Small Airway Disease Syndromes

Piercing the Quiet Zone

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Abstract

The role for direct assessment of small airway function in subjects with respiratory symptoms but normal airflow by spirometry is discussed. Small airway disease syndrome is described in numerous disease states using a multidisciplinary approach. Data demonstrate that small airway disease is related to presence of respiratory symptoms, exposure to inhaled toxins, presence of local and systemic inflammation, and presence of histologic abnormalities within the distal lung. Investigation of immunological derangements associated

with distal airway dysfunction in the setting of normal spirometry may provide insight into pathophysiological mechanisms that are present at disease onset. For the purposes of this symposium, data were reviewed in selected clinical conditions (obesity, environmental inhalational injury, and cigarette smoking) that have been recently studied in the André Cournand Pulmonary Physiology Laboratory at Bellevue Hospital using the forced oscillation technique.

Keywords: airway function; small airway; obesity; cigarette smoking; forced oscillation technique

(Received in original form October 4, 2017; accepted in final form October 30, 2017)

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Ann Am Thorac Soc Vol 15, Supplement 1, pp S26–S29, Feb 2018

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DOI: 10.1513/AnnalsATS.201710-767KV

Internet address: www.atsjournals.org

The role for direct assessment of small airway function in subjects with respiratory symptoms but normal airflow by spirometry is discussed. The relevance of this line of investigation was established by histologic identification of small airway abnormalities at a time when the pathologic changes were potentially reversible but when other tests (e.g., spirometry) were not appreciably altered (1). The limitation of spirometry to detect small airway dysfunction was established by both computational analysis and direct assessments of airway resistance (2, 3). Briefly, the multiplicity of airways in the periphery produces an increasing cumulative cross-section area, with a corresponding reduction in both airflow and airway resistance (Figure 1). Thus, disease localized in small airways may not be apparent on spirometry (i.e., the quiet zone) until the extent of disease is severe (4).

Accordingly, data will be reviewed to establish the role of small airway assessments in symptomatic individuals at an early stage of disease, when spirometry parameters remain within normal limits. Interest in this area of research has been present for several decades (5, 6). Numerous disease states (e.g., asthma and chronic obstructive lung disease) have been studied with a variety of techniques that capitalize on nonuniformity of airflow distribution and/or density dependence of inspired air (7, 8). For the purposes of this symposium honoring the achievements and legacy of André Cournand and Dickinson Richards, data were reviewed in selected clinical conditions (obesity, environmental inhalational injury, and cigarette smoking) that have been recently studied in the André Cournand Pulmonary Physiology Laboratory at Bellevue Hospital using the forced oscillation technique (FOT).

Obesity

Although recent studies have indicated that obese individuals may be at increased risk for development of asthma, there are several aspects of the obese state *per se* that may produce lower respiratory symptoms. Excess body weight with mass loading on the respiratory system results in lung and airway compression. The effect of mass loading and reduction in functional residual capacity is evident when the elevated respiratory resistance is reexpressed as specific conductance yielding normal values (9–13). Although resistance abnormalities are readily attributable to reduced lung volume, additional studies using the FOT have demonstrated heterogeneity of peripheral airway function that is independent of lung volume and associated with increased dynamic elastance (14–16). These findings may reflect expiratory flow limitation

Figure 1. Schematic of the respiratory system illustrating the branching nature of the airway tree and corresponding airway generation number. The red-blue shaded area illustrates the increase in cumulative cross-sectional area that occurs within the peripheral airways. The peripheral airways, beyond the 16th generation, only account for about 20% of the total airways resistance (R_{aw}).

and/or airway closure in the tidal range (13, 15, 17–19).

Central vascular congestion is a component of the obese state that may also produce small airway dysfunction (13, 14, 20–24). The link between circulatory congestion and small airway dysfunction reflects to the proximity of the airways to the vasculature within the distal lung unit. The role of circulatory congestion is difficult to assess clinically, but the magnitude of small airway dysfunction in obesity has been shown to correlate with the increase in pulmonary capillary blood volume (21). Potential mechanisms for small airway dysfunction in this setting include airway dysfunction due to interstitial edema from elevated capillary hydrostatic pressure and/or airway closure due to increased ventricular afterload with capillary distension. The latter mechanism may be less likely, because pulmonary vascular resistance has been shown to remain normal in obese subjects despite presence of pulmonary vascular congestion (25). Regardless of the precise underlying mechanism, a link to obesity cardiomyopathy has recently been suggested by demonstration that these individuals may not achieve the high cardiac output state of obesity (21).

The relative contribution of the aforementioned lung compression, circulatory congestion, and/or capillary

leak is difficult to determine clinically. Nevertheless, these functional abnormalities are causally due to obesity *per se* and do not necessarily indicate presence of coexistent disease. In this context, it is not surprising that weight loss may result in simultaneous improvement in respiratory mechanics, reduction of circulatory congestion, and resolution of respiratory symptoms (11).

Environmental Inhalational Injury

Study of individuals exposed to dust from the collapse of the World Trade Center on September 11, 2001 provided the opportunity for in-depth studies of small airway injury. Early observations after the disaster indicated that individuals with new-onset respiratory symptoms frequently demonstrated normal spirometry (26–28). Small airway dysfunction in these subjects was subsequently demonstrated by both noninvasive testing using FOT and assessment of frequency dependence of compliance by esophageal manometry (29). Because spirometry remained within normal limits, these findings were attributable to disease localized within the small airways. Of note, the magnitude of small airway abnormality was directly correlated to both severity and frequency of wheeze (30). Moreover, attribution of

respiratory symptoms to isolated dysfunction of small airways was confirmed by FOT during methacholine challenge testing (31, 32). A link between small airway dysfunction and systemic inflammation was established by analysis of serum C-reactive protein levels (33). Finally, small airway and distal lung injury was confirmed in this population of subjects on histologic evaluation (34). Taken together, these observations highlight that oscillometry overcomes the poor sensitivity of spirometry in the diagnosis of airway disease.

On the basis of the above observations, a case-control study was performed in collaboration with the New York City Department of Health and Mental Hygiene using FOT as a screening test in both symptomatic (case) and asymptomatic (control) subjects (35). Spirometry did not identify disease in symptomatic cases; normal airflow was observed in the overwhelming majority (~81%). Addition of FOT yielded elevated resistance in the majority (~67%) of these cases, indicating dysfunction not detected by spirometry. Although FOT abnormalities were noted in some asymptomatic subjects, they were predominately confined to overweight or obese individuals, in accord with prior observations. Finally, multivariate analyses confirmed that lower respiratory symptoms were associated with both intensity of

World Trade Center dust exposure and presence of small airway dysfunction.

Cigarette Smoking

The onset of chronic obstructive pulmonary disease (COPD) within the small airways leads to irreversible tissue destruction and airflow obstruction (1, 6). Narrowing and loss of small conducting airways was demonstrated by micro computed tomography of surgical specimens in early-stage COPD (36). Because these distal airways contribute minimally to total resistance, spirometric abnormalities required for the diagnosis of COPD using the Global Initiative for Chronic Obstructive Lung Disease criteria may not be evident in the earliest stages of disease.

On the basis of these considerations, a study was performed based on the hypothesis that if small airway dysfunction is an early manifestation of a disease that may evolve to COPD, it should be associated with inflammation at the site of injury (e.g., the distal lung) (37). Accordingly, asymptomatic cigarette smokers with

normal spirometry were recruited to undergo evaluation of distal lung function by FOT and evaluation of distal lung inflammation using bronchoalveolar lavage.

The data demonstrated that FOT abnormalities, consistent with distal lung dysfunction, were associated with presence of inflammation within the distal lung. Importantly, these findings occurred at a point during disease progression when a clinical diagnosis of COPD on the basis of symptoms and lung function could not be established using Global Initiative for Chronic Obstructive Lung Disease criteria. The pattern of inflammation indicated activation of both innate and cellular immune responses with a pattern that has been shown to predict disease progression in patients with established COPD. Specifically, there were elevated inflammatory cells (neutrophils and lymphocytes) as well as elevated chemoattractants (interleukin-8 and eotaxin) and inflammatory cytokines (fractalkine). These findings are compatible with observations of inflammatory markers in subjects with established COPD (6, 38).

Thus, investigation of distal respiratory mechanics in asymptomatic smokers who do not meet criteria for COPD may identify subjects who are at risk for progression to clinical disease.

Conclusions

Small airway disease syndrome is described in numerous disease states using a multidisciplinary approach. Data demonstrated a relationship between small airway disease to development of symptoms, inhaled toxin exposure, presence of local and systemic inflammation, histologic abnormalities, and response to therapy. These findings indicate a role for assessment of small airway function in subjects with respiratory symptoms but normal airflow by spirometry. Investigation of immunological derangements associated with distal airway dysfunction in the setting of normal spirometry may provide insight into pathophysiological mechanisms that are present at disease onset. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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