



Tracheal compliance and limit flow rate changes in a murine model of asthma

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Trachea is the unique passage for air to flow in and out. Its tone is of importance for the respiration system. However, investigation on how tracheal tone changes due to asthma is limited. Aiming at studying how the mechanical property changes due to asthma as well as the compliance and flow limitation, the following methods are adopted. Static and passive pressure-volume tests of rats' trachea of the asthmatic and control groups are carried out and a new type of tube law is formulated to fit the experimental data, based on which changes of compliance and limit flow rate are investigated. In order to give explanation to such changes, histological examinations with tracheal soft tissues are made. The results show that compliance, limit flow rate and material constants included in the tube law largely depend on the longitudinal stretching ratio. Compared with the control group, the tracheal compliance of asthmatic animals decreases significantly, which results in an increased limit flow rate. Histological studies indicate that asthma can lead to hyperplasia/hypertrophy of smooth muscle cells, and increase elastin and collagen fibres in the muscular membrane. Though decreasing compliance increases stability, during the onset of asthma, limit flow rate is much smaller due to the lower transmural pressure. Asthma leads to a stiffer trachea and the obtained results reveal some aspects relevant to asthma-induced tracheal remodelling.

trachea, asthma, collapse, tube law, compliance, limit flow rate, remodelling

Asthma is a chronic inflammatory disorder that results in recurrent episodes of reversible airflow obstruction, being a major cause of chronic illness throughout the world^[1]. The most important functional disturbance in asthma is increasing resistance to airflow. The associated mechanisms, which are primarily attributed to changes in the resistance of large and medium-sized airways^[2], include (1) decrease of the physical dimensions of the airways as a consequence of bronchoconstriction; (2) luminal narrowing due to airway wall edema; and (3) luminal obstruction resulting from hypersecretion of mucus^[3]. Those definitely change the tone of the airway, such as its compliance, and affect limit flow rate. Many studies have been carried out to analyze how resistance, compliance and limit flow rate change due to asthma^[4–9]; however, most reports focus

on the whole respiration system or peripheral airway, and only a few studies on these aspects relevant to central airway.

Though trachea is a big tube fairly rigid with muscles connecting a group of cartilage rings, when negative transmural pressure happens, the flattening cartilage may lose its curvature and the deformable muscles get loose and floppy, and droop down into cartilage causing an occlusion. In normal conditions, trachea does not constrict to closure even when maximally stimulated^[10], and most asthmatic patients do not exhibit flow limitation during resting breathing^[4]. Moreover, compared

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with large airways, bronchi are more vulnerable by extra stimuli and pathological changes are more prominent^[11]. But when the state of illness becomes severe, the closure may nearly occur, which can be observed in some quadruped mammals^[12]. Though the closure has not been observed commonly, tracheal collapse and limited flow indeed happen in the central airway during the stable period of asthmatic humans^[5], as well as during resting breathing in patients with chronic obstructive pulmonary disease^[13,14]. Being the unique passage for airflow, tracheal tone may affect the bio-function of the whole respiration system, especially when collapse is located in trachea.

Many experimental tests have been reported^[10,15–17] with the aim of obtaining airway pressure-volume (p - V) curves, which is recognized as the most efficient way to study the mechanical properties of airways. In this paper, static p - V tests of trachea in a series of longitudinal stretching ratios (LS-ratio) were carried out both in control and ovalbumin-induced asthmatic murines. A new form of tube law was proposed to fit the p - V data, based on which compliance and flow limitation were studied. Our aim is to investigate how compliance changes due to asthma and the further affection on maximal flow rate after collapse. In addition, we also analyzed how LS-ratio affects those parameters. In order to combine those changes with structural remodeling, histological examination on the components of the tracheal muscular membrane (smooth muscle cells, elastin fibre and collagen fibre) was also conducted.

1 Materials and methods

1.1 Materials and pressure-volume (p - V) tests

Murine model of asthma is well known that exhibits a TH2-lymphocyte driven eosinophilic pulmonary inflammation and airway hyper-responsiveness, which is an important feature of human asthma. This animal model has been shown to be an excellent tool to test hypotheses associated to the different mechanisms of asthma^[18–21]. In this study, 15 male Sprague Dawley mice weighing 150–200 g were used, eight asthmatic and seven for control. The animals designated as asthmatic were sensitized with a subcutaneous injection of 1 mL 0.9% NaCl solution containing 100 mg ovalbumin (OVA), 100 mg Al(OH)₃ and 5×10^9 unit of deactivated

hemophilus pertussis. Two weeks later, they were served 1 min of 2% OVA aerosol once per day to induce asthma. The procedure for the control group was the same, but only with 0.9% NaCl solution.

After 15-day's inducing, animals were sacrificed with over-dose pentobarbital sodium. The trachea, from larynx to bifurcation, was removed and immersed in thermostatic bath at atmospheric pressure filled with saline solution, whose temperature was controlled at 23°C by a dipped auto-controlled heater. Meanwhile the length (L) between the rings below the larynx and above the bifurcation *in vivo* with supine position was measured and the one in rest, L_0 , was also recorded to determine the tracheal LS-ratio *in vivo* (L/L_0). The specimen was mounted on an apparatus to make p - V tests following the protocol in a previous study^[10]. Usually the bio-function of living tissues varies with LS-ratio^[22,23]. To establish the effects of this variable, tests with different LS-ratios (indicated by λ_z) were performed. Briefly, for each LS-ratio, the saline solution was pumped into the trachea slowly to vary the transmural pressure from -50 to 10 mmHg (1 kPa=7.5 mmHg), at the same time, the signals of pressure and the volume pumped in were measured by a pressure sensor (TP3, AEP, Italy) and a displacement sensor (LVDT, SX 20 ME $\times$ 200, Sensorex, France), and subsequently stored in the computer digitally through an A/D card (NI PCI-6013, National Instruments, USA). For each LS-ratio, the preconditioning was made 3 times with pressure varying from -30 to 5 mmHg, and then the test was repeated 3 times, with each loading taking 1 min. Before carrying out the tests, the overall compliance of the apparatus (replacing the specimen with a stiff glass tube) was measured by applying a pressure ranging from 20 to -80 mmHg. The compliance of the testing system is 0.117×10^{-4} mL/mmHg. It was taken into account when p - V data were processed.

After the mechanical test, the muscular membrane of the lower part of the trachea was harvested and fixed in formalin solution, and then embedded in paraffin for histological examination. Multiple cross sections of 3–5 μ m in thickness were obtained. Twenty sections were stained following a previously described technique^[24], ten were stained with Verhoeff elastic staining, which caused the elastic fibers to appear dark purple or black, and the rest were stained with Van Gieson's, which col-

ored the collagen fibers pink and nucleolus dark.

1.2 Tube law, compliance and limit flow rate

For the tube law of collapsible tubes, segmented exponent-type functions and amended exponent-type functions have been suggested^[25,26]. Polynomial functions have also been used to fit the tracheal transmural pressure and cross-sectional area curve^[5]. However, when transmural pressure covers a positive and negative range, the tracheal p - V curve forms an ‘arctan’ shape. The function

$$v = \frac{V}{V_0} = a_1 \arctg(a_2 p + a_3) + a_4 \quad (1)$$

could fit experimental data very accurately in a wide pressure range. In eq. (1), V denotes the tracheal volume change per unit length and V_0 means the one at rest, p is the transmural pressure and a_i ($i=1, \dots, 4$) are material constants, which will be determined by fitting experimental data. From the definition of compliance, we get

$$C = \frac{dv}{dp} = \frac{a_1 a_2}{1 + (a_2 p + a_3)^2}. \quad (2)$$

From the above equation, when $a_2 p + a_3 = 0$, C reaches the maximum value, that is, when

$$p = p^* = -\frac{a_3}{a_2}, \text{ then } C|_{p=p^*} = C_{\max} = a_1 a_2. \quad (3)$$

With $p=0$, we get zero pressure compliance, which is a more commonly used parameter, since it is independent of extra loading and reflects an intrinsic mechanical property.

$$C|_{p=0} = C_0 = \frac{a_1 a_2}{1 + a_3^2}. \quad (4)$$

If flow in the trachea is assumed to be ideally laminar, and the conception of wave velocity in an elastic tube is introduced, when a negative transmural pressure collapses the trachea, limit flow rate is governed by^[27]

$$q_{\max} = \frac{Q_{\max}}{A_0} = \frac{A}{A_0} \sqrt{\frac{V}{\rho} \frac{dp}{dV}} = v \sqrt{\frac{v}{\rho C}}, \quad (5)$$

where ρ is the air density, A denotes the cross section area and A_0 is its value at rest, both of which can be replaced by V and V_0 , respectively. A_0 does not vary with p , thus $q_{\max}$ does not reflect the local mean velocity. Though it has the dimension of velocity, $q_{\max}$ associates with flow. That is why it is called limit flow rate in this paper. The densities of mercury (Hg) and air are 13.6 and 1.2×10^{-3} g/mL, respectively, and the gravity acceleration is approximated by 1000 cm/s^2 . From eq. (1), the

relationship between limit flow rate, pressure and material constants can be rewritten as

$$q_{\max} = \frac{[a_1 \arctg(a_2 p + a_3) + a_4]}{\sqrt{\frac{[a_1 \arctg(a_2 p + a_3) + a_4]^2 [1 + (a_2 p + a_3)^2]}{a_1 a_2 \rho}}}. \quad (6)$$

In turn, the meaning of a_i ($i=1, \dots, 4$) can also be compared with mechanical parameters as follows. When $p=0$, v should be 1, that is,

$$a_1 \arctg(a_3) + a_4 = 1. \quad (7)$$

Theoretically when $p \rightarrow -\infty$, trachea collapses completely, that is $V = 0$, which results in

$$\frac{\pi}{2} a_1 + a_4 = 0. \quad (8)$$

From eqs. (3), (4), (7) and (8) the mechanical meaning of the material constants included in the tracheal tube law become clear.

$$\begin{aligned} a_1 &= \frac{-1}{\arctg \sqrt{\frac{C_{\max}}{C_0} - 1} + \frac{\pi}{2}}, \\ a_2 &= -C_{\max} \left(\arctg \sqrt{\frac{C_{\max}}{C_0} - 1} + \frac{\pi}{2} \right), \quad a_3 = \pm \sqrt{\frac{C_{\max}}{C_0} - 1}, \\ a_4 &= \frac{\frac{\pi}{2}}{\arctg \sqrt{\frac{C_{\max}}{C_0} - 1} + 1}. \end{aligned} \quad (9)$$

2 Results

We assume that when transmural pressure is lower than -40 mmHg , trachea collapses completely, which is supported by the experimental fact; when the transmural pressure changes from -30 to -40 mmHg , the volume change is less than 5% of the one from 0 to -30 mmHg (see the data points in Figure 1). And numerical results reported by Costantino et al.^[28] also showed that except for rings close to the larynx, a transmural pressure of -30 mmHg is low enough to make the tracheal posterior membrane close to the inner wall of cartilage, and the inside volume becomes negligible. Statistical results in this study were performed in SPSS10. It is also convenient to point out that if there is no special notation, the legends in figures marked by ‘A’ denotes the data of asthmatic specimens and ‘C’ refers to the control group.

2.1 Regression results

As shown in Figure 1, eq. (1) fits the experimental

data points very well for the different LS-ratios. As an example, the regression results of subject n1-6 are listed in Table 1. The standard deviations of a_1 , a_2 and a_4 are quite small, less than 10% of their mean values, indicating the 3 tests repeated very well. Table 1 also shows that a_i ($i=1, \dots, 4$) vary largely with the LS-ratio. Furthermore, the variation of a_i ($i=1, \dots, 4$) with λ_z is visualized in Figure 2 with the comparison between asthmatic and control groups. Except for a_2 the difference of a_i ($i=1, 3, 4$) between two groups is not big, though there are significant differences in the value of a_1 for λ_z being 1.5 and 1.6. It can be seen from eq. (9) that a_i ($i=1, 3, 4$) are associated with the ratio of $C_{\max}$ to C_0 , thus the change of $C_{\max}$ due to asthma should be similar to the one of C_0 . On the contrary, a_2 decreases prominently in the asthmatic group, especially when λ_z being 1.2~1.7. From the mechanical meaning of a_2 , this tendency predicts the compliance of asthmatic subjects will be lower than that of the non-asthmatic ones, which will be discussed in detail in the following section.

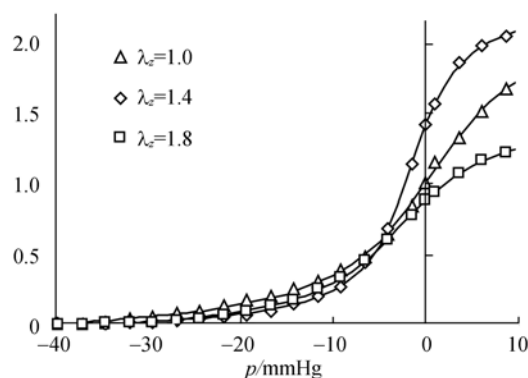


Figure 1 Experimental p - V data points for different LS-ratios and the corresponding regressed curves of subject n1-6.

2.2 Compliance and limit flow rate

It is well known that asthma results in stiffer peripheral airways and decreases the distensibility^[8,9,29,30]. The result from our murine model indicates the fact that asthma also reduces central airway distensibility. The change of compliances is visualized in Figure 3. Both maximal compliance and zero pressure compliance of asthmatic animals are smaller than those of control, especially at the interval of $1.2 \leq \lambda_z \leq 1.7$. The decrease of C_0 reflects that remodeling due to asthma makes trachea stronger in order to have a higher resistance to a negative transmural pressure.

Compliance, one of the most important mechanical properties, is closely associated with tracheal structure. Collapse does not only increase the resistance to air flow, but also increase the stress in tracheal muscle and cartilage^[28]. This changed mechanical environment leads to living tissue remodeling^[22, 31, 32, 45] characterized by changes in the structure of the tissue. Though there are many extra stimuli contributing to tracheal remodeling, stress is one of the important factors. In order to figure out the correlation between compliance and microstructure, the tracheal muscle was isolated to make histological examinations (only the part near the bifurcation was used). The results are listed in Table 2 (optical densities of collagen and elastin fibres, and the thickness of smooth muscle cells in cross section were measured). The amount of elastin fibre, collagen fibre and smooth muscle cell in the asthmatic group increased significantly. Those changes are in a good agreement with the mechanical changes due to asthma.

Table 1 Material constants of subject n1-6 for different LS-ratios (mean $\pm$ SD)

λ_z	a_1	a_2 (1/mmHg)	a_3	a_4
1.0	0.7006 $\pm$ 0.0219	0.1604 $\pm$ 0.0178	0.0100 $\pm$ 0.0589	0.9950 $\pm$ 0.0275
1.1	0.6888 $\pm$ 0.0085	0.2000 $\pm$ 0.0083	0.3266 $\pm$ 0.0162	1.0086 $\pm$ 0.0135
1.2	0.6981 $\pm$ 0.0239	0.2226 $\pm$ 0.0228	0.3289 $\pm$ 0.0276	1.0213 $\pm$ 0.0335
1.3	0.6790 $\pm$ 0.0263	0.2532 $\pm$ 0.0178	0.3603 $\pm$ 0.0178	0.9908 $\pm$ 0.0384
1.4	0.6370 $\pm$ 0.0240	0.2966 $\pm$ 0.0124	0.3749 $\pm$ 0.0347	0.9310 $\pm$ 0.0340
1.5	0.6225 $\pm$ 0.0141	0.2930 $\pm$ 0.0165	0.3867 $\pm$ 0.0132	0.9099 $\pm$ 0.0224
1.6	0.5769 $\pm$ 0.0233	0.2964 $\pm$ 0.0155	0.4639 $\pm$ 0.0290	0.8368 $\pm$ 0.0376
1.7	0.5432 $\pm$ 0.03256	0.2518 $\pm$ 0.0149	0.4652 $\pm$ 0.0312	0.7836 $\pm$ 0.0521
1.8	0.4711 $\pm$ 0.0217	0.1517 $\pm$ 0.0073	0.3325 $\pm$ 0.0305	0.6425 $\pm$ 0.0301

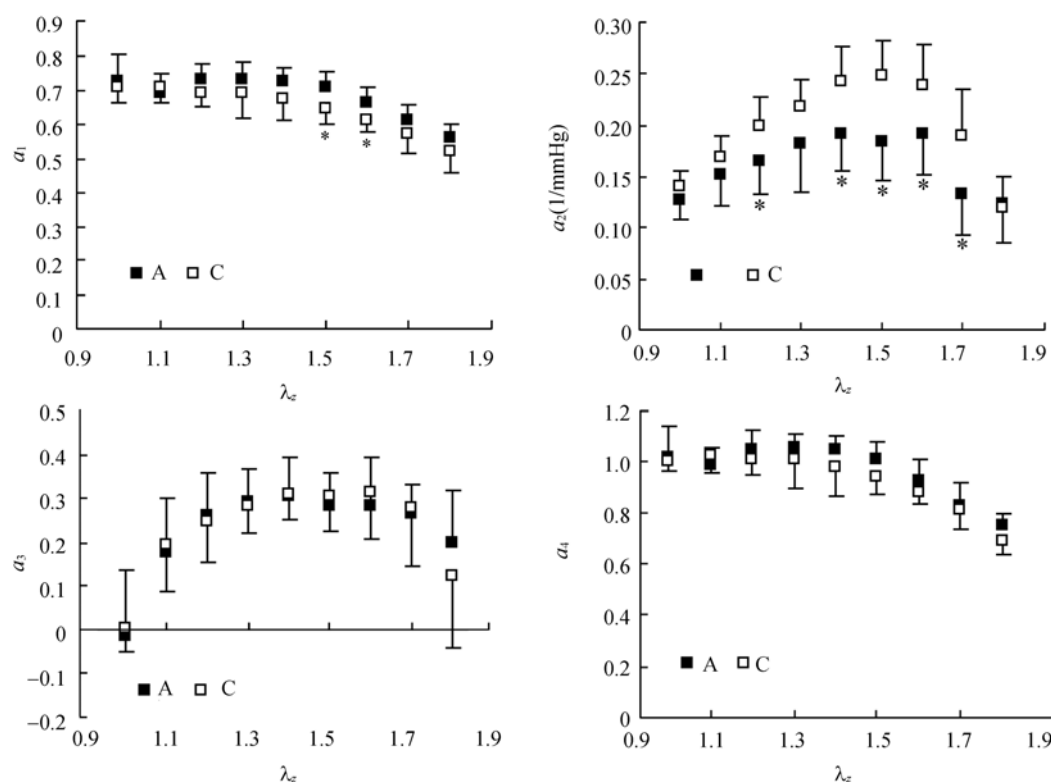


Figure 2 Comparisons of material constants between asthmatic and control groups. * means significant difference ($P < 0.05$); A, results from asthmatic specimen; C, control specimen.

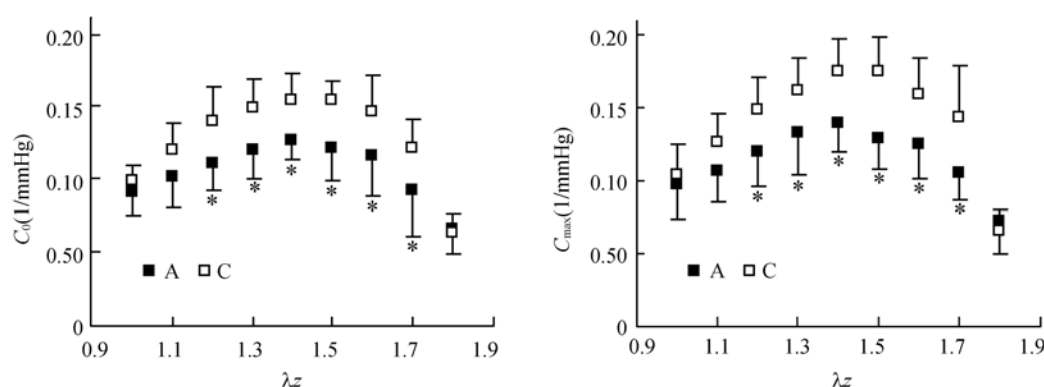


Figure 3 Comparisons of compliances between asthmatic and control groups. * means significant difference ($P < 0.05$); A, results from asthmatic specimen; C, control specimen.

Table 2 Comparisons of components in tracheal muscle between asthmatic and control groups

	Elastin fibres*	Collagen fibres*	Smooth muscle cells* (μm)
Asthma	0.49 ± 0.02	1.17 ± 0.21	211.00 ± 35.70
Control	0.30 ± 0.07	0.86 ± 0.06	182.00 ± 33.46

* means significant difference ($P < 0.05$)

The change in compliance will finally affect limit flow rate. The values of limit flow rate with different local

transmural pressure and different LS-ratio are plotted in Figure 4. As long as a negative transmural pressure appears, from 0 to -30 mmHg, limit flow rates of the asthmatic group are always larger than those of control. Typically when λ_z ranges from 1.2 to 1.7, there are significant differences (see figure 4). This phenomenon can be predicted from the changes of compliance and tissue structure, because trachea in asthmatic animals is stiffer and the distensibility is smaller (eq. (5)).

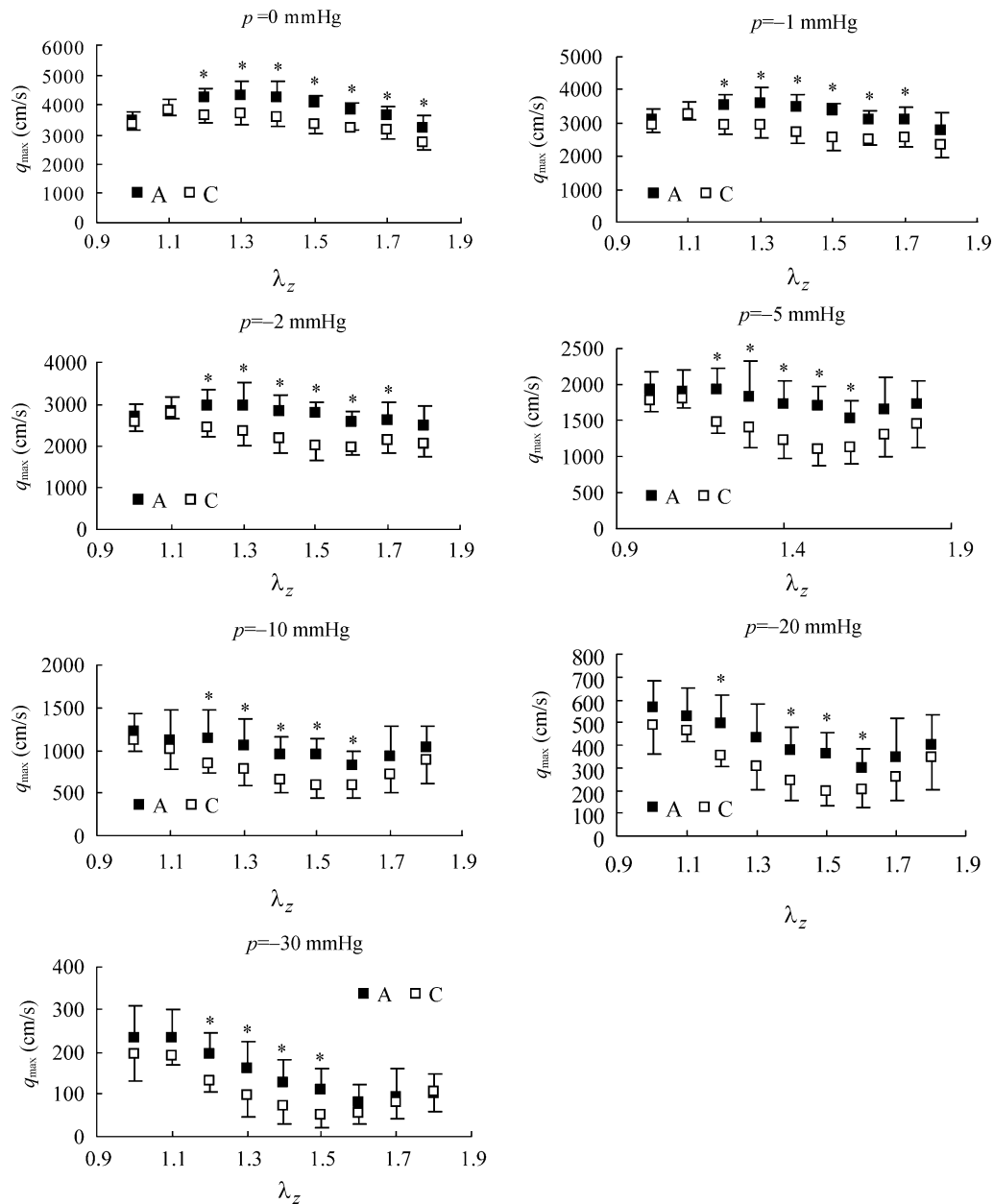


Figure 4 Comparisons of limit flow rate under different local transmural pressure between asthmatic and control groups. * means significant difference ($P<0.05$); A: results from asthmatic specimen; C: control specimen.

tells that the limit flow rate has a positive relationship with the 1.5-order of cross section area and negative with the square root of compliance. When the transmural pressure is negative, the remaining internal area of asthmatic animals is bigger than that of control; additionally the value of compliance is also smaller. Those two factors lead to a higher limit flow rate in asthmatic subjects when the local transmural pressure is the same.

3 Discussion

In this study, an inverse cotangent function has been proposed as a tube law for collapsible trachea. The regression results suggest that it is an ideal function to describe the relationship between transmural pressure and tracheal volume (see Figure 1). Furthermore, in the regression results, material constants rely little on the initial guessed values. Results do not change when initial

values increase or decrease 10 times. The material constants included in the tube law can be explained in terms of compliance, as has been expressed in eq. (9). From those expressions, theoretically, $a_4 = -\pi/2a_1$ (eq.(8)), however the results listed in Table 1 or plotted in Figure 2 do not meet this relationship exactly which should be due to the diversity between the theoretical solution and experimental data. If the tube law is forced to meet this restriction, the experimental data cannot be fitted perfectly.

The mechanical properties of trachea should be determined by the inherent tissue components and microstructures. The structural changes that occur in the peripheral airways of asthmatic subjects are usually thought to come about by repeated injury and repair^[33–36]. However the mechanism of remodeling in trachea could be different from the one of peripheral airways. It has been reported that the amount of inflammatory cells in small airways is much larger than in big ones^[11] (the big airways in ref. [11] are those with cross-areas covering 0.15 to 4.1 mm², which are much smaller than central trachea). Though there is lack of direct pathological evidence, the inflammatory severity in trachea should be much lighter than in small airways. The authors suggested that the remodelling in the central trachea should closely associate with mechanical stress. When collapse happens, the muscular membrane is over-stretched leading an increased mechanical force^[28]. Even in the stable period, expiratory flow limitation exhibits in some asthmatic patients^[4], that is, negative transmural pressure does not only appear during the onset period. It has been widely accepted that a changed mechanical environment will lead to living tissue remodeling^[22,31,32,45], which is characterized by changes in components and structures. Though there are many extra stimuli involving in tracheal remodeling, stress is the most important and the structure change may rather be induced by the mechanical environment than the inflammatory stimuli in trachea. It has been reported that airway muscle can generate higher isometric force due to asthmatic inflammation^[37], thus if inflammatory factors exist in trachea, they could also contribute to the change of mechanical environment.

In this study, histological examinations indicate that the amounts of elastin and collagen fibres as well as smooth muscle cell increase in asthmatic tracheal muscular membranes significantly. However, results ob-

tained by Thomson et al.^[38] from 2nd to 4th generations' bronchi showed no significant differences between asthmatic patients and control groups in the amount of smooth muscle cells, extracellular matrix between muscle cells and connective tissue within smooth muscle bundles, even though their proportions in the muscular area were bigger than those of control. Although mechanical behaviors of trachea and 2nd to 4th generations' bronchi should be similar because all of them are cartilaginous airways, their remodeling process may be totally different. Similar tissues at different locations or of different species may remodel very differently^[39,40]. Aiming at figuring out a proper tracheal remodelling law, the stress in muscle or cartilage needs to be determined quantitatively, but research on this aspect is very limited. Begis et al.^[41] and Costantino et al.^[28] developed finite-element models to simulate the collapse of trachea rings as well as the stress distribution. However residual stress/strain in the trachea^[39,40,42] was not taken into account in those reports. The result in this study also shows that asthma does not change tracheal internal cross section area. When transmural pressure equals zero, the internal cross-sectional area, V_0 , is the internal size of trachea. There is no significant difference in any LS-ratio between asthmatic and control groups (see Figure 5).

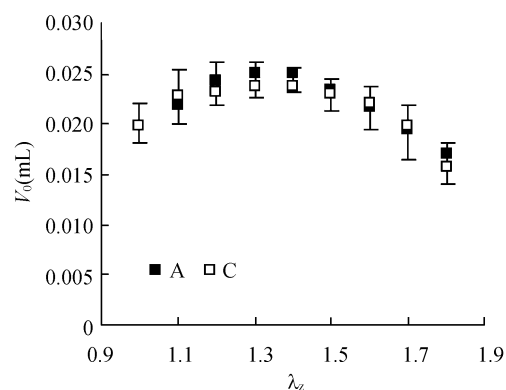


Figure 5 The internal cross-sectional area in asthmatic and control groups. A, results from asthmatic specimen; C, control specimen.

The obtained results demonstrate that remodelling leads to an increasing limit flow rate when transmural pressure is lower than 0 mmHg and λ_z is around 1.4 (see Figure 4). This may lead to a wrong conclusion that asthma could improve flow situation. Contrarily, during the onset of asthma, the negative transmural pressure collapses the trachea, causing a much smaller cross sec-

tion area and compliance. From eq. (5), compared with compliance, the weight of the cross section area for limit flow rate is higher. Therefore when collapse happens, the value of flow is much smaller than the one in the remissive period as well as the one of control. Figure 6 gives quantitative comparisons. During the onset period, the pressure is in the range marked by 'M', which is below -4 mmHg. But, in the normal physiological condition, the pressure should be above -4 mmHg, marked by 'N'. Flows in range 'M' are much smaller than those in 'N'. When pressure equals -20 mmHg, the value of flow limitation in asthmatic trachea is less than 15% of that of control when pressure is 0 mmHg. In pathologic condition, the transmural pressure in the trachea of asthmatic patients could be lower than -7.5 mmHg and as low as -45 mmHg^[5].

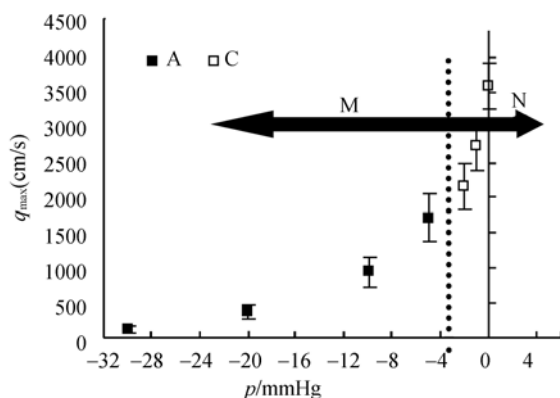


Figure 6 The flow limitation in different loading ranges. M, pathological loading range; N, normal physiological loading range, $\lambda_z=1.4$; A: results from asthmatic specimen; C: control specimen.

According to the *in vivo* measurements in asthmatic patients, when transmural pressure is -10 mmHg, the limit flow is around 4000 cm/s^[5], while the result in Figure 5 is slightly above 1000 cm/s ($\lambda_z=1.4$). The maximal compliance and the one at zero transmural pressure of control are around 0.15 and 0.17 mmHg⁻¹, respectively, which are bigger than the range between 0.018 and 0.072 mmHg⁻¹ of preterm lamb^[6,17,28,43], and smaller than 0.102 mL/mmHg of the static lung compliance of mice^[44] (the one in this study would be 0.003 mL/mmHg). Those differences may be due to either different species or parts.

The experimental results obtained in this study are in agreement with the LS-ratio, including the values of material constants in the tube law equation, limit flow

rate and compliance. The 2-order polynomial is used to fit a_i ($i=1,\dots,4$) and compliances vs. LS-ratio, and the regressed coefficients are listed in Table 3 as well as the values of λ_z^* , where dependent variables reach the peak points. Except for a_1 and a_4 , the values of λ_z^* of the rest of variables are about 1.4. According to the measurement, when the animal faces upward, the LS-ratio *in vivo* is around 1.6 (Control: 1.593 ± 0.055 ; Asthma: 1.589 ± 0.066 ; without significant difference). If the animal is in normal posture, the ratio is smaller. This match, for compliance, may suggest that the *in vivo* LS-ratio probably is an optimal status.

As mentioned in eq. (3), compliance reaches its maximal value at p^* . p^* varies with the LS-ratio (see figure 7) as well. At the interval of $1.2\leq\lambda_z\leq1.7$, values of p^* of asthmatic animals are significantly lower than those of control (see Figure 3). This difference may be due to the pressure environmental change. Since the pressure in asthmatic subjects is lower, the smaller value of p^* could be a new optimized pressure point because of adaptation.

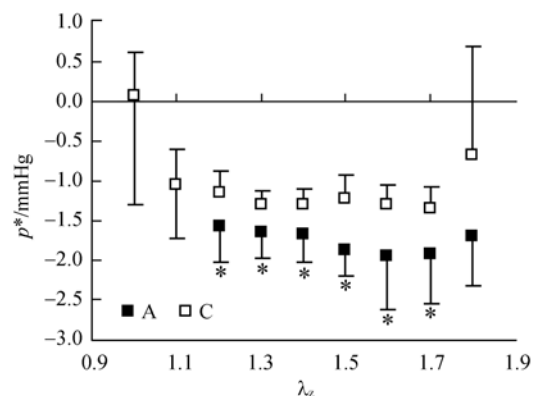


Figure 7 The comparison of p^* between asthmatic and control groups. * means significant difference ($P<0.05$); A: results from asthmatic specimen; C: control specimen.

Conclusively, asthma results in a stiffer trachea in murines; this change is similar to peripheral airways. The decreased compliance leads to a higher limit flow rate. However, during the onset period, the limit flow rate in asthmatic murines is still much smaller than that of control, due to the lower transmural pressure. The results from histological examination provide support from micro-structure aspect to the change in tracheal mechanical properties. Conclusion drawn above could have implications in tracheal remodelling.

Table 3 Relationships between parameters and longitudinal stretching ratio ($y=a\times\lambda_z^2+b\times\lambda_z+c$)

Asthma	a	b	c	λ_z^*	Control	a	b	c	λ_z^*
a_1	-0.5440	1.3454	-0.0952	1.24	a_1	-0.3530	0.7574	0.3040	1.07
a_2	-0.4208	1.1748	-0.6308	1.40	a_2	-0.7067	1.9933	-1.1621	1.41
a_3	-1.2907	3.8059	-2.4845	1.47	a_3	-1.4933	4.3314	-2.8083	1.45
a_4	-1.0265	2.5652	-0.5469	1.25	a_4	-0.8331	1.9677	-0.1388	1.18
C_0	-0.2889	0.7890	-0.4139	1.37	C_0	-0.4666	1.2871	-0.7288	1.38
$C_{\max}$	-0.3218	0.8838	-0.4712	1.37	$C_{\max}$	-0.5419	1.5062	-0.8709	1.39

y denotes a_i ($i=1,\dots,4$), C_0 and $C_{\max}$, the corresponding units of a , b and c have not been shown.

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