

# Bronchoconstriction and Airway Biology

## Potential Impact and Therapeutic Opportunities

Reinoud Gosens, PhD; and Chris Grainge, PhD

Recent work has demonstrated that mechanical forces occurring in the airway as a consequence of bronchoconstriction are sufficient to not only induce symptoms but also influence airway biology. Animal and human in vitro and in vivo work demonstrates that the airways are structurally and functionally altered by mechanical stress induced by bronchoconstriction. Compression of the airway epithelium and mechanosensing by the airway smooth muscle trigger the activation and release of growth factors, causing cell proliferation, extracellular matrix protein accumulation, and goblet cell differentiation. These effects of bronchoconstriction are of major importance to asthma pathophysiology and appear sufficient to induce remodeling independent of the inflammatory response. We review these findings in detail and discuss previous studies in light of this new evidence regarding the influence of mechanical forces in the airways. Furthermore, we highlight potential impacts of therapies influencing mechanical forces on airway structure and function in asthma. CHEST 2015; 147(3):798-803

**ABBREVIATIONS:** ASM = airway smooth muscle; EGFR = epidermal growth factor receptor; ICS = inhaled corticosteroid; LABA = long-acting  $\beta$ -agonist; MLCK = myosin light chain kinase; TGF- $\beta$  = transforming growth factor- $\beta$

Airway remodeling is a pathologic feature of asthmatic airways characterized by airway smooth muscle (ASM) thickening, subepithelial fibrosis, mucus cell hyperplasia, and airway neovascularization.<sup>1</sup> Airway remodeling is most profound in severe asthma where it may underlie, at least in part, persistent airway narrowing, airway hyperresponsiveness, lung function decline, and corticosteroid resistance.<sup>2,3</sup> Recent research has implicated mechanical forces in the initiation of these pathologic features. We review these developments

and discuss them in light of previous studies and therapeutic opportunities.

It is well recognized that mechanical forces influence tissue biology. Weight-bearing exercise induces mineralization of bone, leading to decreased fracture rates; high BP leads to cardiac and blood vessel remodeling; and weight lifting leads to skeletal muscle hypertrophy. Mechanical forces caused by bronchoconstriction have been shown in animal and human in vitro and in vivo work to not only induce symptoms but also influence airway biology akin to the

Manuscript received May 12, 2014; revision accepted August 11, 2014.

**AFFILIATIONS:** From the Groningen Research Institute for Asthma and COPD (Dr Gosens), Department of Molecular Pharmacology, University of Groningen, Groningen, The Netherlands; and Hunter Medical Research Institute (Dr Grainge), University of Newcastle, Newcastle, NSW, Australia.

**FUNDING/SUPPORT:** Dr Gosens received grant support from Chiesi and Boehringer Ingelheim Pharma GmbH.

**CORRESPONDENCE TO:** Reinoud Gosens, PhD, Groningen Research Institute for Asthma and COPD, University of Groningen, Hanzeplein 1, PO Box 30.001, NL-9700 RB Groningen, The Netherlands; e-mail: r.gosens@rug.nl

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-1142

changes induced by mechanical force in other tissues.<sup>1,4,5</sup> As the influence of mechanical force on the airways is more understood, practicing respiratory physicians may be able to take advantage of this knowledge and improve outcomes for their patients.

### What Are the Mechanical Forces Within the Airway?

Forces acting on the airways are complex and varied and occur from the earliest stages of development. In utero, the lung epithelium is a secretory structure, and normal lung development depends on pressure generated by liquid secretions and resistance from the developing larynx.<sup>6</sup>

Following birth, the lung stretches to fulfill its function, expanding and contracting physiologically each breath with lung inflation and deflation. Excessive lung stretch, which may be induced by mechanical ventilation, induces lung injury, with protective ventilator strategies used as standard practice to reduce this risk.<sup>1,7</sup> Whereas lung stretch is physiologic, forces generated in the airway by symptomatic bronchoconstriction are believed to be present only in disease.

### What Are the Consequences of Mechanical Forces During Bronchoconstriction: What Is Happening Physically?

ASM contraction leads to a reduction in airway caliber, increased resistance to airflow, and the clinical syndrome of asthma.<sup>2,3,8</sup> As the airway narrows, either individual epithelial cells must reduce in size or the internal surface of the airway must fold. Bronchial epithelial cells sit on a relatively noncompressible subepithelial membrane, and epithelial cells resist acute changes in size.<sup>1,4,5,9,10</sup> This leads to epithelial folding during bronchoconstriction, with areas of high pressure generated as the airway folds back on itself.<sup>6,11,12</sup> Figure 1 shows diagrammatically our current understanding of the mechanical results of bronchoconstriction.

### How Does the Epithelium Respond to Mechanical Stress?

Various in vitro models have been used to address whether the bronchial epithelium responds to compressive stress resulting from bronchoconstriction. Compression of bronchial epithelial cells, either apically to mimic airway folding or laterally to mimic direct lateral stress, has shown the bronchial epithelium to be mechanoresponsive.<sup>13-15</sup> Human bronchial epithelial cells grown at an air-liquid interface apically compressed using warmed humidified air (at pressures up to 30 cm H<sub>2</sub>O)

show an increased release of endothelin 1 and endothelin 2 as well as transforming growth factor- $\beta$  (TGF- $\beta$ ) 2 into basal medium.<sup>16</sup> Endothelin 1 induces smooth muscle contraction<sup>17</sup> and is implicated in airway remodeling,<sup>18</sup> and genetic polymorphisms have been associated with asthma, although small trials of endothelin receptor antagonists in asthma have been disappointing.<sup>19</sup> TGF- $\beta$ 2 is considered to be a fundamental molecule in the pathogenesis of airway remodeling, although attempts to modulate its actions in the airway have also been disappointing.<sup>20</sup>

Only short periods of apical compressive stress (minimum of 1 h) were sufficient to commit the cells to induce signaling in this model. To model the airway in more detail, a coculture method was developed where epithelial cells above a porous membrane were cultured with fibroblasts below the membrane and pressure applied only to the epithelial cells.<sup>14</sup> This model demonstrated that epithelial compression induced production of collagen I, III, and IV by fibroblasts in a time- and pressure-dependent manner. Lateral epithelial compression shows similar results, with three-dimensional gel-embedded coculture models undergoing compressive strain leading to increased production of collagen by fibroblasts just beneath the epithelium, indicating a concentration gradient from the epithelial surface.<sup>21</sup>

Mechanical stress also alters epithelial barrier function, disrupting tight junctions and increasing the transduction of lentivirus across the epithelial surface.<sup>22</sup> Repeated apical stress on cultured epithelial cells induces epithelial metaplasia with an increase in mucus production, even when apical stress is applied for as little as 10 min/d,<sup>23</sup> as well as inducing the release of YKL-40, a mediator associated with asthma severity and a reduction in lung function.<sup>24</sup>

These data suggest that the epithelium is receptive to mechanical (especially compressive) stress, inducing the release of mediators that drive extracellular matrix deposition in the airway following such stress. In addition, mechanical stress associated with bronchoconstriction increases mucus production and may induce changes in epithelial tight junctions and barrier function, all of which may be relevant in asthma pathology.

### How Does the Epithelium Detect Mechanical Stress?

To react to mechanical stress, the bronchial epithelium must detect this stress, and understanding the underlying mechanism may provide opportunities for intervention. Using air-liquid interface cultures of human bronchial

Download English Version:

<https://daneshyari.com/en/article/2899772>

Download Persian Version:

<https://daneshyari.com/article/2899772>

[Daneshyari.com](https://daneshyari.com)