Mechanisms for the mechanical response of airway smooth muscle to length oscillation

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LUNG VOLUME HISTORY is known to play an important role in regulating airway tone. In normal human subjects subjected to bronchoconstriction, deep inspiration decreases airway resistance and increases expiratory flow (15, 21). Normal tidal breathing may also play an important role in limiting airway responsiveness (31, 33). The effects of lung volume history on airway reactivity to contractile mechanisms (17, 23); however, non-cross-bridge mechanisms may also play a role in regulating the effects of length oscillation on smooth muscle contractility. There is evidence that the organization of contractile filaments within smooth muscle cells can be modified in response to changes in muscle length and that these alterations in contractile filament organization play a role in determining the effect of imposed length changes on the contractile response of the muscle (10, 13, 14, 24). Both contractile and noncontractile components of smooth muscle cells also possess viscoelastic characteristics that may affect the mechanical response of airway smooth muscle to length oscillation.

Each of the cellular mechanisms that contribute to the mechanical response of airway smooth muscle to length oscillation may be affected by both the rate and amplitude of the oscillation. Mechanisms that contribute to this mechanical response may also be affected by the level of contractile activation of the muscle or the nature of the contractile stimulus. Thus the predominance of any particular cellular mechanism may be a function of the conditions of oscillation as well as the conditions of muscle activation.

In this and the following companion paper, we have evaluated the properties of airway smooth muscle under oscillatory conditions. First, in this study, we characterize the rate and amplitude dependence of the mechanical response of airway smooth muscle to oscillatory length perturbations during contraction with acetylcholine (ACh). In the succeeding study, we evaluate the effects of different pharmacological stimuli on the response to length oscillation. The results of these studies allow us to evaluate the cellular mechanisms likely to predominate in determining the mechanical response of airway smooth muscle to oscillatory conditions similar to those likely to occur during breathing in vivo.

METHODS

Tissue preparation. Mongrel dogs weighing 20–25 kg were anesthetized with pentobarbital sodium and killed by exsanguination. A 10- to 15-cm segment of trachea was immediately analyzed.
ately removed and immersed in physiological saline solution at 22°C (composition (in mM): 110 NaCl, 3.4 KCl, 2.4 CaCl₂, 0.8 MgSO₄, 25.8 NaHCO₃, 1.2 KH₂PO₄, and 5.6 glucose). The solution was aerated with 95% O₂-5% CO₂ to maintain a pH of 7.4. Rectangular strips of trachealis muscle were dissected from the trachea after removal of the epithelium and connective tissue layer. Muscle strips (2–3 mm wide × 5–8 mm long) were mounted horizontally in a 25-ml rectangular Plexiglas tissue bath containing physiological saline solution at 37°C that was bubbled with 95% O₂-5% CO₂. One end of each strip was fixed tightly to a stationary platinum hook while the other end was attached to a servo-regulated electromagnetic lever (model 300B; Cambridge Technology). The static compliance of the entire system excluding the muscle was negligible with respect to muscle compliance.

After placement in the tissue bath, muscles were equilibrated for 60–90 min. During this time, they were stimulated by electrical field stimulation at 2- to 5-min intervals using 20-V, 15 pulses/s, 0.5-ms duration square waves by means of rectangular platinum electrodes (55 × 10 × 0.3 mm) connected to a Grass stimulator and a current amplifier. To determine the muscle length at maximal active force ($L_o$), muscle length was increased progressively after each stimulation until the force of active contraction reached a maximum. After $L_o$ was determined, muscles were subjected to different experimental protocols. ACh was injected into the tissue bath by micropipette.

Length oscillation of muscle strips. Length oscillation of the muscle was performed by using a waveform generator (model 75A, Wavetek, San Diego, CA). Triangle waves were used so that the rate and amplitude of the length oscillation cycle could be varied independently. Amplitudes ranged from 1 to 10% $L_o$ and rates of length change (ramp rates) ranged from 0.005 to 0.4 $L_o$/s (Fig. 1). When the oscillation amplitude was varied, the upper length limit was maintained constant at 0.80 $L_o$ and the muscle was shortened to different lower lengths. When the effect of a given rate of oscillation was studied at different oscillation amplitudes, the oscillation frequency was adjusted so as to maintain a constant rate of length change. All data were captured on a Nicolet digital oscilloscope and transferred to a computer for further analysis. The area of the force-length loop for each cycle was computed by integration with the use of the digitally recorded data.

Data analysis. Muscle force during length oscillation at the longest and shortest lengths of the oscillation cycle was computed as a proportion of the static isometric force at 0.80 $L_o$ (the peak length of the oscillation). Hysteresis area for each rate and amplitude of length oscillation was computed cycle by cycle from three to six successive force-length loops. The first loop obtained after changes in the rate or amplitude of length oscillation was not included. The hysteresivity constant ($\eta$), which normalizes hysteresis area for differences in length and force excursions, was computed from the hysteresis area of the length-force loop ($A$), the peak-to-peak length excursion ($DL$), and the peak-to-peak force excursion ($DF$), as described by Fredberg et al. (5)

$$\eta = \tan \phi$$

$$\phi = \sin^{-1} (4A/DF DL)$$

where $\phi$ is the phase lag between length and force.

Fig. 1. Muscle force and length during length oscillation in individual muscle strips after 5 min of isometric contraction at 0.8 $L_o$ (muscle length at maximal active force). A: oscillation at amplitude of 10% $L_o$ (between 0.8 and 0.7 $L_o$). Oscillation rate was imposed at successive rates of 0.4, 0.2, 0.02, 0.01, and 0.005 $L_o$/s. B: oscillation at a constant ramp rate of 0.02 $L_o$/s. Oscillation was imposed successively at amplitudes of 1, 3, 6, and 10% $L_o$. ACh, acetylcholine.
Statistical analysis. All data are presented as means ± SE. Comparisons between two groups were made using a two-way analysis of variance with repeated measures or paired t-tests. For all statistical tests employed, *P* < 0.05 was considered statistically significant. In each case, *n* is number of muscle strips used for each experiment.

**RESULTS**

Rate and amplitude of length oscillation affect force and hysteresivity in muscles contracted with ACh (10^{-5} M). The effect of the rate and amplitude of length oscillation on the mechanical response of the muscle was determined in six muscle strips. A range of rates both faster and slower than the probable active shortening velocity of the muscle was used. Rates and amplitudes of length oscillation of the muscle also included conditions that approximate those likely to occur during inflation and deflation of the airways in vivo during tidal breathing.

Each muscle was contracted isometrically with 10^{-5} M ACh at 0.8 Lo for 5 min before length oscillation. In successive contractions, the muscle was then oscillated at amplitudes of 1% (0.79–0.80 Lo), 3% (0.77–0.80 Lo), 6% (0.74–0.80 Lo), and 10% Lo (0.70–0.80 Lo). At each oscillation amplitude, the effect of length oscillation was determined at rates of 0.005, 0.01, 0.02, 0.2, and 0.4 Lo/s (see Fig. 1A). The muscle was oscillated for 30 s to 3 min at each rate to obtain at least three cycles at each rate. The oscillation frequency was a function of the oscillation rate and amplitude and ranged from 0.025 to 20 Hz (see Table 1). Hysteresis area and contractile force during oscillation were analyzed at each rate and amplitude from at least three cycles. The first cycle after a change of rate was not included. Some additional experiments were also performed in which the oscillation amplitude was varied during a single contraction while the rate of length change was maintained constant to evaluate the effect of oscillation amplitude during a single contraction (see Fig. 1B).

Changes in force in response to length oscillation are illustrated for individual muscle strips in Figs. 1 and 2. Muscle force remained slightly higher than the static isometric force at the peak length of the oscillation cycle at all rates and amplitudes of length oscillation. However, during the shortening phase of the oscillation cycle, force decreased markedly below the static isometric force and remained so for most of the period of stretch. The length-force curve traced the same path during shortening at all amplitudes of length oscillation (Fig. 2B); however, the force at the short length of the oscillation cycle decreased further as the amplitude of the length cycle was increased. Mean data showing the effects of length oscillation on muscle force are shown in Fig. 3. Muscle force during length oscillation was significantly lower than the static isometric force even at the slowest oscillation rate (ramp rate, 0.005 Lo/s) and at the smallest oscillation amplitude (1% Lo) (Figs. 2 and 3). As the rate of oscillation was increased, the dynamic force during oscillation decreased further.

Both the oscillation rate and amplitude also affected the shape and hysteresis area (hysteresivity) of the force-length loop of muscles contracted with ACh (10^{-5})

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**Table 1. Oscillation frequencies at each rate and amplitude**

<table>
<thead>
<tr>
<th>Rate, Lo/s</th>
<th>Oscillation amplitude, 1%</th>
<th>Oscillation amplitude, 3%</th>
<th>Oscillation amplitude, 6%</th>
<th>Oscillation amplitude, 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>15</td>
<td>5</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>0.01</td>
<td>30</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>0.02</td>
<td>60</td>
<td>20</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>0.2</td>
<td>600</td>
<td>200</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>0.4</td>
<td>1,200</td>
<td>400</td>
<td>200</td>
<td>120</td>
</tr>
</tbody>
</table>

Lo, muscle length at maximal active force.
Hysteresivity increased linearly as the amplitude of the oscillation cycle was increased from 3 to 10% (Fig. 4A). The resolution of the digital data was not sufficient to enable us to accurately compute hysteresivity for the smallest oscillation amplitude (1% Lo). The effect of oscillation amplitude on hysteresivity was a function of the nonlinearity of the descending limb of the length-force loop (Fig. 2B), which meant that increases in oscillation amplitude resulted in disproportionate increases in hysteresis area. In contrast, the relationship between hysteresivity and the oscillation rate was very nonlinear. Hysteresivity increased very steeply at all oscillation amplitudes as the rate of length change was decreased to \(0.02 \text{ Lo/s}\) (Fig. 4B). This increase in hysteresivity with decreasing rate was associated with a shift in the shape of the stretch limb of the oscillation cycle from concave to convex (Fig. 2A).

**DISCUSSION**

Dependence of force-length hysteresis on the rate and amplitude of length oscillation. We evaluated the effect of length oscillation at different rates and amplitudes (ranging from 1 to 10% Lo) on the active force of tracheal muscle during the oscillation. Oscillations were imposed during the plateau phase of isometric contractions induced by ACh. Under all conditions, the force-length loop obtained during the oscillation cycle changed progressively during the first few oscillation cycles, but a constant reproducible force-length loop was then achieved. The constant force-length loop exhibited a pattern in which the dynamic muscle force decreased markedly below the static isometric force during the shortening phase of the oscillation cycle. This occurred even at the slowest rate of length oscillation. The dynamic force remained below the static force during the shortening phase of the cycle until the muscle was stretched back to the peak cycle length, where dynamic muscle force remained close to or slightly higher than the static isometric force (Fig. 2).

The depression of dynamic force relative to static force increased with increasing rate or amplitude of length oscillation. This pattern of depression of active contractile force caused by length oscillation is consistent with our previous observations in both tracheal and bronchial muscle strips and in intact bronchial segments contracted with ACh (6, 11). The effects of length oscillation on force are also similar when stimuli other than ACh are used to contract the muscle (25).

We evaluated the effects of the rate and amplitude of length oscillation on normalized hysteresis area, computed as the hysteresivity constant \(\eta\) (5). Hysteresivity increased abruptly when the rate of length change was decreased below \(0.02 \text{ Lo/s}\). This abrupt increase in hysteresivity coincided with a qualitative change in the shape of the hysteresis loop. At the fastest rates of cycling (0.2 and 0.4 Lo/s), both the shortening and lengthening limbs of the force-length loop exhibited a concave shape, whereas at the slower rates of cycling (0.02 to 0.005 Lo/s) the stretch limb of the force-length loop became convex while the shortening limb of the loop remained concave (Fig. 2).
loop remained concave. This pattern of shape change was observed for all oscillation amplitudes studied (3–10%); however, the effects of rate on hysteresivity were more pronounced at larger oscillation amplitudes. This increase in hysteresivity and coincident change in the shape of the force-length loop probably reflect a rate-dependent change in the cellular processes that predominate in determining the dynamic response of the muscle.

Rate of contractile element shortening as a determinant of the behavior of tracheal muscle strips during length oscillation. When the rate of imposed length change is much faster than the active shortening velocity of the muscle, the primary effect of length oscillation should be to stretch and retract passive viscoelastic components of the tissue, with little coincident active shortening or lengthening of the contractile element. However, if the rate of length change is reduced significantly below the active shortening velocity for the prevailing muscle load, active shortening of the contractile element and the formation of new cross-bridge attachments should occur during both the stretch and retraction phases of the length cycle (18, 19). In addition, as the muscle strips are stretched, some cross-bridge attachments that form earlier in the length cycle will be forced to yield (18, 19). If the rate of contractile element shortening were the primary determinant of muscle force during length oscillation, the dynamic force of the muscle during imposed shortening should approximate the load appropriate to the imposed shortening velocity, as represented by the force-velocity relationship of the muscle.

In our companion study (25), we found that isotonic shortening velocities after 5 min of contraction at a load of 10% L₀ were significantly less than 0.04 L₀/s for ACh, KCl, or the muscarinic agonist McN-A-343. Shortening velocities measured for McN-A-343 and KCl were <0.02 L₀/s. These velocity measurements were similar to those we have previously reported for these stimuli (8, 9). As the imposed rates of length change of 0.2 and 0.4 L₀/s are an order of magnitude greater than the active shortening velocity of the muscle at a load of 10% L₀, relatively little active shortening of the contractile element is likely to occur during length oscillation at these rates. The narrow force-length loop and much lower hysterescity obtained at these faster oscillation rates may be due to a greater predominance of the passive elastic properties of the muscle during the oscillation, as the passive elastic elements are likely to have a relatively low level of series viscosity (17). In contrast, at imposed rates of length change <0.02 L₀/s, significant active contractile element shortening would be expected to take place as these rates are similar to or slower than the predicted shortening velocity of the muscle under these loading conditions. Thus the increase in hysterescity and associated increase in the convexity of the force-length loop at the oscillation rates <0.02 L₀/s may reflect the active formation and yielding of cross bridges.

The slowest rate of shortening imposed on the muscle, 0.005 L₀/s, is a small fraction of the maximal unloaded shortening velocity of canine trachealis muscle, estimated to be ~0.2 L₀/s (27). At a shortening rate of 0.005 L₀/s, muscle force would be predicted to be within 10% of the isometric force from the force-velocity relationship of canine trachealis muscle (27). However, when we shortened muscles from 0.8 to 0.7 L₀ at this rate, force was ~50% of the isometric force at 0.7 L₀ during the shortening. In a previous study, we found that muscle force during length oscillation remained markedly below the isometric force even when the imposed rate of length oscillation was ten times slower, only 0.0005 L₀/s (6). In this study, even when the length oscillation was stopped in the middle of a cycle and the muscle was allowed to reactisometrically, the isometric force appropriate to that muscle length was never reestablished (6). This suggests that the pattern of force depression during length oscillation cannot be accounted for on the basis of the force-velocity characteristics of the muscle.

Shortening deactivation or active relaxation as mechanisms to account for the depression of force during the length oscillation of airway smooth muscle. If a shortening step is imposed on actively contracted airway smooth muscle, isometric force redevelopment at the shorter length is depressed below the force that is achieved when the isometric contraction is initiated at the shorter length (6, 7, 13). The isotonic shortening velocity of airway smooth muscle can be similarly depressed by an imposed shortening step (13). The mechanisms responsible for the depressive effect of imposed shortening on airway smooth muscle contractility are also likely to underly the depression of airway smooth muscle force caused by length oscillation.

Shortening-activated striated muscles have been shown to decrease the Ca²⁺ activation of the contractile filaments, resulting in a depression of force development and contractility. This phenomenon is referred to as “shortening deactivation” (2, 4, 30). The presence of an analogous phenomenon in smooth muscle could provide an explanation for the depressive effects of imposed shortening on tracheal muscle contractility. A decrease in the Ca²⁺ activation of the contractile filaments in smooth muscle should result in a decrease in myosin light chain phosphorylation, whether the reduction in activation is caused by shortening deactivation or active relaxation. However, in canine tracheal smooth muscle, the depression of force that results from an imposed shortening step is not associated with a depression of myosin light chain phosphorylation (16). Similarly, the level of myosin light chain phosphorylation during isometric contraction at a given muscle length is the same whether the contraction is initiated at that length or the muscle is stretched to that length (16). These observations indicate that the depression of active force caused by the length oscillation of canine tracheal muscle cannot be attributed to a stretch-inducd or shortening-induced deactivation of contractile proteins. This also means that it is unlikely that either stretch or shortening depresses muscle force by causing the release of an endogenous relaxing mediator, as this would also decrease myosin light chain phosphorylation.
phosphorylation. The fact that the depression of force caused by length oscillation is similar, regardless of the contractile stimulus or the degree of activation of the muscle (25), is also inconsistent with the force depression during length oscillation resulting from a decrease in the activation of contractile filaments.

Role of contractile filament plasticity in determining the effects of length oscillation on airway smooth muscle tone. We have previously proposed that the depressive effects of imposed shortening on tracheal smooth muscle contractility may be a function of a plasticity of the cellular organization of the contractile filaments in smooth muscle (10, 13). There is evidence that the organization of the contractile filaments in smooth muscle cells can change in response to acute changes in cell shape caused by external stress or strain; this change in organization may enable muscle contractility to be optimized to the physical environment of the smooth muscle cell at the time of contractile activation (10, 13, 14, 20, 24).

This hypothesis is illustrated in Fig. 5. When a muscle cell is activated at a short length, the contractile filaments are orientated so as to maximize force development by a short, thick cell; whereas when the muscle cell is activated at a long length, the arrangement of the contractile elements adjusts to optimize force development by a long, narrow cell. Such changes in the organization of the cellular cytostructure might involve changes in the sites of attachment of actin filaments to the membrane (22, 32) as well as changes in actin or myosin filament length or orientation (10, 13, 24).

Our previous observations suggest that this process of remodeling of the contractile filament organization may occur slowly in resting muscles relative to the rate of contractile events and that it may occur even more slowly after contractile activation (10, 12, 13). Contractile activation of the muscle may cause stabilization of the structural organization of the cell, resulting in an increase in cell stiffness and a decrease in structural plasticity (10, 12). Thus, when a change in muscle length is imposed on the muscle after contractile activation, the contractile filament organization may not be able to adjust to the change in cell shape, resulting in a depression of both muscle force and shortening velocity (10, 12, 13) (see Fig. 5). In contrast, in the resting muscle, the organization of contractile filaments is plastic, allowing the organization of the contractile filaments to adapt to changes in cell length, thereby optimizing the contractile response of the muscle to the muscle length at which contractile activation is initiated.

The continuous stretching of the muscle that occurs during length oscillation causes the contractile filaments to adopt an organization that optimizes force to the longest length of the oscillation cycle. The contractile filaments cannot adjust their organization rapidly enough to adapt to the continuous changes in muscle length that occur during the oscillation, and thus they remain fixed in a conformation optimal for the longest muscle length of the cycle. This results in a depression of muscle force when the muscle is shortened below that length. This hypothesis can also account for our previous observations that a decrease in muscle length immediately before contractile stimulation depresses the contractility of the muscle (7, 10, 16), as the structural adaptions in contractile filament organization would not be fast enough to adjust to a length change that occurred immediately before contractile activation.

Breathing as a modulator of airway tone. After bronchoconstriction, inflation of the airways during maximal inspiration results in a decrease in airway tone (15, 21). Our present results provide additional evidence that the mechanism for this effect results from the intrinsic properties of smooth muscle cells rather than from reflex or humoral responses to stretch or

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**Fig. 5.** Proposed mechanism for depression of contractility observed in airway smooth muscle when a length change is imposed on actively contracted muscle (see Refs. 10, 12, 13). Diagram illustrates a single smooth muscle cell containing actin and myosin filaments, with actin filaments linked to the smooth muscle membrane at dense plaque sites. When the length of the resting muscle cell is changed, the arrangement of contractile filaments adapts to the change in the conformation of the cell, thus optimizing force production for that cell length (heavy black arrow). Orientation of contractile filaments within cell thus differs depending on length of resting muscle cell at time of activation. Contractile activation stabilizes organization of contractile filaments, making further rearrangements of contractile filaments more difficult as long as cell remains activated. Therefore, when muscle is shortened after activation, contractile filaments cannot adjust to new conformation of the cell, resulting in reduced contractility (see bottom left cell). [Modified from Gunst et al. (10).]
retraction of the airways. Our hypothesis provides an explanation for the effects of lung volume changes on airway smooth muscle contractility. During tidal breathing at functional residual capacity (FRC), the contractile filament organization within the smooth muscle cells is adapted to optimize airway smooth muscle contractility to the maximal airway circumference that occurs during a tidal volume oscillation. Deep inspiration stretches the airways, forcing the muscle cells to longer lengths and disrupting the contractile filament organization adopted at the lower lung volume. When tidal breathing at FRC is resumed, the contractile filament organization within the muscle cells is no longer optimal for airway muscle contractility at the lower lung volume, resulting in lower airway tone. Eventually, with the resumption of tidal breathing at FRC, the organization of the contractile filaments again adjusts to the airway smooth muscle cell length at that lung volume, and muscle contractility increases.

By analogy, this hypothesis also explains why tidal breathing or small oscillations in muscle length can reduce airway smooth muscle contractility relative to the static condition (31, 33). The tidal oscillations continuously stretch the muscle, forcing the conformation of the cells to adjust to the longest muscle length of the tidal volume oscillation cycle, so that airway contractility is reduced below that which would be expected if airways were contracted statically at the shorter muscle lengths present at FRC. Finally, this hypothesis also provides an explanation for the observation that lung volume history immediately before methacholine challenge affects airway reactivity (15), as stretch caused by deep inspiration would be expected to alter the organization of contractile filaments of unactivated smooth muscle cells, thereby altering their subsequent contractile response.

Contractile filament plasticity provides an important mechanism underlying the effects of lung volume changes on airway smooth muscle contractility, by providing a means of adapting contractile element length to changes in smooth muscle cell length caused by stretch. However, for oscillations over a constant volume range, active cross-bridge mechanisms are likely to be an important determinant of the rate-dependent changes that occur in the oscillatory response of the muscle, when the imposed oscillation is at rates at which active shortening of the contractile element can occur. To relate the length oscillation rates used in this study to breathing frequencies, frequencies in cycles per minute were computed for each rate and amplitude of length oscillation (Table 1). At all oscillation amplitudes, rates of 0.2 and 0.4 L_o/s clearly resulted in much higher frequencies of length oscillation (60 to 400 cycles/min) than might ever be expected to occur during normal breathing under physiological conditions. However, oscillation frequencies at rates of length change of 0.02 L_o/s or less approximate tidal breathing rates at some oscillation amplitudes. As discussed earlier, these rates are within the range of the active shortening velocities of the muscle predicted for these stimuli under these loading conditions, making it probable that active shortening and yielding of the contractile element occur during the length oscillation cycle. Active shortening of the contractile element during length oscillation resulting in the continuous formation and yielding of cross bridges would be expected to result in more force and greater hysteresivity, as was observed at the slower rates of length oscillation.

Oscillation amplitudes of 3–6% of muscle length are likely to most closely approximate the magnitude of muscle stretch that occurs during tidal breathing in vivo (11). In the present study, amplitudes of length oscillation as low as 1% of L_o reduced the active force of the muscle at all oscillation rates. These data support our previous suggestion that small oscillations in muscle length that occur during tidal breathing may function to reduce airway reactivity (31, 33). Recent evidence suggests that the greater airway reactivity associated with asthma might result from a reduction in the coupling between the airways and the lung parenchyma that reduces or prevents the bronchodilating effects of lung inflation (26). Studies of airway muscle taken from normal and asthmatic subjects have not identified intrinsic differences in their properties that could account for the differences in reactivity observed in vivo (1, 3, 29). If the hyperreactivity of asthmatic subjects in vivo is due to a reduction in the effectiveness of tidal ventilation in stretching the airway wall, possibly resulting from an uncoupling of the airways and lung parenchyma caused by chronic inflammation, this could explain why differences in the reactivity of asthmatic subjects are observed in vivo but not in vitro.

Conclusions. The results of this study demonstrate that continuous length oscillation depresses the active force generated by airway smooth muscle below the force generated during static isometric contraction. The active force generated by the muscle decreases markedly below the isometric force during the shortening phase of the length oscillation cycle and increases back to the isometric force as the muscle is lengthened. At rates comparable to those that occur during tidal breathing, active shortening and yielding of contractile elements contribute to the modulation of force during length oscillation. However, the depression of force that occurs during the oscillation cannot be fully accounted for on the basis of the force velocity characteristics of the muscle, nor can it be explained by effects of either stretch or shortening on the Ca^{2+} activation of contractile proteins or by active relaxation induced by stretch. We propose that the depression of contractility during length oscillation is a function of the plasticity of the organization of contractile filaments within airway smooth muscle cells that allows contractile element length to be reset in relation to smooth muscle cell length as a result of changes in the length to which the muscle is stretched.

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