Lessons from structure-function studies in asthma: myths and truths about what we teach

Asthma is a syndrome that is distinguished and diagnosed on the basis of abnormalities of pulmonary function (7). Patients with asthma should exhibit airflow obstruction characterized by periodic falls in forced expiratory volume in 1 s (FEV1), airflow obstruction that responds or normalizes to a bronchodilator, and airway hyperresponsiveness. Accordingly, asthma is unique among pulmonary diseases because it can be distinguished solely on the basis of pulmonary function tests. However, the mechanisms that cause asthma pathophysiology are still very unclear.

In the current issue of the Journal of Applied Physiology, Brown and colleagues (3) have performed an assessment of structure-function relationships in patients with moderate to severe asthma. The images of the structure of the airways were obtained with high-resolution computed tomography (HRCT) and then correlated to pulmonary function; in this case, the measures are simple spirometry and subdivisions of lung volume. Airway hyperresponsiveness, more precisely the role of active bronchoconstriction, was assessed by measurements before and after maximally dilating the airways with a β-agonist. The change in the airway structure-function relationship that occurred was considered to be a manifestation of the baseline tone of the airway smooth muscle or other processes sensitive to a β-agonist. This is basically a straightforward and obvious investigation, but the surprise here is that the findings are anything but straightforward and that they are certainly not predictable.

So what makes the results of this study so remarkable and what does this have to do with the dogma that we teach? Brown et al. (3) reach the surprising conclusion that the fall in FEV1 due to increased airway tone or other factors in the individual with asthma is mitigated by a rise in total lung capacity (TLC). Moreover, the fall in FEV1 was believed to be due to the fall in forced vital capacity (FVC) secondary to the rise in residual volume (RV). In addition, they suggest that FEV1 and FVC fall only when the compensatory rise of TLC is inadequate. In reaching this startling conclusion, the authors draw into question some commonly held assumptions about structure-function relationships in asthma. First, we commonly assume, and teach, that the fall in FEV1 is due to airway narrowing; yet, Brown and colleagues show that, whereas airway diameters dilate in response to a β-agonist as assessed by HRCT (Table 6 in Ref. 3), these dimensional changes are not related to the fall in FEV1! To explain this unexpected finding, they propose the following theory. The fall in FEV1 after bronchodilation is highly correlated to the fall in FVC; if the fall in FEV1 is principally the result of the fall in FVC then the boundaries of the vital capacity (either RV or TLC) must have changed. Asthma (baseline smooth muscle tone) was associated with, on average, a rise in RV of nearly 1 liter (0.091 liter), but because the TLC also rose by over 0.6 liter the FVC only fell by 0.27 liter. In other words, the fall in FVC was mitigated by a rise in RV of nearly 1 liter (0.091 liter), but because the measurements of Vtg are artificially elevated in the current study, the conclusion that FVC is preserved by a rise in TLC is probably still valid. TLC rises due to a loss of chest wall elastic recoil and/or a loss in lung elastic recoil. Investigators over 25 years ago noted and speculated on this phenomenon (6, 12) and yet surprisingly little has been done since. Brown et al. (3) suggest that altered respiratory muscle activity and/or loss of lung elastic recoil might explain how TLC rises in the presence of active asthma. Of course, the increase in TLC must be finite because the thorax has some structural limit. This would nicely account for why FEV1 falls in individuals with more severe asthma, because this structural limit is reached and a rise in TLC can no longer defend against the fall in FVC. The question remains, what and where is the sensor for this increase? Is it in the airways, parenchyma, or chest wall? What signal is sensed? Is it inflammation, stretch, or something else altogether? Clearly, further work is needed, but one clue is the observation by Brown et al. (Fig. 7 in Ref. 3) that the increase in TLC is correlated to changes in large airway dimensions induced by the ravages of asthma. The second clue is the finding that patients with the highest FVC had the greatest compensatory rise in TLC; given that we spend most of our time breathing at functional residual capacity (FRC), it is intriguing to think that FRC might be monitored in some way through sensing of events within the airway wall.

The second myth that we teach that this study exposes concerns the true nature of FEV1, and hence the mechanism by which it improves with a β-agonist. In the current study, the authors did something quite usual; they gave a maximal β-agonist treatment, assuming that any remaining lung dysfunction was the result of more permanent, presumably structural, alterations. The response appears principally to be a dilation of airway dimensions (Table 6 in Ref. 3), as assessed with HRCT, which is not related to improved spirometric metrics but is instead related to less gas trapping (Fig. 7 in Ref. 3). One possibility not considered by the authors is that neither FEV1 nor FVC adequately assesses large-airway function. Indeed this is well known, and as our laboratory has previously shown, some individuals with asthma (~15%) have bronchodilator responses limited to the more central airways that are not assessed by spirometry measurements (16). A more provocative notion is that β-agonists, in addition to relaxing airway smooth muscle, also reverse airway closure by stimulating surfactant release from type II pneumocytes, which would then serve to restabilize airway patency (4, 9).

The third important finding of this study is that HRCT dimensions of large airways (r = 0.71, P = 0.003), but not

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Further investigations clearly need to be conducted. There is a need to explore the mechanism of the increase in TLC, especially the identity and location of the sensor mechanism for hyperinflation. The measurement of lung volumes and the reporting of FVC and FEV₁/FVC needs to become commonplace in contemporary asthma research. Lung volumes should be measured plethysmographically because gas-diffusion techniques are generally uninformative (7). The stage is clearly set for drug or other therapy interventions to further explore structure-function relationships in asthma, because the study of Brown et al. (3) shows the potential power of this approach. The clinical implications of this study are many. The major response of the lung to asthma appears to be airway closure and not, as previously thought, airway narrowing. If so, then the focus of current research needs to shift from small-airway narrowing to large-airway narrowing linked to abnormal airway closure. The results of the current study suggest that RV, TLC, and FVC are better markers of the true nature of asthma pathophysiology and airway remodeling respectively than is FEV₁. Given the rapid and breath-taking advances being made in imaging modalities, one predicts that structure-function studies will yield many new and exciting insights into asthma pathogenesis over the next decade.

REFERENCES


medium (\(P = 0.54\)) or smaller (\(P = 0.57\)) airways, are correlated to the ratio of FEV₁ to FVC (FEV₁/FVC; Fig. 1). It is currently taught that FEV₁/FVC is a measure of airway caliber (1, 7), and it turns out that this is true! Unclear is why only the larger conducting airways are structurally remodeled and the smaller ones are not. Animal models suggest that structure is affected in airways of all calibers. In any event, the finding that FEV₁/FVC is linked to airway structure provides a more convenient way to assess this remodeling compared with the invasiveness or cost of biopsy or the radiation exposure of HRCT. It also gives some credence to the current practice of biopsying the large-airway wall as a means to assess structural remodeling. An alternate view is that remodeling is not directly related to a fall in FEV₁/FVC but represents a protective mechanism, as postulated by McParland et al. in this journal (11). Natural history or longer term treatment studies are now needed to elucidate the mechanistic linkage of this provocative finding, but the study of Rasmussen et al. (13) illustrates the importance of assessing FEV₁/FVC in longitudinal studies or in other similar data sets.

What is not at issue is the mechanism of the elevation in RV. Here the mechanism is airway closure (8, 10) as supported by imaging studies (14), especially in an acute situation such as the reversal due to the inhalation of a β-agonist. However, the mechanism that links airway closure to airway responsiveness (Fig. 6 in Ref. 3) is more difficult to understand. Our laboratory has postulated and demonstrated in an animal model that structural alterations in airway wall dimensions and an increase propensity for airway closure can lead to airway hyperresponsiveness (2, 17). In this situation, airway hyperresponsiveness is caused by lung volume derecruitment and not airway narrowing per se, and, as suggested by Gibbons et al. (5), excessive lung volume derecruitment is related to more severe asthma.


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