# Revisiting Peter Macklem's old dream through the PRISm of lung volumes

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**In healthy asymptomatic smokers with normal $FEV_1$/FVC, abnormal CT lung volumes that reflect small airway dysfunction and emphysema could be used as a biomarker to identify susceptible smokers at increased risk of progressing to COPD** https://bit.ly/3XZDj1s

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In the 1960s, Peter Macklem and, later, Sonia Buist shared the vision of a marker to identify smokers who will progress to COPD based on small airway function assessment [1–3]. While this discussion has continued, the unmet need of prediction remains the same.

In this issue of *ERJ Open Research*, Zeng *et al.* [4] add another piece to the evidence that small airway dysfunction is at the early origin of airflow limitation leading to COPD. Taking advantage of the massive COPDgene cohort, the study highlights the heterogeneity of COPD, since parenchymal and airway abnormalities were associated with a different functional lung volume pattern at baseline but also with different trajectories and disease evolution and prognosis. The authors reported an analysis based on >2000 "healthy" current and ex-smokers (>10 pack-years) with preserved spirometry at baseline, with a follow up of 5 years and up to 10 years for some of the patients. The aim of the study was to determine if computed tomography (CT)-measured lung volumes defined by total lung capacity ($TLC_{CT}$), functional residual capacity ($FRC_{CT}$) and their ratio ($FRCT_{CT}/TLC_{CT}$) could predict future lung function decline and progression to COPD. The hypothesis of the study was that healthy smokers who progress to COPD have predominant small airway disease (SAD) at baseline, compared to the patients with a predominantly emphysema phenotype. At baseline, more than half of the patients were women, with a mean age of 58 years, and half of them were current smokers. The authors validated in a sample of the cohort (n=432 patients) a very high level of correlation between plethysmographically and CT-measured lung volumes. The authors highlighted the ability of CT-derived volumes at baseline (*i.e.* $TLC_{CT}$, $FRC_{CT}$ and $FRC_{CT}/TLC_{CT}$) to identify the "susceptible smokers" who will progress to spirometric COPD and decline in decrease of the ratio forced expiratory volume in 1 s ($FEV_1$) to forced vital capacity (FVC). They showed that higher CT-derived volumes were significantly associated with a greater decline in $FEV_1$/FVC during the 5 years of follow-up, whether the CT volumes were expressed as continuous or as categorical variables (low, intermediate or high tertile). Indeed, $TLC_{CT}$ and $FRC_{CT}$ considered individually were associated with a higher risk of spirometric COPD progression overtime in a linear regression model ($p<0.001$). Interestingly, the pattern of decline in $FEV_1$/FVC was different when participants were categorised by high $TLC_{CT}$ *versus* high $FRC_{CT}/TLC_{CT}$. Participants with higher $TLC_{CT}$ had a relatively stable $FEV_1$ but a relatively increasing FVC over the 5-year follow-up period ($p<0.001$) while those with higher $FRC_{CT}/TLC_{CT}$ had a relative decline in both $FEV_1$ and FVC over the 5-year follow-up time ($p<0.002$ and $p<0.007$, respectively). This observation is of particular interest since it emphasises the role of both lung (parenchyma) and chest wall compliance in the respiratory system. The loss of elastic recoil in the wall of the small airways, leading to air trapping, is also driven by chest compliance and not only by the reduction of elastic tissue in the pulmonary parenchyma during COPD [5]. The chest wall can also contribute significantly to changes in respiratory system elastance. That means that patients with a greater thoracic

compliance (high $TLC_{CT}$) will experience less SAD, at the expense of the chest wall, *i.e.* the respiratory muscles (*e.g.* diaphragm), thoracic cage and mediastinum. Indeed, thoracic compliance will help to keep the airways open, resulting in less small airway collapse and air trapping, and less lung hyperinflation (higher $FRC_{CT}/TLC_{CT}$ ratio). This profile corresponds to patients without SAD and high $TLC_{CT}$.

The severity of spirometric COPD that was developed was also different: those with higher $TLC_{CT}$ were more likely to develop Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 disease and less likely to develop preserved ratio and impaired spirometry (PRISm) or GOLD 2 disease. Conversely, those with higher $FRC_{CT}/TLC_{CT}$ were less likely to develop GOLD 1 disease but more likely to develop PRISm and GOLD 2 stage. Because of the distinct pattern of evolution when participants were categorised by their baseline upper tertile of $TLC_{CT}$ *versus* $FRC_{CT}/TLC_{CT}$, patients at baseline were then categorised into three mutually exclusive groups: 1) high $TLC_{CT}$ (but not high $FRC_{CT}/TLC_{CT}$), also called the emphysema group ("hyperexpanded", 30% of the patients); 2) high $FRC_{CT}/TLC_{CT}$ ratio (but not high $TLC_{CT}$) linked to an increase in $FRC_{CT}$ related to SAD ("air trapped", 30%); and 3) patients with both high $TLC_{CT}$ and high $FRC_{CT}/TLC_{CT}$ ("hyperinflated", 5%). The authors demonstrated that subjects with $TLC_{CT}$ in the upper tertile had higher emphysema scores at baseline and less SAD (parametric response mapping (PRM) air trapping and airway thickness measured by the Pi10 index (*i.e.* square root of wall area of a 10-mm lumen perimeter)) compared to the subjects with $FRC_{CT}/TLC_{CT}$ in the upper tertile. The air-trapped group had higher PRM gas trapping and Pi10, independently of smoking status. After 5 years of follow-up, 13% of the smokers at baseline developed spirometric COPD, >30% in the both high $TLC_{CT}$ and $FRC_{CT}/TLC_{CT}$ group, >10% in the high $FRC_{CT}/TLC_{CT}$ alone group and 15% in high $TLC_{CT}$ alone group. Mean annualised $FEV_1$ decline was 43 $mL \cdot year^{-1}$ and was similar between the three groups, despite a nonsignificative trend in the group with both high $TLC_{CT}$ and high $FRC_{CT}/TLC_{CT}$ (mean of −60 $mL \cdot year^{-1}$).

This study once again reaffirms that a subgroup of smokers, called susceptible smokers, will develop spirometric COPD and that small airway dysfunction precedes airflow obstruction. The study also highlights that current spirometric definition is not accurate enough to define early COPD. Dissemination of COPDgene-developed tools (PRM and lung volume measurements) are needed to further validate functional and imaging tools in the real world [6, 7]. We do believe that the democratisation of CT scanning, notably through lung cancer screening programmes, in this at-risk population offers a unique opportunity that should not be missed if coupled to up-to-date post-acquisition software, in order to achieve the old dream of early identifying smokers who will develop COPD. Whereas $FEV_1$ is a validated prognostic biomarker in COPD [8], it is clearly a late signal given that significant lung lesions have already occurred before it falls. In COPDgene, nearly 43% of the smokers with preserved lung function already have lesions on chest CT scan [9] and nearly 25% of small airways are already lost in GOLD 1 disease compared to GOLD 0 [10]. Indeed, lung volume assessment by plethysmography should be performed in smokers to detect early SAD through hyperinflation by the increase of ratio FRC/TLC or residual volume (RV)/TLC. RV is also first volume to increase in obstructive lung disease and can be a good measure to evaluate early-onset disease [11]. The present study cannot help guide how often plethysmography should be repeated. The high tertile with both high $TLC_{CT}$ and high $FRC_{CT}/TLC_{CT}$ did have more severe emphysema and SAD than the high tertiles with one anatomical damage, and over a third of people will develop spirometric COPD. It would be of interested to determine if within this group, the distribution of emphysema was similar to the high tertile of $TLC_{CT}$; notably, whether they have predominant paraseptal emphysema or a centrilobular pattern [12]. Another question that has not been addressed in the study is the quantification of airway mucus plugging that may contribute to increased FRC and TLC or both [13, 14]. These mucus plugs seemed always to be trapped at the same location in another analysis of COPDgene and it is regrettable that these datasets could not be linked. To what extent reversal of the small airway plugging will be required, once treatable, to improve lung volumes will be of major significance in preventing progression toward COPD. It would also have been a great opportunity to assess candidate serum biomarkers (*e.g.* club cell secretory protein) [15, 16]. Furthermore, the prevalence of interstitial lung abnormality was not mentioned in the study. Indeed, patients with the lowest volumes but small airway dysfunction may represent the early onset of COPD with developmental lung defect growth and it is highly likely that other markers, beyond PRM, will be required. For example, dysanapsis is a size mismatch between the growth of the airway tree and parenchyma during childhood, resulting in that airway branches grow slower than lung volumes, leading to "undersized" airways relative to the volume of the lungs. Dysanapsis is an independent risk factor of COPD, both in smokers and nonsmokers [17]. Alternatively, genetic factors might become informative, such as single-nucleotide polymorphisms in the *HHIP* [18] and *FGF10* [19] loci, as they have been associated with early COPD onset and abnormalities in airway branching. Early-life events (*in utero* exposure to maternal smoking, viral exacerbations, childhood asthma, prematurity and family history of obstructive diseases) are also associated with the paediatric roots of COPD [20]. Other unaddressed questions relate to the impact of changes in lung volumes with the

immediate lung neighbourhood. Impaired diaphragmatic course predisposing to difficulties in mechanical ventilation weaning, excessive dorsal kyphosis and heart failure with preserved ejection fraction (gaseous tamponade) are some of the so-called comorbidities that can actually be attributed to the sole thoracic distension [21].

Lung volumes can efficiently predict progression to COPD. Thoracic distension and lung hyperinflation as consequences of SAD represent attractive alternatives to $FEV_1$ measurement for assessing early interventions.

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## References


1 Macklem PT, Fraser RG, Brown WG. Bronchial pressure measurements in emphysema and bronchitis. *J Clin Invest* 1965; 44: 897–905.
2 Buist S, Nagy J. A longitudinal study of smokers and nonsmokers. 5–6 year follow-up using spirometry and the single breath $N_2$ test. *Chest* 1980; 77: 259.
3 Lange P, Celli B, Agustí A, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; 373: 111–122.
4 Zeng S, Luo G, Lynch DA, *et al.* Lung volumes differentiate the predominance of emphysema *versus* airway disease phenotype in early COPD: an observational study of the COPDGene cohort. *ERJ Open Res* 2023; 9: 00289-2023.
5 Papandrinopoulou D, Tzouda V, Tsoukalas G. Lung compliance and chronic obstructive pulmonary disease. *Pulm Med* 2012; 2012: 542769.
6 Martinez FJ, Agusti A, Celli BR, *et al.* Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med* 2022; 205: 275–287.
7 Han MK, Agusti A, Celli BR, *et al.* From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med* 2021; 203: 414–423.
8 Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
9 Regan EA, Lynch DA, Curran-Everett D, *et al.* Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015; 175: 1539–1549.
10 McDonough JE, Yuan R, Suzuki M, *et al.* Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011; 365: 1567–1575.
11 Zeng S, Tham A, Bos B, *et al.* Lung volume indices predict morbidity in smokers with preserved spirometry. *Thorax* 2019; 74: 114–124.
12 Shiraishi Y, Shimada T, Tanabe N, *et al.* The prevalence and physiological impacts of centrilobular and paraseptal emphysema on computed tomography in smokers with preserved ratio impaired spirometry. *ERJ Open Res* 2022; 8: 00063-2022.
13 Diaz AA, Orejas JL, Grumley S, *et al.* Airway-occluding mucus plugs and mortality in patients with chronic obstructive pulmonary disease. *JAMA* 2023; 329: 1832–1839.
14 Dunican EM, Elicker BM, Henry T, *et al.* Mucus plugs and emphysema in the pathophysiology of airflow obstruction and hypoxemia in smokers. *Am J Respir Crit Care Med* 2021; 203: 957–968.
15 Guerra S, Halonen M, Vasquez MM, *et al.* Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study. *Lancet Respir Med* 2015; 3: 613–620.
16 Bourdin A, Kotsimbos T, Nguyen K, *et al.* Non-invasive assessment of small airway remodelling in smokers. *COPD* 2010; 7: 102–110.
17 Smith BM, Kirby M, Hoffman EA, *et al.* Association of dysanapsis with chronic obstructive pulmonary disease among older adults. *JAMA* 2020; 323: 2268–2280.
18 Soler Artigas M, Wain LV, Miller S, *et al.* Sixteen new lung function signals identified through 1000 Genomes Project reference panel imputation. *Nat Commun* 2015; 6: 8658.
19 Smith BM, Traboulsi H, Austin JHM, *et al.* Human airway branch variation and chronic obstructive pulmonary disease. *Proc Natl Acad Sci USA* 2018; 115: E974–E981.
20 Christenson SA, Smith BM, Bafadhel M, *et al.* Chronic obstructive pulmonary disease. *Lancet* 2022; 399: 2227–2242.
21 van der Molen MC, Hartman JE, Vanfleteren LEGW, *et al.* Reduction of lung hyperinflation improves cardiac preload, contractility, and output in emphysema: a clinical trial in patients who received endobronchial valves. *Am J Respir Crit Care Med* 2022; 206: 704–711.