Small airway disease: when the "silent zone" speaks up

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BACKGROUND

The human airways consist of approximately 23 generations of dichotomously branching tubes from the trachea to the alveoli. From generation 8 downstream, the small airways (< 2 mm in diameter) lack cartilaginous support, being more easily compressible/collapsible. Given the exponential increase in airway numbers, there is a rapid increase in total cross-sectional area; thus, airflow velocity decreases, and small airways resistance comprises only 10-20% of total airways resistance. It follows that extensive functional abnormalities in the so-called "silent zone" might not be detected by routine pulmonary function tests.[1]

OVERVIEW

A 68-year-old nonsmoker male (BMI = 41.2 kg/m^2) was referred for respiratory assessment due to insidious exertional dyspnea and dry cough. He had undergone hematopoietic stem cell transplantation approximately one year prior in the setting of acute myeloblastic leukemia. There was no clinical or laboratory evidence of graft-versus-host disease. Spirometry revealed no obstruction, and $FEF_{25-75\%}$ was reduced in proportion to a low FVC. Plethysmography showed a trend toward low "static" lung volumes and high specific airway resistance. Taken together, these results were considered equivocal in a severely obese subject[2] with a history of right upper lobectomy for congenital disease. Given concerns of incipient bronchiolitis obliterans, he was referred for more sensitive tests of small airway disease (SAD), the results of which were as follows: increased phase III slope and closing capacity (single-breath N_2 washout), increased ventilation heterogeneity in acinar airways relative to conducting airways (multiple-breath N_2 washout), and increased difference between resistance at 5 Hz and 20 Hz (impulse oscillometry). As it can be seen in Chart 1, these results were indeed consistent with SAD. Despite mild gas trapping without mosaic attenuation on chest CT, the consistency of the functional findings prompted immunosuppressive therapy. At the three-month follow-up visit, there was resolution of symptoms and uniform improvement in all functional markers of SAD.

Diagnosing SAD might be clinically relevant in the initial stages of several obstructive lung diseases, including asthma,[3] cystic fibrosis, and COPD. Tests of SAD may also reveal unsuspected airway abnormalities in sarcoidosis and some interstitial lung diseases, such as hypersensitivity pneumonitis and nonspecific interstitial pneumonia. Detecting SAD may change management in connective tissue diseases (e.g., rheumatoid arthritis, mixed disease), inflammatory bowel diseases, bone marrow and lung transplantation, common variable immunodeficiency disorders, diffuse panbronchiolitis, and diseases related to environmental exposures to pollutants, allergens, and drugs.[4] As herein described, insidious SAD might be a late complication of hematopoietic stem cell transplantation, even in the absence of graft-versus-host disease. Prompt aggressive treatment is paramount to improving survival.[5]

CLINICAL MESSAGE

Although physiological tests interrogating the "silent zone" are not widely available, they can provide valuable information in cases when the diagnosis and quantification of SAD might impact on clinical decision making. The lack of reliable reference values and cut-offs for abnormality remains an extant issue: in many circumstances, longitudinal worsening—or improvement in response to treatment—is more useful. If feasible, combining techniques (Chart 1) further improves diagnostic accuracy.

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Chart 1. Selected techniques aimed at diagnosing and quantifying the severity of small airway disease.

Technique fundamentals	Rationale for key variables	Caveats and limitations
Spirometry Abnormally slow airflow relative to forced expired volume signals airway obstruction. Air from larger proximal airways is expired earlier and at a greater speed, whereas air from smaller distal airways is expired later and at a slower speed.	• ⇩ **$FEF_{25-75\%}$** As lung volume falls, diseased small airways collapse at an earlier time and closer to the alveolus. This reduces the maximum expiratory flow that can be achieved during mid- to late expiration. • ⇩ **FEV_3/FVC and/or ⇧ 1 − (FEV_3/FVC)** By considering flows over a longer period, FEV_3 includes a larger fraction of small airways, estimating the growing proportion of units with longer time constants. • ⇩ **FEV_1/FEV_6 and/or ⇩ FEV_3/FEV_6** Using FEV_6 may reduce the impact of a variable FVC in these ratios. • ⇧ Slow VC (SVC)-FVC difference In the presence of SAD, more air is exhaled when there is less airway compression during the slow maneuver. This might lead to low FEV_1/SVC despite preserved FEV_1/FVC.	Bronchodilating effects of deep inspiration might increase FEVs, masking (mild) bronchoconstriction. $FEF_{25-75\%}$, in particular, is highly dependent on FVC: changes in FVC will markedly affect the portion of the flow-volume curve examined. None of these variables is specific to SAD; moreover, they are a) relatively insensitive to early disease, b) redundant to FEV_1/FVC in more advanced disease, and c) effort-dependent. There is a lack of reference values for FEV_1/SVC: this ratio declines with aging faster than does FEV_1/FVC, potentially over-diagnosing obstruction in the elderly.
Plethysmography ⇧ changes in box pressure relative to variations in mouth ("alveolar") pressure at end-tidal expiration signal ⇧ lung volume (FRC): RV is given by FRC − ERV. ⇧ changes in the pressure required to generate flow indicate ⇧ airway resistance at a given lung volume (sR_{aw}).	• ⇧ **RV and/or ⇧ RV/TLC** RV and RV/TLC are elevated in the presence of premature airway closure and air trapping. RV/TLC may be a more useful marker of gas trapping as TLC might be increased in obstructive lung disease. • ⇧ **sR_{aw} and/or ⇩ 1/sR_{aw} (sG_{aw})** sR_{aw} and sG_{aw} might be abnormal in the presence of widespread SAD. FEV_1 is sensitive to changes occurring upstream from the choke point, whereas sR_{aw} is sensitive to changes in resistance anywhere along the airway. sR_{aw} may change without significant change in FEV_1.	RV is not directly measured: errors in IC and/or SVC may lead to spuriously high RV. High RV/TLC in the presence of preserved TLC may be seen in patients with expiratory muscle weakness. sR_{aw} and sG_{aw} are very sensitive to central airway pathology but less sensitive to peripheral changes (unless there is widespread SAD). Both have wide limits of normal.
Single-breath N_2 washout After inhalation of 100% O_2, exhaled N_2 is measured from TLC to RV. In phase I, N_2 is not detected ($V_{D_{ana}}$). Subsequently, exhaled N_2 rises swiftly (phase II) followed by a slowly rising alveolar "plateau" (phase III). In phase IV, exhaled N_2 increases when better-ventilated units close and less-ventilated regions (less exposed to O_2; thus, richer in N_2) empty.	• ⇧ **phase III slope** A flat phase III slope indicates that all units received the same amount of O_2, emptying simultaneously. A steep phase III slope indicates the sequential emptying of units with different N_2 concentrations due to patchy disease. • ⇧ **volume above RV at which phase IV starts (closing capacity)** The higher the closing capacity as a fraction of VC, the earlier the closure of the gravity-dependent small airways. Thus, the higher the closing capacity, the greater the trend toward gas trapping.	The pleural pressure gradient may contribute to regional differences in N_2 concentration: regional differences in air-space compliance may create differences in the time required to fill and empty different lung regions. Changes in any of the generations of the conducting airways may affect the phase III slope. Closing capacity increases with increasing intraabdominal pressure, age, decreased pulmonary blood flow, and pulmonary parenchymal lung disease associated with poor compliance.
Multiple-breath N_2 washout After inhalation of 100% O_2, sequential single breaths are followed as N_2 is progressively washed out. Whereas the phase III slopes of the initial breaths are strongly influenced by S_{acin}, the progressive increase in slopes thereafter is thought to be influenced by S_{cond}.	• ⇧ **lung clearance index** The higher the lung turnovers (FRC equivalents) required to wash out the tracer gas (N_2) to 1/40th of the original concentration, the lower the gas mixing efficiency across the whole lung, i.e., poor global ventilation homogeneity. • **S_{acin} and S_{cond}** ⇧ S_{acin} indicates ventilation inhomogeneity distal to the terminal bronchioles, i.e., in the small airways. As such, it is frequently seen in smokers with preserved FEV_1. Conversely, S_{cond} is more closely related to sG_{aw} and forced expiratory flows, i.e., larger airways function.	There are conflicting data on whether S_{cond} does provide a better metric of SAD compared with S_{acin} across different obstructive airway diseases; there are technical controversies over the best approach to measure the phase III slope across multiple breaths; and a variable effect of different tidal volumes. There is critical dependence on accurate time matching between the flow sensor and the gas analyzer.

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Chart 1. Selected techniques aimed at diagnosing and quantifying the severity of small airway disease. (Continued...)

Technique fundamentals	Rationale for key variables	Caveats and limitations
Impulse oscillometry Airflow oscillations are artificially generated by a loudspeaker at frequencies from 2 Hz to 30 Hz and superimposed on the natural flows at tidal volume. Resistance represents impedance to airflow changes. At high frequencies, the oscillations might be "blocked" at the level of narrowed larger airways. At lower frequencies, the oscillations can pass over the larger airways, reflecting the whole lung resistance. Reactance represents impedance to volume changes.	• ⇧ $R_5 - R_{20}$ Since R_5 reflects the resistance of the entire trachea-bronchial tree where R_{20} is primarily influenced by the large airways caliber, their difference is biased to reflect the functional properties of the small airways. • ⇩ X_5 Since the lungs' ability to store capacitive energy is primarily manifest in the small airways, low reactance at low frequencies signals SAD. • ⇧ **AX** AX is the integrated low frequency respiratory reactance magnitude between 5 Hz and the resonant frequency, i.e., when inflation pressure and elastic recoil cancel each other in the transition from passive distension to active stretching. AX is related to respiratory compliance and therefore to small airway patency. AX closely correlates with $R_5 - R_{20}$.	Results vary by manufacturer. Impulse oscillometry measurements are influenced by extrathoracic upper airway artifacts (swallowing, glottis closure). Elastance or capacitance refers to energy return properties of the lung, like electric circuits, not stiffness during inflation (more intuitive for clinicians). Therefore, the reactance at lower frequencies would change in the same direction in fibrosis, emphysema, or SAD, i.e., it would become even more negative. Hence, the direction of change in reactance does not differentiate between obstructive and restrictive diseases.

⇩: decreased; FEV_3: forced expiratory volume in three seconds; ⇧: increased; FEV_6: forced expiratory volume in six seconds; SAD: small airway disease; FRC: functional residual capacity; ERV: expiratory reserve volume; sR_{aw}: specific airway resistance; sG_{aw}: specific airway conductance; IC: inspiratory capacity; $VD_{ana:}$ anatomic dead space; S_{acin}: ventilation heterogeneity in acinar airways; S_{cond}: ventilation heterogeneity in conducting airways; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5Hz; and AX: reactance area.

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