Numerical Simulation of the Effect of Smooth Muscle Layer Thickening on Stress Distribution in the Airway Wall

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Abstract: Many chronic respiratory diseases are associated with airway remodeling such as hyperplasia and/or hypertrophy of the smooth muscle cells. It is well known that the hyperplasia and hypertrophy of the smooth muscle cells directly affects the mechanical properties of the smooth muscle layer. Consequently, it may cause uneven distribution of stress and thus local stress stimulation of the cells and tissues in the airway wall, possibly leading to pathogenesis of airway dysfunction such as airway hyperresponsiveness. However, it is difficult to experimentally study the effect of smooth muscle layer on stress distribution in the airway wall. Therefore, in the present work, we built a finite element model which simplified the anatomical structure of the airway wall as a three-layer structure that included an inner wall layer, a smooth muscle layer and an adventitia layer. Based on this model, we varied the smooth muscle layer thickness either uniformly or locally and then computed the stress distribution in the modeled airway wall. The results revealed that the minimum stress occurred in the adventitia layer, and the maximum stress occurred in the smooth muscle layer. More importantly, the smooth muscle layer thickening, occurred either uniformly or locally, led to elevated stress level and enhanced stress concentration in the smooth muscle layer. And the enhancement of stress level and concentration was variable depending on the pattern of smooth muscle layer thickening. For a given extent of smooth muscle layer thickening, the stress level and concentration appeared to be determined by the number of locations and the separation distance between the locations at which the smooth muscle layer thickening occurred. In other words, the maximum stress level in the smooth muscle layer increased from 2.712kPa to 2.842KPa depending on whether the local thickening occurred at one location, 3 or 5 equally separated locations, 2 connected and 1 distanced location, or 3 all connected locations. These simulation results provide important insight for better understanding the mechanism through which the airway smooth muscle is involved in the alteration of airway dysfunction in health and disease, which may be helpful in developing novel diagnosis/therapy via targeting smooth muscle hyperplasia and/or hypertrophy for the prevention/treatment of asthma.

Keyword: Airway, Airway smooth muscle, Hyperplasia, Stress, Numerical simulation.

1. INTRODUCTION

Asthma is a common chronic airway disease, which affects over 300 million patients worldwide [1, 2]. However, the underlying mechanisms of asthma is still not fully understood. One of the most puzzling questions regarding asthma is why and how the asthmatic airways exhibits hyperresponsiveness, *i.e*. the asthmatic airways, when stimulated, contract too much and too easily, a phenomenon clinically known as airway hyperresponsiveness (AHR) [3]. At present, it is well known that asthmatic airways are associated with airway thickening mainly due to airway smooth muscle hyperplasia and/or hypertrophy. In addition to contribution to airway wall thickness, airway smooth muscle hyperplasia and/or hypertrophy directly influences the mechanical behavior of the airway wall including its ability to contract or relax [4]. Although it is generally recognized that the smooth muscle layer is the primary determinant of the mechanical behaviors of the airways, the detailed picture of how the smooth muscle layer affects the airway wall mechanics under either physiological or pathological conditions, still remains elusive. The reason for lack of such revelation is largely due to the lack of effective approach and technique to experimentally study airways containing smooth muscle layer either *in vivo* or *in vitro*. To overcome this difficulty, computational analysis may be employed as alternative approach. Especially, in the recent years, the computational power of both the computer hardware and the finite element analysis software are greatly advanced, together with the medical imaging techniques that are capable of obtaining highly realistic anatomical structures [5]. These advances make it possible to carry out accurate analysis of the time and space dependent variations of stress and strain in the airway wall in relation to the structural changes of the smooth muscle layer. For example, Laurence *et al* have reconstructed a three-dimensional model of the real airways from CT-scanned images, and thus analyzed the air flow field in the airways while simulating either the physiological or pathological airway narrowing [6]. On the other hand, Politi *et al*. proposed a multi-layer airway model to

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E-ISSN: 2409-3394/16

obtain constitutive equation of the airway soft tissues including the airway smooth muscle [7]. Based on these developments, here in this study, we established a numerical model of a three-layer airway wall model with simplified anatomical structure. Subsequently, we analyzed the stress distribution in the airway wall as the thickness of the smooth muscle layer was increased either uniformly or locally to simulate pathological structural remodeling of the airways in asthma.

2. MATERIALS AND METHODS

2.1. Numerical Model of the Airway Wall Geometry Structure

Figure **1** show the anatomical structure of a real cross-sectioned airway, which from the inside to the outside consists of several layers of different tissues including mucosal layer, submucosal layer, smooth muscle layer and adventitial layer. The mucosal layer is composed of a mucous membrane epithelium, a mucous cilia device and an intrinsic layer. The submucosal layer is formed by connective tissue. The outer layer is composed of cartilage and loose connective tissue. From the trachea to bronchial airways, the cartilage in the outer layer gradually disappears, and the smooth muscle layer gradually forms a complete circular band around the airway wall.

Considering that the cilia and other tissues of the inner wall are negligible in terms of the airway mechanical properties, we adopted a three-layer model of the airway wall according to the multi-layer structure model as proposed by Politi *et al.* [7]. In this simplified model, the airway wall is composed of an inner wall layer, a smooth muscle layer and an adventitial layer. Figure **2** shows a schematic diagram of the airway wall model, which satisfies the following relationship:

$$WA_{tot} = \frac{R_{outer}^{\ 2} - R_{lum}^{\ 2}}{R_{outer}^{\ 2}} \quad (1)$$

$$WA_{in} = \frac{R_{asm}^{\ 2} - R_{lum}^{\ 2}}{R_{outer}^{\ 2}} \quad (2)$$

$$WA_{out} = \frac{R_{outer}^{\ 2} - R_{adv}^{\ 2}}{R_{outer}^{\ 2}} \quad (3)$$

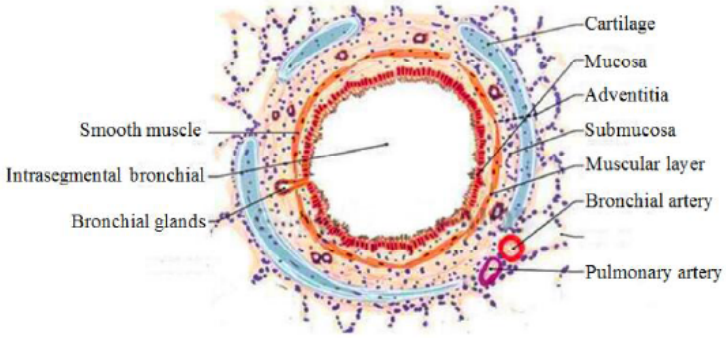

Figure 1: Cross-sectional diagram of typical airway wall structure [8].

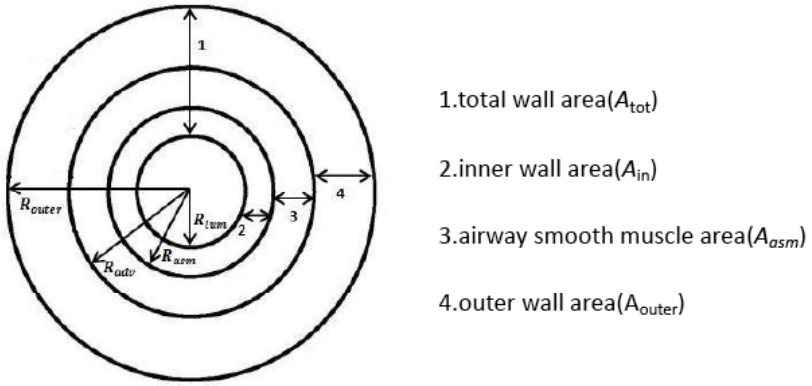

Figure 2: Schematic representation of traced airway radius and the area subsequently calculated.

According to the small airway geometry size as measured by Alan L. James *et al* [9], we got the airway lumen radius and the outer edge of smooth muscle layer radius, which are 0.2mm, 0.276mm respectively.

Under normal physiological conditions, the airway wall accounts for 0.65 proportion of the cross-sectional area of the airway wall and the proportion of inner layer is 0.38. According to Eq. 1-3, the radii of the outer wall layer, the airway smooth muscle layer and the lumen layer were calculated respectively to achieve the airway geometry parameters: R_{outer} =0.338mm, R_{adv} =0.276mm, R_{asm} =0.256mm, R_{lum} =0.2mm.

Based on the above described parameters, we established the geometrical model of the airway wall by using Solidworks software, and then imported the geometrical model into the ABAQUS software to analyze the stress in the airway in the case of 25mm H_2O pressure [7]. In this study we only focused on the effects of smooth muscle layer on the mechanical properties of the airway. Therefore, we completely fixed the outer wall of the airways in order to simplify the boundary conditions and exclude the effects due to the outer wall and the lung. The model was made up of tetrahedron elements, the total cell number was 90254, and the number of airway wall, smooth muscle layer and outer membrane unit was 13604, 59085, and 19365 respectively.

2.2. Materials Equation

In this model, each layer of the airway was regarded as an isotropic, incompressible hyper elastic material [10]. The strain energy function was expressed as left Cauchy-Green tensor B and invariants. The representation of its principal value was given as,

$$I_1 = \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \quad (1)$$

$$I_2 = \lambda_1^2\lambda_2^2 + \lambda_2^2\lambda_3^2 + \lambda_3^2\lambda_1^2 \quad (2)$$

$$I_3 = \lambda_1^2\lambda_2^2\lambda_3^2 \quad (3)$$

The strain energy function was further expressed as a series of infinite series as follows.

$$W(I_1, I_2, I_3) = \sum_{p,q,r=0}^{\infty} C_{pqr}(I_1 - 3)^p (I_2 - 3)^q (I_3 - 1)^r \quad (4)$$

Since the material was incompressible, the constant I_3 equaled to 1, and then the first order Neo-Hookean strain energy function was simplified as,

$$W(I_1, I_2) = C_1(I_1 - 3) \quad (5)$$

The material parameter of the airway wall was established by using the histology and tensile tests results as previously reported by Trabelsi and coworkers [11], and fitting the material with Neo-Hookean material model in the ABAQUS. The coefficient C_1 for the smooth muscle layer, the inner layer and the outer layer was set to 1MPa, 0.577MPa, and 0.577MPa, respectively.

3. RESULTS

3.1. The Effect of Uniform Thickening of the Smooth Muscle Layer on Stress Distribution in the Airway Wall

For healthy airways, the airway wall area accounts for 65% of the total airway cross section area [12]. For asthmatic airways, however, the airway wall area increases due to various reasons including thickening of the epithelial layer, hypertrophy and/or hyperplasia of the airway smooth muscle as well as enhanced deposition of extracellular matrix proteins, which all lead to thickening of both the inner layer and the smooth muscle layer.

In order to evaluate the effect of the smooth muscle layer thickening on the mechanical properties of the airway wall, we first assumed that the smooth muscle layer thickened uniformly, resulting in four different geometries of the airway wall with WA_{tot} = 0.65, 0.7, 0.75, 0.8, respectively, and the corresponding airway geometric parameters were shown in Table **1**.

Then we simulated the stress distribution in each of these four cases. Figure **3** displays the stress distribution map in the three-layer airway wall when the airway wall area increased by 10% from the normal value (WA_{tot} = 0.75 vs. 0.65). In overall, the results show that the stress varied across the airway wall when a pressure due to physiological airflow was applied to the inner side of the airway wall. Nevertheless, the stress appeared to concentrate in the smooth muscle layer. This phenomenon of stress concentration was most likely due to the fact that the smooth muscle layer was composed of muscle fiber whose mechanical strength was much greater than that of the connective tissue that composed the other layers of the airway. Therefore, in the smooth muscle layer both the magnitude of stress and the extent of stress concentration increased with the smooth muscle layer thickening.

Table 1: Increase of the Airway Wall Area (WA_{tot}) and the Thickness of the Smooth Muscle Layer

WA_{tot}	0.65	0.7	0.75	0.8
R_{lum}	0.2	0.185	0.169	0.151
R_{asm}	0.256	0.248	0.240	0.232
R_{adv}	0.276	0.270	0.270	0.260
R_{outer}	0.338	0.338	0.338	0.338

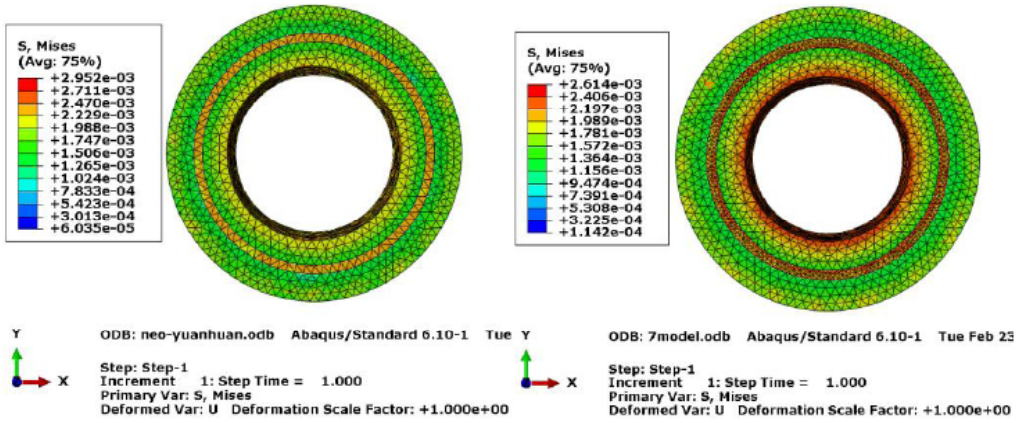

Figure 3: Stress distribution contour in the three-layer airway wall when WA_{tot} =0.65, WA_{tot} =0.75.

3.2. Effect of Local Thickening of the Smooth Muscle Layer on Stress Distribution in the Airway Wall

Unlike the above cases in which the smooth muscle layer thickened uniformly, in the case of acute asthma, the smooth muscle layer often thickens non-uniformly because the hyperplasia of the smooth muscle cells can occur randomly in different locations along the airway smooth muscle layer due to the local condition of airway inflammation. In order to evaluate how localized thickening of the smooth muscle layer would affect the stress distribution in the airway wall, we assumed that the smooth muscle layer thickened by 10% of its area but the thickening occurred locally in different patterns as shown in Figure **4** and **5**. Then we evaluated the stress distribution in each case of the smooth muscle thickening patterns in the airway wall, namely the total 10% area increase of the smooth muscle layer occurring in either one location as shown Figure **4**(**b**), in **3** or **5** locations equally distributed along the smooth muscle layer as shown in Figure **4**(**c**) or **4**(**d**), in 3 locations that were all connected as shown in Figure **5**(**c**), or in **2** connected locations and 1 distanced location as shown in Figure **5**(**b**), or **3** equally distanced locations as shown in Figure **5**(**a**).

The simulation results indicate that when the local thickening occurred in one location, the stress concentration occurred at the top and adjacent region of the thickened part of the smooth muscle layer, with the maximum stress value in the smooth muscle layer increasing from 2.229KPa to 2.727KPa, by 22.3% (Figure **4**(**b**) vs. **4**(**a**)). In contrast, the maximum stress value in the smooth muscle layer increased to 2.747KPa, and 2.765KPa, respectively, when the local thickening occurred in 3 or 5 equally distributed locations, respectively (Figure **4**(**c**) or **4**(**d**) vs. **4**(**a**) or **4**(**b**)).

When the local thickening occurred in 3 equally distanced locations, the maximum stress value in the smooth muscle layer was 2.712KPa (Figure **5**(**a**)). When the local thickening occurred in 2 connected locations with 1 distanced location, the maximum stress value of the smooth muscle layer is 2.737KPa (Figure **5**(**b**)). When the local thickening occurred in 3 all connected locations, the maximum stress value was 2.842KPa (Figure **5**(**c**)).

4. DISCUSSION AND CONCLUSION

Airway smooth muscle is an important part of the respiratory tract. Since the structure is known to be

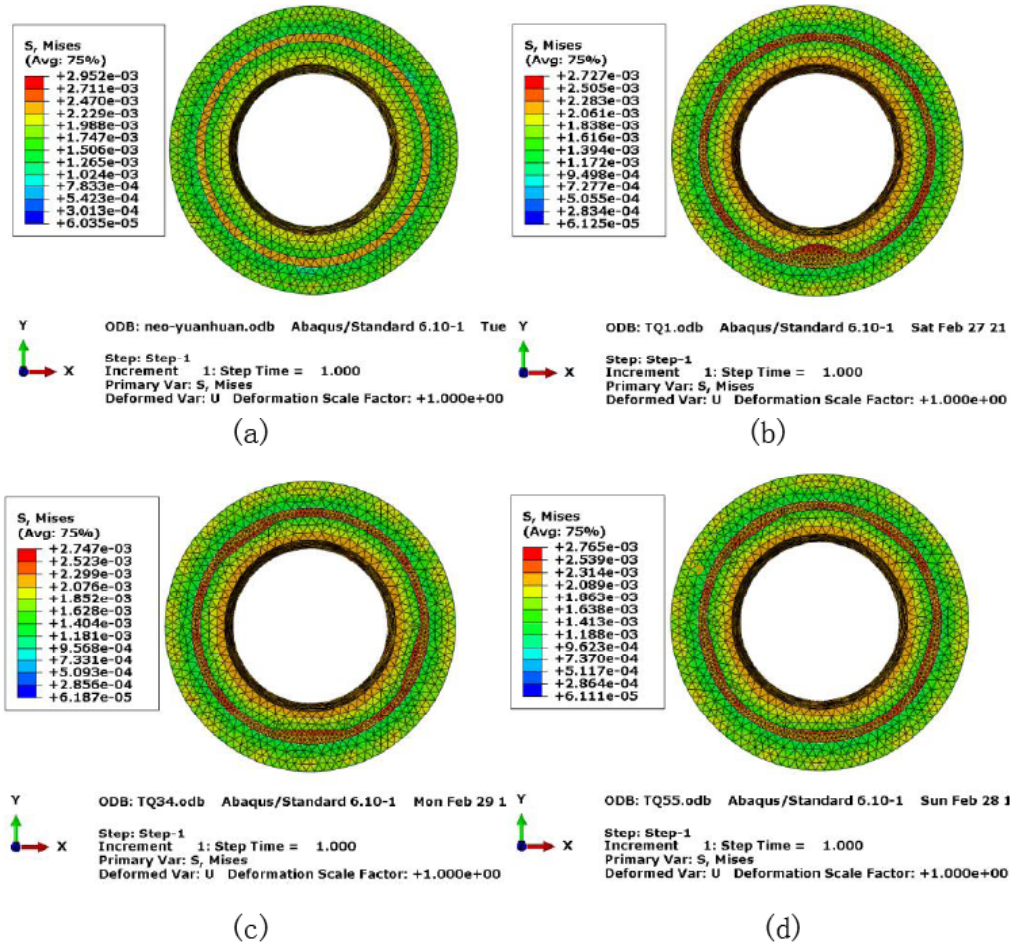

Figure 4: Effect of the number of local thickening of the smooth muscle layer on the stress distribution in the airway wall. (**a**) in the absence of local thickening, (**b** to **d**) local thickening at 1, 3, 5 locations, respectively.

closely related to its functions, any alteration of the smooth muscle layer must have important effect(s) on the function, particularly the mechanical properties of the airways. In chronic airway disease such as asthma, it is well known that the volume of the airway smooth muscle increases drastically, probably due to the smooth muscle cell hypertrophy and/or hyperplasia induced by inflammation and other pathological conditions [13]. Thus the smooth muscle layer thickens, which ultimately leads to alteration of the mechanical properties of the airway wall.

In the present study, the effect of the smooth muscle layer thickening on the stress distribution in the airway wall was evaluated by a computational simulation approach. We first adopted a three-layer structure model for the airway wall, then analyzed this airway wall model using finite element method for the variation of stress distribution in the airway wall when the smooth muscle layer thickness was artificially increased in various patterns to mimic different types of smooth muscle hyperplasia/hypertrophy. Our simulation results demonstrated that the stress value in the three-layer airway wall ranged from 2.229KPa to 2.842KPa, which was in the same order of magnitude of stress value (3KPa) for tracheal smooth muscle as reported by Teng *et al* who studied the mechanical properties of the smooth muscle by uniaxial tension (<10 % stretch) [14, 15]. Such agreement between the experimental results and the stimulation results confirms that the simulation method used in this study is satisfactorily reliable and accurate, at least for the analysis of stress value and distribution.

Furthermore, the simulation results indicate that the overall stress level in the smooth muscle layer increased as the thickness of the smooth muscle layer, which is likely to stiffen the smooth muscle layer as well as well. Therefore, the stress and thickness of the smooth muscle layer are positively correlated. On the other hand, stress is known to promote airway smooth muscle cell hypertrophy and hyperplasia, and thus is likely to further enhance thickening of the smooth muscle layer, resulting in a positive feedback to

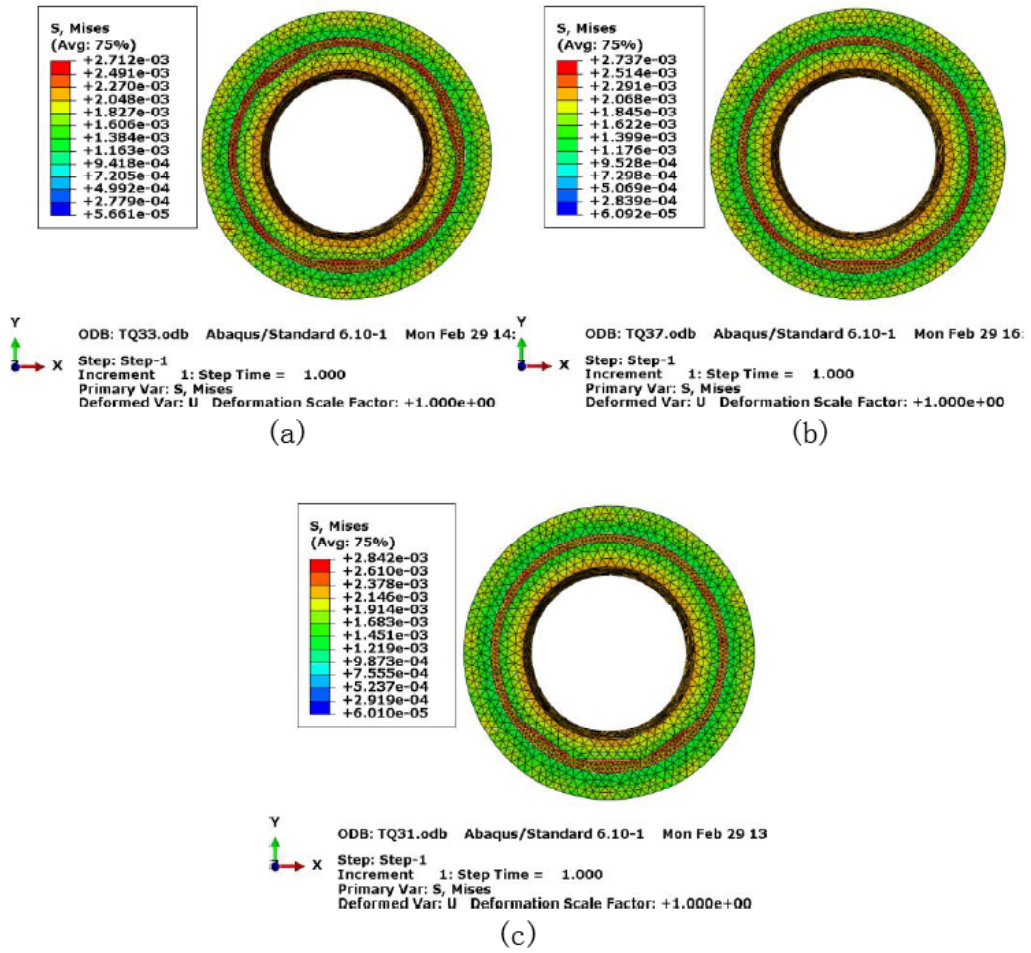

Figure 5: Effect of the local thickening separation on the stress distribution in the airway wall. (**a**) local thickening at 3 equally distanced locations, (**b**) at 2 connected and 1 distanced locations, (**c**) at 3 all connected locations.

deteriorate the thickening of the airway wall. This positive feedback mechanism may be conducive to the pathological tissue remodeling and hyperresponsiveness of the airways.

Interestingly, our simulation results also indicate that the effect of smooth muscle layer thickening on the stress distribution was also dependent on the pattern of the local thickening. Generally speaking, when compared to the same amount of smooth muscle layer thickening, the number of locations and the distance between the locations become secondary determinants of the stress value and distribution in the airway wall. The more locations at which the thickening occurs, and the more closely connected were the local thickening locations, the greater value of the stress was induced in the smooth muscle layer, suggesting effective interactions between the localized spots of airway smooth muscle associated with hyperplasia and/or hypertrophy.

However, there are clear limitations to the present study, which may be addressed in future. These include, but not limited to, that: 1) the structure of the three-layer airway wall model is overly simplified as compared to the real airway structure, 2) all the materials in the three-layer airway wall model were considered as linear hyper-elastic, which is remarkably different from the real airway tissues that are highly deformable and nonlinear viscoelastic soft materials. Therefore, future studies need to focus on development of more realistic models of the airway wall by incorporating geometrical feathers and mechanical properties that are as close as possible to those of the real airways *in vivo*.

In summary, smooth muscle hyperplasia and/or hypertrophy is known to be involved in alteration of the mechanical properties of the airways, which generally imposes a negative impact on the airway function. Based on our present numerical study, we further revealed that the thickening of the smooth muscle layer

due to hyperplasia/hypertrophy elevated the stress level and enhanced stress concentration in the smooth muscle layer. Moreover, the enhancement of stress level and concentration was variable depending on the pattern of smooth muscle thickening. These findings not only provide important insight as regards the role of smooth muscle layer in regulation of airway function in both health and disease, but also may be very useful in exploration of novel therapeutic approach to target smooth muscle hyperplasia and/or hypertrophy for prevention/treatment of asthma.

ACKNOWLEDGEMENT

This study was support by National Natural Science Foundation of China (Grant No. 11532003, 11402037).

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Received on 08-04-2016 Accepted on 19-04-2016 Published on 30-04-2015

http://dx.doi.org/10.15379/2409-3394.2016.03.01.02