Airway Hyperresponsiveness: From Molecules to Bedside
Invited Review: Airway wall remodeling: friend or foe?

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McParland, Brent E., Peter T. Macklem, and Peter D. Paré. Invited Review: Airway wall remodeling: friend or foe? J Appl Physiol 95: 426–434, 2003; 10.1152/japplphysiol.00159.2003.—Airway wall remodeling is well documented for asthmatic airways and is believed to result from chronic and/or short-term exposure to inflammatory stimuli. Airway wall remodeling can contribute to airway narrowing as well as to the airway hyperresponsiveness, which is a characteristic abnormality in asthma. However, the potential for airway narrowing could be much worse if it were not for some of the protective effects of remodeling that may help to limit airway narrowing in asthmatic patients. This mini-review discusses the evidence for airway wall remodeling and its effects, friend and/or foe, on airway narrowing in asthmatic patients.

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Although asthma is a clinical syndrome that is principally defined by a set of symptoms, it has been increasingly recognized that chronic airway inflammation, remodeling, and hyperresponsiveness are characteristic structural and functional abnormalities underlying the disorder. Nonspecific bronchial hyperresponsiveness, which is the focus of this Highlighted Topics series of the Journal of Applied Physiology, is characterized by excessive airway narrowing in response to relatively low provocative levels of a wide variety of pharmacological and nonpharmacological stimuli. The ultimate mechanism by which these stimuli narrow the tracheobronchial tree is by inducing airway smooth muscle (ASM) contraction. There is evidence that the leftward shift in the dose-response relationship to contractile stimuli (sensitivity) and the ability of the airway to narrow excessively are separately determined. We believe that, of these two abnormalities, it is the exaggerated airway narrowing that is the most important, and we suggest that airway wall remodeling is likely to be the basis for this aspect of hyperresponsiveness. Although airway narrowing in response to very low levels of stimulus would be bothersome, it is the excessive airway narrowing that impairs quality of life and places asthmatic patients at risk of fatal attacks. Nonasthmatic individuals appear to be protected against excessive airway narrowing that occurs in asthmatic patients; although their airways narrow in response to these stimuli, the degree of airway narrowing reaches a plateau in most “normal” subjects after only modest amounts of narrowing (79). In this article, we will briefly review the structural abnormalities that have been reported in asthma and discuss how these structural changes could contribute to and/or protect against excessive airway narrowing (22, 23, 106, 118). An alternative explanation to explain the phenomenon of “plateaus” on dose-response curves could be complete closure of some airways in parallel to patent airways. Brown and Mitzner (12) have provided convincing evidence that complete airway closure can occur in vivo in anesthetized dogs at functional residual capacity when the contractile agonist is delivered directly to the airway mucosa. In addition, King et al. (57), using radionuclide techniques, have shown that airway closure can be detected in asthmatic individuals following inhalation of a contractile agonist. Irrespective of the mechanism of limited airway narrowing in normal patients and exaggerated airway narrowing in asthmatic patients, whether it is the homogeneous limitation of ASM shortening or heterogeneous airway closure, airway remodeling will exaggerate the response. There are considerable data to show that airway wall structure is abnormal in asthmatic patients (4, 15, 25–27, 47, 49, 53, 59, 100, 104, 107). The structural changes occur in genetically susceptible individuals as a result of repeated injury and repair due to long- and/or short-term inflammatory insults within the airway wall (45). Although changes in the structure of the airway wall have been recognized as a feature of asthma for over 80 years, the term remodeling was coined only recently. An Ovid Medline database search with the key words asthma and remodeling yields only...
one citation in the 1980s, 172 in the 1990s, and 279 between 2000 and the end of 2002. Remodeling can be defined as changes in the composition, content, and organization of the cellular and molecular constituents of the airway wall.

REMODELED CONSTITUENTS OF THE AIRWAY WALL

**Epithelium.** Although there is considerable evidence that there is increased fragility of the airway epithelium in asthma, there also appears to be an increase in total epithelial cell volume (5, 53, 54, 60, 93). In addition, there is an increase in the number of mucous-secreting goblet cells and their presence extends more peripherally down the tracheal-bronchial tree (44, 84).

**Subepithelial collagen layer.** Probably the most studied and consistent structural change in the airways of asthmatic individuals is an increase in the thickness of the subepithelial collagen layer, known as the lamina reticularis. In asthmatic bronchi, this layer is between 10 and 15 μm in depth, which is typically twice the thickness found in nonasthmatic bronchi (5–8 μm) (6, 11, 24, 64, 82, 99). The thickened layer is found under a normal subepithelial basal lamina (type IV collagen and laminin) and is composed of a dense condensation of the fibrillar collagens (types III and V) proteoglycans and fibronectin (48, 99, 115). The connective tissue proteins are probably secreted by subepithelial myofibroblasts because the myofibroblast number correlates with the magnitude of subepithelial thickening (11).

**Bronchial wall layers.** All of the layers of the bronchial wall below the lamina reticularis have been reported to be thickened in asthma. These include the inner airway wall between the ASM layer and the lamina reticularis (15, 53, 59), the ASM layer (15, 25–27, 41, 49, 53, 59, 100, 107), and the adventitia (15, 53, 59).

The inner airway wall contains a rich vascular plexus, and there is some evidence that the increased thickness of the inner airway in asthma may be partly due to a greater number and size of the vessels within this plexus (15, 16, 46, 59, 65, 85, 86). The amount of elastic fibers within the inner airway wall also appears to be increased in asthma (17, 34, 49), and, although the number of longitudinal bundles is related to the number of mucosal folds, the number of folds is not increased or decreased in airways of asthmatic patients (17). Interestingly, myofibroblasts colocalize with the longitudinal elastic fibers (17). Some of the elastic fibers within the inner wall are attached to the subepithelial collagen layer and are fragmented in airways from asthmatic patients (7, 71). Besides the increase in vessels and elastic tissue, there is a generalized increase in extracellular matrix presumably due to increased synthesis and/or decreased removal by structural cells such as fibroblasts and airway myocytes (56, 120).

The increase in the ASM layer in asthma has been shown to be a result of both hyperplasia and hypertrophy of ASM cells (26, 27). In addition, Thomson et al. (108) showed that the increase in ASM mass in asthma may be contributed to by a 50% increase in extracellular matrix between the ASM cells (108). Of the airway wall compartments in human airways, the adventitia makes up the largest proportion of the wall area and like the inner wall area is composed of loose connective tissue (59) as well as lymphatics and a plexus of bronchial microvessels connected to the submucosal capillary network by vessels that penetrate through the ASM.

Much of the work that demonstrates an increase in bronchial wall areas in asthma has relied on the concept, originally supported by the work of James et al. (52), that the basement membrane perimeter length of airways is constant despite different degrees of ASM contraction and different degrees of lung inflation at the time of fixation. This concept has been challenged by McParland et al. (72). These investigators showed that when human bronchi were inflated to a transmural pressure of 21 cmH2O the basement membrane length increased by ~50% over its calculated length at zero transmural pressure. Because the airways of asthmatic patients, especially fatal asthmatic individuals, are constricted at the time of pathological examination (and often not inflated with fixative) and the comparison lungs of nonasthmatic individuals are not constricted and are often inflated, a systematic overestimate of all airway wall compartment areas in asthma may have occurred in many of these studies.

AIRWAY WALL REMODELING AS A FRIEND

Although most of the structural changes that occur in the airways of asthmatic patients are likely to be detrimental and contribute to fixed airway narrowing as well as exaggerated narrowing after bronchoconstricting stimuli, some aspects of remodeling could have beneficial effects.

**Stiffening the airway.** The increased extracellular matrix and the thickening of all layers of the airway wall in asthmatic patients result in a decrease in airway compliance (distensibility) (91, 116). The thickened airway wall could also cause a decreased compressibility such that the airways are better able to resist dynamic compression. Because the airway lumen cross-sectional area-pressure relationship is an important determinant of peak expiratory flow, a decrease in airway compliance at flow-limiting sites (choke points) could help to maintain peak expiratory flow despite decreased airway luminal diameter (20, 91). Animal studies of allergen-induced airway hyperresponsiveness have shown that prolonged ovalbumin exposure results in increased deposition of fibronectin and collagen, which was accompanied by a progressive decrease in airway hyperresponsiveness (87, 109), indicating that thickening/stiffening of the airway may be protective against airway hyperresponsiveness.

**Providing a parallel elastic impedance and/or a radial constraint to ASM.** Ultimately, airways narrow because activated ASM shortens. Shortening of the ASM may be influenced by structures surrounding the ASM cells. Bundles of collagen fibers run parallel to the
ASM cells in a circumferential pattern in the airway. During shortening, these fibers fold and this deformation is thought to provide an elastic afterload to the ASM limiting its ability to narrow airways. An increase in the volume of such fibers could increase the magnitude of this load and attenuate ASM shortening. The connective tissue, within which ASM cells are imbedded, also provides a radial constraint to a layer of ASM. When ASM cells contract, their volume is thought to be conserved and therefore they become short and fat. Meiss (76) has shown that constraining the muscle’s ability to “fatten” during contraction causes a decrease in maximal shortening. Each ASM cell is normally surrounded by a basal lamina, but this connective tissue sheath increases in volume during remodeling (108). This effect has been shown experimentally by placing stiff Silastic bands around the tracheal smooth muscle, which reduced maximal shortening by ~15% (76). The concept that parallel elastic impedance and/or radial constraint by structures external to the ASM can attenuate shortening has been supported by the observation that ASM shortening increases after the treatment of ASM preparations with collagenase (8, 76). In addition, single smooth muscle cells isolated from taenia coli of guinea pigs using collagenase treatment completely shortened in ~2 s after stimulation vs. ~7 s for maximally activated whole tissue preparations (78). An explanation for this difference is that digestion removes the radial constraint and parallel elastic impedance, thus allowing the unloaded smooth muscle to achieve a higher velocity of shortening.

*Providing a series elastic load.* During ASM shortening, there is a distortion of the airway tissue internal and external to the ASM layer. The airway does not narrow concentrically; rather, the mucosal membrane buckles and is thrown into folds. Elements within the wall undergo both compressive and tensile stresses. To the extent that the tissue resists this distortion, this structural reorganization provides a series elastic load that could theoretically attenuate ASM shortening (61). Because the bending stiffness of a layer is directly related to its thickness cubed, airway wall thickening alone, without a change in the mechanical properties of the tissue, could be protective. To the extent that the added tissue is stiffer or less stiff than the normal components of the wall, this effect could be more or less than the geometry would predict. Wiggs and colleagues (114) attempted to model the potential importance of mucosal folding by using finite-element analysis in a computer model of the process. By doubling of the stiffness of the subepithelial collagen layer, mimicking the increased thickness observed in asthmatic airways, they found that a greater force would be required to induce an equivalent degree of folding and narrowing. However, their results also predicted an increased number of mucosal folds, which does not appear to be the case in asthmatic patients (17). One study supporting a potential protective role for airway remodeling showed an inverse relationship between airway responsiveness as measured by 1-s forced expiratory volume and a reduction in forced vital capacity and reticular basement membrane thickness in a group of asthmatic patients (77). McParland et al. (74) attempted to quantify the physiological load opposing ASM shortening provided by mucosal folding and airway distortion. They maximally narrowed human bronchial segments (5th generation) using acetylcholine at 0 cmH2O transmural pressure and then measured the stored recoil pressure developed during agonist washout. The recoil pressures were found to be between 1 and 7 cmH2O (74), and these recoil pressures were even greater if the tissues were relaxed with isoproterenol (100 μM; unpublished observations), indicating that in the presence of endogenous tone the airways stored a substantial amount of recoil energy that was opposing airway narrowing. These loads may not appear substantial, but when compared with the force-generating ability of similarly sized human airway preparations, which was ~9 cmH2O under isometric conditions (83), the opposing load is substantial.

**Additional beneficial effects of remodeling.** Theoretically, the increased vascularity of the airway wall that accompanies the remodeling process could facilitate removal of contractile agonists and inflammatory cytokines, although these same vessels are the source of edema fluid and infiltrating inflammatory cells. Similarly, the increase in goblet cell number and the expected increase in mucus lining the airway could serve a protective function against inhaled toxins and excessive mucosal dehydration. However, it is much easier to demonstrate or speculate on how various aspects of the remodeling process could contribute to airway dysfunction and nonspecific airway hyperresponsiveness.

**AIRWAY WALL REMODELING AS A FOE**

**Amplifying the effect of smooth muscle shortening.** Moreno and colleagues (81) mathematically modeled the effect of thickening the inner airway wall to show how it can amplify the degree of luminal narrowing for a given degree of ASM shortening. Their analysis showed that increasing the thickness of the inner wall produced simulated agonist-response curves that closely resembled in vivo airway challenges in asthmatic individuals, at least with respect to the increase in maximal airway narrowing. This mathematical model has since been used in more realistic computational schema incorporating measured values for airway wall dimensions from asthmatic and normal airways, and these studies have confirmed the predictions of Moreno et al. (53, 63).

**Increasing the ability of the airways to generate radial stress.** One of the most consistent of the pathologic findings in asthma is an increase in ASM mass. Lambert et al. (63) concluded from biomechanical modeling that “for a given maximal muscle stress, greater muscle thickness allows the development of greater tension and thus more contraction of the lumen.” If the smooth muscle in asthmatic airways is capable of generating the same stress as normal ASM, then the greater cross-sectional area of muscle will lead to greater force development to more easily overcome the
preloads and afterloads that normally moderate smooth muscle shortening and airway narrowing. Armour et al. (1) demonstrated that isometric force generated in vitro is directly related to ASM mass in human bronchial ring preparations. If exaggerated airway narrowing in asthmatic patients is importantly dependent on increased ASM, then in vitro bronchial preparations from asthmatic patients should demonstrate exaggerated force production. These experiments have been performed and in the majority, force production from asthmatic tissues was not increased (2, 3, 10, 18, 19, 21, 38, 98, 101, 108, 113) (Table 1). The reason for this finding is not known but could be due to an altered (less contractile) phenotype of the ASM in asthma patients. Another explanation could be that force generation in vitro may not reflect the ability of ASM to shorten, which is what causes airway narrowing in vivo (69). Evidence that force generation does not necessarily reflect the ability of the ASM to shorten is provided by a study by Jiang et al. (55), who showed that antigen-sensitized ASM from dogs having in vivo hyperresponsiveness demonstrated an increased velocity and degree of ASM shortening without a concomitant increase in isometric force production. Solway and Fredberg (105) have postulated that increased ASM shortening velocity, without increased force production, could account for exaggerated airway narrowing.

Uncoupling of ASM from parenchymal recoil. Thickening of the adventitia can act as a geometric buffer by decreasing the outer wall radii length change during ASM shortening and luminal narrowing. The smaller change in the outer wall radii will lead to less distortion of the surrounding parenchymal attachments, which decreases the forces of interdependence (62, 63, 67, 69, 88). Bronchi distend as the lungs are inflated as a consequence of the decrease in pleural pressure. Pleural pressure is transmitted to the peribronchial space by the parenchymal attachments to the airways (parenchymal tethering) (75). As the lungs inflate and lung elastic recoil pressure increases, the lung parenchyma progressively increases its tendency to recoil away from the airway wall, whereas the airway tends to recoil away from the parenchyma. The resulting negative pressure provides an elastic load against which the ASM must act to narrow the lumen. If the peribronchial space fills with edema or inflammatory exudate, the effect will be to allow the airway to recoil inward and the parenchyma to recoil outward. The peribronchial pressure will become less negative and the elastic load on ASM will decrease. The magnitude of the load and how it changes during bronchoconstriction are two of the most important determinants of the degree of airway narrowing as evidenced by Macklem's theoretical analysis (69) and the experiments of Ding et al. (23), which showed that at low lung volumes and low transmural pressure the degree of airway narrowing in response to a contractile agonist is markedly increased. In addition to these studies, it is at least theoretically possible for exudate, edema fluid, and blood to shift from the submucosa to the peribronchial space during bronchoconstriction because of the pressure gradient between these two layers of the airway wall (68).

A consequence of lung parenchymal-airway interdependence is that airway caliber and the load on ASM can be altered by breathing at different lung volumes. Increasing end expiratory lung volume during acute attacks of asthma serves as a protective mechanism, but there is evidence that over time this hyperinflation can induce loss of lung elastic recoil, compromising this defense mechanism (28, 37, 92, 117). A possible explanation for the diminished elastic recoil is that over time the parenchymal attachments creep when subjected to high stress (43). Loss of recoil may be a substantial risk factor for life-threatening asthma attacks (35, 50).

These subacute changes in lung elastic properties should not be confused with the consequences of the dynamic changes in airway caliber that can occur during deep inspiration, such as occurs during spontaneous sighs. The effect of acute changes in lung volume

<table>
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<tr>
<th>Investigator(s)</th>
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<tr>
<td>Schellenberg et al., 1984 (101)</td>
<td>Bronchi, n = 1</td>
<td>No increase in maximal tension to leukotrienes or methacholine but increased response to histamine</td>
</tr>
<tr>
<td>Roberts et al., 1985 (98)</td>
<td>Bronchi, n = 1</td>
<td>No increase in maximal tension in response to methacholine</td>
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<tr>
<td>Cerrina et al., 1986 (19)</td>
<td>Bronchi, n = 5</td>
<td>No increase in maximal tension in response to histamine</td>
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<td>†Goldie et al., 1986 (38)</td>
<td>Bronchi, n = 7</td>
<td>No increase in maximal tension in response to carbachol or histamine; decreased relaxation to isoproterenol</td>
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<td>†De Jongste et al., 1987 (21)</td>
<td>Bronchi, n = 1</td>
<td>Increase in maximal tension in response to leukotriene C₄, methacholine, and histamine</td>
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<tr>
<td>Whicker et al., 1988 (113)</td>
<td>Bronchi, n = 5</td>
<td>No increase in maximal tension in response to histamine or ACH</td>
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<tr>
<td>Cerrina et al., 1989</td>
<td>Bronchi, n = 4</td>
<td>No increase in maximal tension in response to histamine or ACH</td>
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<tr>
<td>†Bai, 1990 (2)</td>
<td>Trachea, n = 7</td>
<td>Increase maximal tension to ACH, histamine, and EFS</td>
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<tr>
<td>†Bai, 1991 (3)</td>
<td>Bronchi, n = 7</td>
<td>No increase in maximal tension in response to ACH, histamine, or EFS</td>
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<tr>
<td>†Bramley et al., 1994 (10)</td>
<td>Bronchi, n = 1</td>
<td>Increased maximal stress in response to ACH, histamine, and EFS; increased maximal smooth muscle shortening</td>
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<tr>
<td>*Thomson et al., 1996 (108)</td>
<td>Bronchi, n = 1</td>
<td>Increased maximal stress; increased maximal smooth muscle shortening</td>
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Sample number is denoted by n. Numbers in parentheses identify reference number. EFS, electrical field stimulation. †Increase in force generation. †Tissue was obtained at an autopsy rather than from a resection.
on airway caliber is related to the relative hysteresis of the length-stress relationships of the airways and the lung parenchyma. Deep inspiration induces bronchodilation if bronchial hysteresis exceeds parenchymal hysteresis and induces bronchoconstriction when parenchymal hysteresis exceeds bronchial hysteresis (33, 89, 94).

Reducing parallel elastance to the ASM. This mechanism is the opposite to the potential beneficial effect of airway remodeling discussed above (Providing a series elastic load). Although the amount of connective tissue is increased between the ASM cells and in the inner airway wall in asthmatic airways (8), it is possible that proteolysis associated with airway inflammation fragments and reorganizes the connective tissue proteins such that they are less effective in providing parallel elastance and/or smooth muscle constraint during contraction (9, 76).

Latch bridge formation. There is some evidence that the cross bridges between actin and myosin in smooth muscle are of two types: rapidly cycling cross bridges, which are attached for only a brief duration, and latch bridges, which are attached for a much longer time. Because the stiffness and hysteresivity of smooth muscle relates to the number of attached cross bridges, a greater number of latch bridges favor a stiff and poorly distensible airway. Cross bridges are continually disrupted in ASM due to the cyclic transmural pressure swings caused by tidal breathing and the larger, but less frequent strains related to periodic deep inspiration. The amplitude of length oscillation is a major mechanism by which smooth muscle shortening can be reduced (39, 40, 42, 58, 96, 102, 110, 111). Stiffening of the airway wall due to connective tissue deposition in all layers could attenuate the ability of tidal breathing and deep inspirations to stretch the smooth muscle. Decreased airway-parenchymal interdependence would do the same thing. This failure to break cross bridges could encourage the formation of “latch bridges,” which further stiffens the airway, leading to a situation where the smooth muscle is subjected to smaller and smaller tidal stretches or as Fredberg suggests “frozen muscle” (30–32).

ASM adaptation to short length. Smooth muscle can function over a much broader range of length than skeletal and cardiac muscle. This ability is vital to the normal action of hollow organs such as the bladder, bowels, and uterus where large volume changes within the hollow organ are required for normal physiological function. The first systematic study examining ASM tetanic force, shortening velocity, and compliance in relation to length was reported by Pratusevich et al. in 1995 (95). They proposed a new theory, smooth muscle plasticity (or adaptation), which could explain why force is (relatively) independent of length and velocity is proportional to muscle length. The theory states that the smooth muscle adapts to length changes by varying the number of contractile units in series. Functional studies indicate that adaptation of ASM to a length change occurs in two steps.

First, there is a decrease in the ability of ASM to generate force immediately after a length change. If the length of an adapted smooth muscle preparation is acutely shortened (95, 112) or lengthened (58, 111), the maximal force achievable by the muscle immediately decreases. It is likely that the mechanism of the decrease in force involves a rearrangement in the contractile filament overlap, partial dissolution of the labile myosin thick filaments, and/or disruption of the actin anchoring sites (i.e., dense bodies, dense plaques). Kuo et al. (58) showed that in relaxed tracheal smooth muscle there is a reduction of myosin thick filament density after a single length change of 30%. The magnitude of the reduction in force and the myosin thick filament density were closely related. This close relationship between force development and density of the myosin thick filaments at rest suggests that the resting density of thick filaments affects the density at the end of contraction, which was shown to increase 20–90% in rat anococcygeus smooth muscle (36, 119) and 144% in swine tracheal smooth muscle (42). It is unknown whether the increased density is due to lengthening of myosin thick filaments or due to formation of new filaments in parallel. Increased filament density is not observed in all smooth muscle types such as contracted guinea pig taenia coli smooth muscle preparations (119), and this finding is thought to be related to the normally cyclic activation of the muscle. It is unknown whether thick filament density changes in bronchial smooth muscle; however, plastic adaptation has recently been reported in a swine bronchial smooth muscle preparation (73).

Second, the reduction of contractile capacity is followed by a period of force recovery during which the muscle adapts to its new length without further perturbation. The time course of force recovery follows an exponential course over a period of ~30 min but with the majority of recovery occurring within 5 min (58, 111, 112). We propose that the acute and chronic smooth muscle shortening in the presence of airway inflammation in asthmatic patients allows remodeling of the airway such that the smooth muscle is maintained at a shortened length. Once plastic adaptation of the ASM occurs at the shortened length, the ASM is able to develop the same force as that previously generated at a longer length before adaptation. Unfortunately for the asthmatic patient, the newly adapted ASM at a shorter length is poised to cause even further airway narrowing when next stimulated by contractile agonists. Deep inspiration can reverse the adaptation process, but in the thickened, remodeled airways of asthmatic individuals the effects of deep inspiration may be attenuated (14, 29, 66, 80, 103).

There is evidence that a deep inspiration in asthma can effectively dilate airways but an increase in shortening velocity makes the dilatation last such a short time that it is difficult to measure (13, 51, 90). In the time it takes to measure airway resistance or forced expiratory flow, the effect may be over. Furthermore, if shortening velocity is increased in asthma, it could counteract the potent bronchodilatory effects of tidal
stretches, as the cross-bridges broken during the stretch reform during expiration. It could also explain, at least in part, the increase in variability of airway obstruction that characterizes asthma (97). If the variability is a fractal, an increase in velocity of shortening of ASM could be an important cause of volatility of airways obstruction (70). The resulting instability, as evidenced by daily variability of peak expiratory flow, is thought to be a risk factor for serious asthma attacks. Why should shortening velocity be increased? The most obvious explanation would be ASM unloading, but increased ASM force development or alterations in myosin light chain kinase might also account for it (55).

SUMMARY AND FUTURE DIRECTIONS

There is little doubt that considerable airway wall remodeling occurs in the airways of asthmatic patients. This review provides several examples of how structural remodeling may provide protection against excessive airway narrowing. Despite these theoretical benefits, the bulk of the evidence suggests that structural remodeling is more foe than friend, especially with respect to exaggerated airway narrowing in asthmatic patients. Studies of the functional consequences of airway remodeling have been hampered by the difficulty in obtaining a sufficient number of tissues from asthmatic patients to make a valid statistical comparison with normal tissue. Although ASM appears to be increased in asthma, in vitro studies do not confirm an increased ability of asthmatic airways to develop force. However, there is some indication that ASM in asthmatic patients may shorten to a greater extent and at an increased velocity, but further studies are required to confirm these observations. The functional consequences of airway remodeling with respect to airway parenchymal interdependence, series and parallel loads, and radial constraint are critically dependent on the mechanical properties and organization of the connective tissue proteins that contribute to the process. Further studies are needed to examine the mechanical properties of these tissues in asthmatic. Our understanding of how remodeling increases airway narrowing will be vastly improved when new techniques are developed, including high-resolution computed tomography, which make it possible to obtain real-time measurements of airway diameter and resistance during bronchial provocation testing and different respiratory maneuvers in asthmatic patients and normal individuals.

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