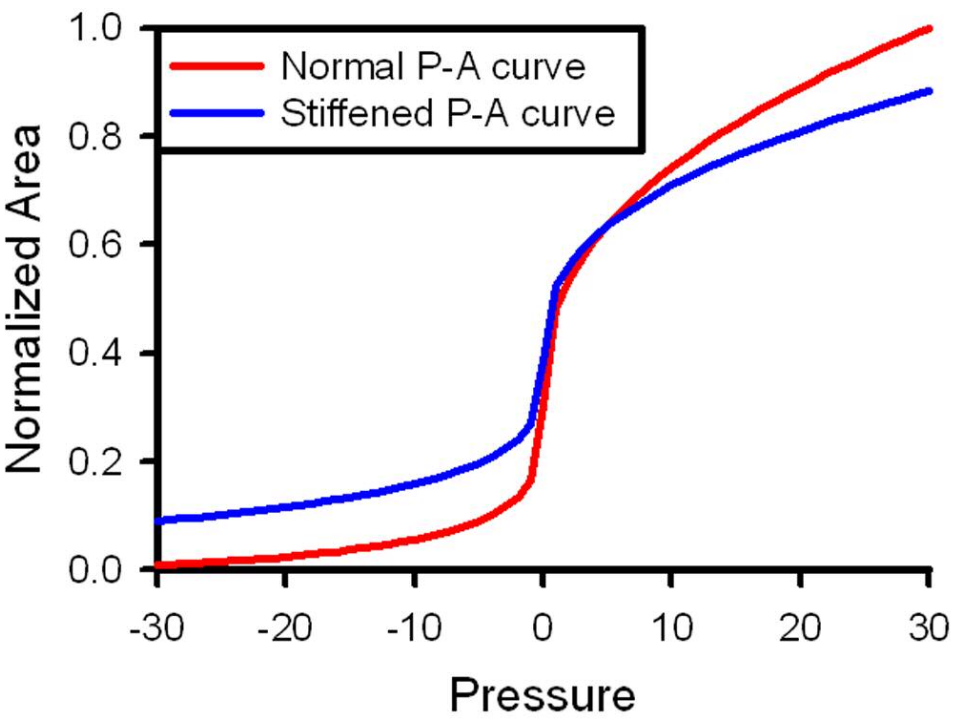


Figure 5: Pressure-Area characteristics for a normal airway and a stiffened airway (see eq. 4 in text)

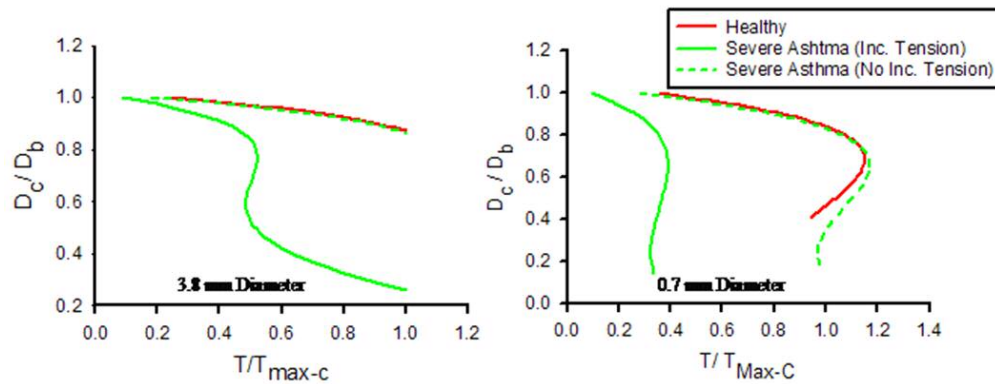


Figure 6: Airway Wall Thickening with and without Proportional Increased ASM Strength. Constricted diameter (D_c) normalized by baseline diameter (D_b) for a larger and peripheral airway as a function of active ASM tension (T) normalized by active ASM tension at maximum constriction ($T_{\text{max-c}}$). Healthy airways shown in red and severe asthmatic airways in green. Left: Central Airway (3.8 mm) Right: Peripheral Airway (0.7 mm). Airway wall thickness increasing for severe asthmatics as described by Kuwano et. al. (2). Solid line assumes asthmatic maximum ASM tension increases in proportion to increased ASM thickness while dashed line presumes no change in maximum ASM tension after ASM thickening.

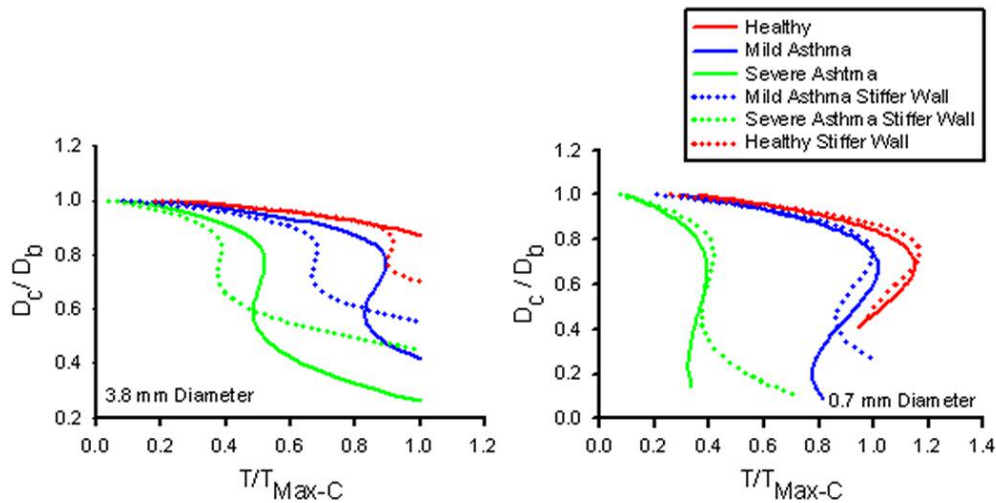


Figure 7: Effect of airway wall stiffening for a thickened asthmatic airway wall. On the left is a central airway (3.8 mm) on the right is a peripheral airway (0.7mm). Healthy airways are shown in red, mild to moderate asthmatics in blue, and severe asthmatics in green; Solid lines invoke baseline P-A curve while corresponding dotted lines invoke stiffer P-A curve from Fig. 5.

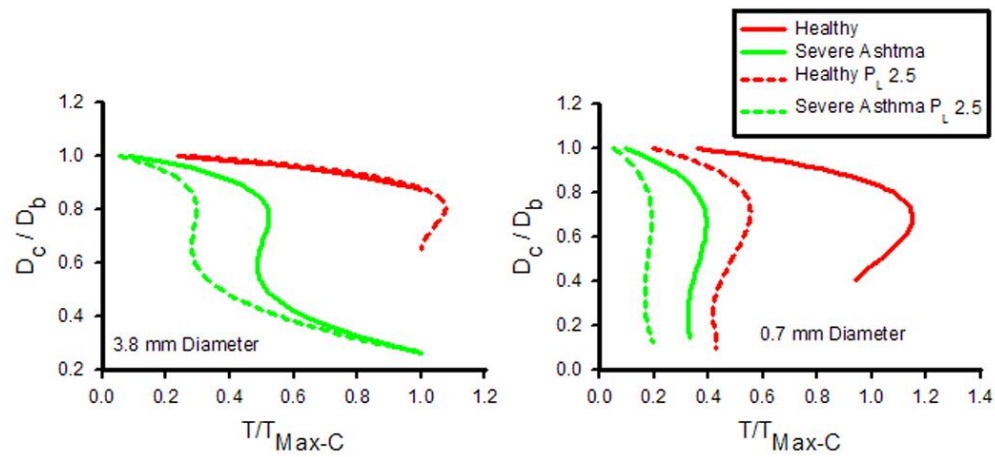


Figure 8: Effect of reduction of FRC on airway reactivity. On the left is a central airway on the right is a peripheral airway. Healthy airways are shown in red, and severe asthmatics are shown in green. Solid lines represent ASM stimulation from FRC ($P_{tp} = 5$ cm H₂O). Dashed lines show impact of ASM stimulation from a reduced lung volume ($P_{tp} = 2.5$ cm H₂O).

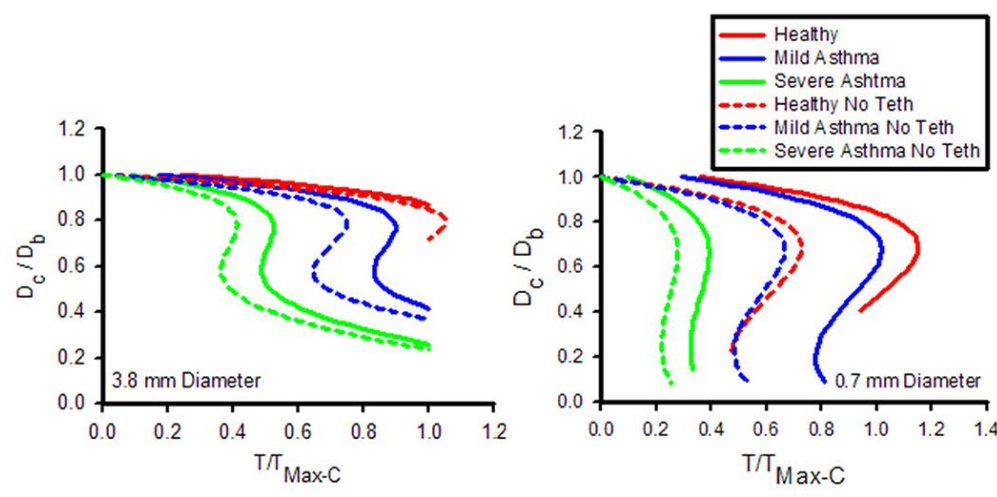


Figure 9: Effects of removing coupling effects between the airway wall and lung parenchyma. On the left is a central airway on the right is a peripheral airway. Healthy airways are shown in red, mild to moderate asthmatic airways in blue, and severe asthmatics in green. Solid lines represent the baseline cases with the shearing forces in play while dashed lines represent the case where shearing of local parenchyma is set to zero to represent decoupling of the lung parenchyma and airway adventitia.

D = 0.7 mm	Healthy	Mild Asthma	Severe Asthma
Sub Mucosa	0.024	0.036	0.052
ASM	0.006	0.011	0.019
Adventitia	0.053	0.064	0.120

D = 3.8 mm	Healthy	Mild Asthma	Severe Asthma
Sub Mucosa	0.061	0.160	0.214
ASM	0.011	0.038	0.082
Adventitia	0.140	0.241	0.458

Table I: Thickness, in mm, of each layer of the airway wall as a function of disease. Top peripheral airway, D=0.7mm. Bottom central airway D=3.8mm.