Lung function in the elderly:
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Panagiotis Panagou,
Evangelos Bouros,
Argyrios Tzouvelekis,
Vassilios Tzilas,
Demosthenes Bouros

First Academic Department of Pneumonology, Interstitial Lung Diseases Unit, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece

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Correspondence to:
Prof. Demosthenes Bouros MD, PhD, FERS, FAPSR, FCCP;
First Academic Department of Pneumonology,
Interstitial Lung Diseases Unit,
Hospital for Diseases of the Chest, "Sotiria",
Medical School, National and Kapodistrian University of Athens, Athens, Greece;
152 Messogion Ave., Athens 11527, Greece
E-mail: debouros@med.uoa.gr
debouros@gmail.com

Pulmonary structure and function change significantly between young adulthood and old age. Aging generates four important changes in the structure and function of the respiratory system.[1] There is a reduction in the elastic recoil of the lung causing "senile emphysema", a condition characterized by reduction in the alveolar surface area (elastic elements of the lung degenerate, parenchymal tissue is lost) without alveolar destruction, which is associated with hyperinflation, increased lung compliance and reduction in alveolar-capillary diffusing capacity. There is a decrease in the compliance of the chest wall, due to calcification of its articulations, dorsal kyphosis and **"barrel chest"**. There is a decrease in the strength of respiratory muscles (intercostal muscle mass and force are reduced) which correlates with cardiac Index, nutritional status and hyperinflation and there is a reduction in the ventilatory response to hypoxia and hypercapnia as well as in the perception of increased airway resistance.[2,3]

Furthermore aging depresses **cough reflexes** and disturbances of innate immunity predispose the elderly to pulmonary inflammation. These changes affect pulmonary function tests and gas exchange, but adaptive changes in breathing frequency and tidal volume serve to maintain adequate ventilation and ventilatory responsiveness to hypoxia and hypercapnia.[4]

Spirometry is **underused** and difficult to perform in older people and there is no spirometric gold standard specific in this population for the diagnosis of obstructive disease, with the most common error being the lack of a plateau at the end of exhalation, so a **FET ≤6 s** can be used. Imaging can to some extent integrate or also substitute for respiratory function data in highly problematic cases, providing important clinical information.[5]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary has defined **stage 1** chronic obstructive pulmonary disease (COPD) as airflow limitation where forced expiratory volume in one second/forced vital capacity (FEV1/FVC)% is ≤70% and FEV1% predicted is ≥80%. **Stage 2** COPD has been defined as a FEV1/FVC% of ≤70% and an FEV1% pred of ≤80%. These criteria are set regardless of age in an attempt to simplify the diagnosis.[6]

The trade-off with simplicity, however, comes at the expense of **misclassification**. Since the FEV1/FVC ratio falls with age,[7] the use of a fixed cut-off point for defining COPD becomes more inaccurate with increasing age. These criteria were proven to lead to a significant degree of over-diagnosis of

chronic airflow obstruction in those aged ≥70 yrs normal subjects and in those ≥80 years to even stage 2 COPD.[8]

Additionally one fifth of older adults with observed FEV1/FVC% above the NHANES-III fifth percentile had FEV1/FVC% ratios <70% (normals misidentified as abnormal).[9]

The lower limit of normal was estimated as: **Predicted-1.65 x residual SD** (i.e. the estimated 5th percentile). Furthermore in normal elderly blacks it was found that they had an FVC about 6% lower than elderly whites, even after correcting for standing height, sitting height (trunk length), and age, so the popular use of spirometry reference values from studies of middle-aged white subjects by applying a 12% race correction factor for black patients appears to overestimate predicted values.[10]

Also in another study cognitive impairment, shorter 6-min walk distance, and lower educational level were found to be independent **risk factors** for a poorer acceptability rate for spirometry (logistic regression analysis). **Male sex and age** were risk factors for a poorer reproducibility of FEV_1 and reproducibility tended to improve with time.[11]

The use of **Forced Oscillation technique** (FOT) by **impulse oscillometry** (IOS) and in particular **respiratory impedance** (Z5), resonant frequency (Fres), and respiratory **resistance** (R5, R20, R5–R20) and **respiratory reactance** (X5) were shown to have good relevance compared with spirometry for geriatric patients, so IOS may serve as an alternative method for spirometry in elderly subjects for the evaluation of the state of lung function.[12]

Expiratory flow limitation (EFL) as assessed by the negative expiratory pressure method during tidal breathing may be also be of value in cases when spirometry is inadequate in the elderly.[13]

The calculation of **spirometric Z-scores** (predicted-measured/RSD) by Lambda-Mu-Sigma (LMS) rigorously accounts for age-related changes in lung function. Recently, the **Global Lung Function Initiative** (GLI)[14] expanded the availability of LMS spirometric Z-scores to multiple ethnicities. Hence, in aging populations, the GLI provides an opportunity to rigorously evaluate **ethnic differences** in respiratory impairment. The LMS describes the mean (Mu) — representing how spirometric measures change based on predictor variables (age and height); the *coefficient-of-variation (Sigma)* — representing the spread of reference values; and *skewness (Lambda, incorporating a spline function)* — representing departure from normality. A **Z-score of -1.64** defines the lower limit of normal as the 5th percentile of the distribution. Notably, using data from large reference populations of asymptomatic lifelong non-smokers, the GLI has recently published equations that expand the availability of LMS-calculated spirometric Z-scores, allowing respiratory impairment to be established across multiple ethnicities.

So by using these reference equations ethnic differences in an aging population was found in respiratory impairment, including prevalence and associations with health outcomes. In particular, African-Americans present a unique public health challenge, with high rates of respiratory impairment being associated with mortality but not respiratory symptoms.[15]

It was recently observed that a small proportion (7%) of subjects with **CT-defined emphysema** were identified by the 0.70 threshold for FEV1/FVC but not by the LLN. However, there is no evidence that CT-emphysema corresponds to a clinical entity that can benefit by *inhaled therapy*.[16]

In a cohort of very old adults, low FEV_1 expressed as $FEV1/Ht^3$ was found to be a short-term predictor of all-cause mortality, hospitalization and decline in physical and mental functioning independently of age, smoking status, chronic lung disease and other co-morbidities. So **FEV_1/Ht^3** may be a potential risk marker for frailty and adverse health outcomes in the elderly.[17]

The **incidence of airflow limitation** per 1000 person-years was 28.2 using a fixed ratio and 11.7 with LLN, corresponding to a 1.41-fold higher incidence rate using a fixed ratio. The incidence increased dramatically with age when using a fixed ratio, but less so when using LLN. In addition, a sex effect was observed with the LLN criterion. LLN airflow limitation was associated with increased 5-year mortality. Presence of fixed-ratio airflow limitation in individuals classified by LLN as non-obstructive was not associated with increased mortality.[18]

In the Perspective of classic spirometry with **MEFV curve** was argued many years ago that it is an overall expression of the lung's mechanical behaviour but reflects a very complex system and a series of mechanical events that is very poorly understood.[19] So we come to the question: *Do we need to measure airway resistance?* Within the lung, at breathing frequencies, 50% of the resistance originates within the large airways, 40% within the lung tissue (due to dissipative frictional losses among the various structural elements), and only 10% within the small airways, again reflecting their enormous cross-sectional area. Because such a small amount of resistance emanates from the small airways, it is very difficult to detect changes in this area using conventional spirometry, and so this region has

been dubbed the **"Silent" or "Quiet"** zone of the lung. Because of this RAW is more sensitive than spirometry to detect changes in the aging lung.

Since **Raw** is highly dependent on lung volume, it is better expressed as specific airway conductance, sGaw, where sGaw = (1/Raw)/ thoracic gas volume (TGV). sGaw is a measure of intrinsic airway resistance, which is volume independent.

Raw can also be measured by the interrupter technique (Rint),[20] and the forced oscillation technique (RFOT), both of which are performed during quiet breathing and require no special maneuvers like the FEV_1. As such, both Rint and R-FOT are also more sensitive indicators of intrinsic Raw than FEV_1.

In addition, the FOT offers additional insight into the elastic properties of the respiratory system and airway distensibility[21-23] as well as into the homogeneity of ventilation. Because these methods are non-invasive and can be performed during quiet breathing, they have special appeal for patients who cannot perform spirometry or may have difficulty with proper technique, including children, the elderly, patients during sleep, or those with neuromuscular disease. Each of the methods has its own advantages and disadvantages.

In conclusion: 1) GLI reference equations for spirometry should be used by all lung function laboratories for all ages and ethnic groups. 2) The GLI LLN 5th percentile may be used along with GOLD guidelines to detect changes in lung function in the elderly in order to avoid overdiagnosis of airway obstruction. 3) In cases of clinical doubt more sensitive RAW measurements may have a role.

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