

anatomic basis for observations by a number of researchers in a variety of respiratory disorders, including World Trade Center (WTC) lung disease (2), asthma/reactive airway dysfunction syndrome (3), and coal workers' lung disease (4). These observations have been characterized as restrictive (2) in the presence of decreased FVC often described as parallel to a decrease in FEV₁ (4) and resultant normal FEV₁/FVC ratio. In nonobstructive chronic bronchitis, follow-up spirometry showed parallel decreases in FVC and FEV₁ and a "restrictive pattern" in 14% (5). Similar findings have been described as "GOLD (Global Initiative for Chronic Obstructive Lung Disease)-unclassified," "PRISM" (preserved ratio impaired spirometry), "nonspecific," or simply "low FVC." Findings include characteristic airway symptoms (cough, sputum, and wheezing); flow rates at low lung volumes may be decreased but are often not reported, and oscillometry is consistent with small airway dysfunction. Unlike the iconic restrictive impairment caused by interstitial lung disease or chest bellows deficit, this "restrictive dysfunction" worsens with bronchoprovocation and improves with bronchodilatation. Unlike classic airway obstruction in chronic obstructive pulmonary disease and most cases of asthma, the FEV₁/FVC ratio is maintained, and FRC or residual volume is not or is minimally increased.

Eddy and associates demonstrated loss of subsegmental airways seen on computed tomography (1). This correlated with increased bronchial wall thickness, decreased luminal area, and ventilatory defects on hyperpolarized 3-He magnetic resonance imaging in patients with severe asthma (FEV₁ 64–65% of predicted, FEV₁/FVC 0.58–0.64) compared with less severe disease (FEV₁ 88% predicted, FEV₁/FVC 0.74). Eddy and colleagues' Figure 1 showing the difference in airway count in patients with severe asthma vividly illustrates the anatomic deficit. Recently, the Mount Sinai WTC group reported increased bronchial wall area on quantitative computed tomography in 167 exposed workers and volunteers with the "Low FVC Spirometric Pattern," confirming Eddy and colleagues' report (6).

Restrictive impairment attributable to asthma was described in 32 of 413 (8%) patients with asthma seen in a small inner-city hospital over 2 years (3). No patients had evidence of another disorder causing restrictive impairment. Plethysmographic FRC was normal or decreased in 22 of 25 patients in whom it was measured. Restriction as opposed to obstruction was attributed to airway closure rather than narrowing, an explanation consonant with Eddy and colleagues' demonstration of airway loss. Restrictive impairment in asthma was not generally recognized before this publication despite two illustrative reports almost a half-century ago cited in this article; Colp and Williams described in 1973 a "restrictive pattern of ventilatory impairment" in two patients with asthma. One patient had mucus plugging of main and lobar bronchi and resultant massive atelectasis clearly explaining her restriction. The other had "diffuse small airway involvement" on pathologic examination, which would cause the loss of airways described by Eddy and colleagues. Three years later, Hudgel and colleagues reported "reversible restrictive lung disease" in a young patient with asthma whose TLC decreased from 5.3 to 2.6 L during an acute episode.

Loss of airways similarly helps explain the characteristic findings of low FVC, normal FEV₁/FVC, and small airway obstruction on oscillometry reported in first responders and area residents with "WTC Lung Disease" (2) and the accelerated

"parallel decline" in FVC and FEV₁ reported in 11 coal miners in the absence of radiographic fibrosis (4). ■

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

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Reply to Miller et al.



From the Authors:

We appreciate the thought-provoking comments of Dr. Miller and colleagues in response to our report on "missing" airways in participants with asthma and, in particular, severe asthma (1).

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R.L.E. was supported by Natural Sciences and Engineering Research Council (NSERC) of Canada postgraduate doctoral award and an NSERC postdoctoral fellowship. G.P. is supported by NSERC and Canadian Institutes for Health Research and holds a Tier 1 Canada Research Chair.

Originally Published in Press as DOI: 10.1164/rccm.202005-2034LE on August 5, 2020

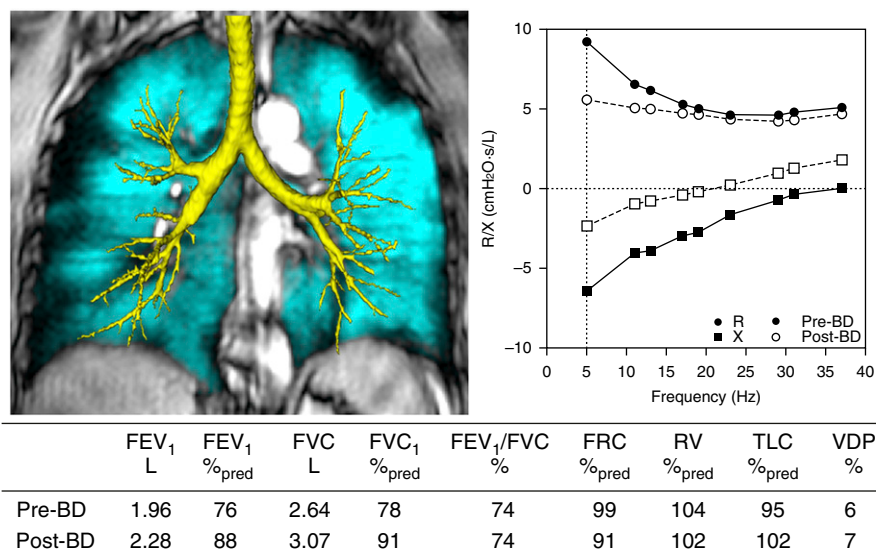


Figure 1. Magnetic resonance imaging (MRI), computed tomography (CT), and oscillometry in a participant with severe asthma. MRI ventilation (cyan) with CT airway tree (yellow) and oscillometry for a 61-year-old female with severe (Global Initiative for Asthma 5) asthma, abnormally low FEV₁ (1.96 L, 76%_{pred}) and FVC (2.64 L, 78%_{pred}), and preserved FEV₁/FVC ratio (0.74) is shown. Both FEV₁ and FVC improved after bronchodilator. CT total airway count (129) and MRI ventilation defect percent (6%) were abnormal, and ventilation defect percent did not improve after bronchodilator. Oscillometry resistance and reactance were abnormally elevated and frequency dependent, which is suggestive of small airway disease. BD = bronchodilator; pred = predicted; R = resistance; RV = residual volume; X = reactance.

We investigated chest X-ray computed tomography (CT) total airway count alongside magnetic resonance imaging ventilation across patients with a range of asthma severity (1). Our findings may help corroborate recent results in World Trade Center workers and volunteers (2, 3), in whom there was restrictive airflow (spirometry) and CT evidence of airway wall remodeling. We can also confirm that in our study of asthma, there was no CT evidence of restrictive parenchymal abnormalities or fibrosis and/or interstitial disease. There was, however, CT evidence of intraluminal airway plugs in 20 of 70 participants, which appeared to have minimally influenced total airway count measurements.

In response to the suggestions of Dr. Miller and colleagues, we retrospectively inspected all spirometry measurements from our study and identified that 10 of 70 (14%) participants reported diminished FEV₁ and FVC with a preserved FEV₁/FVC ratio, which is similar to a previously reported rate (8%) in residents of a small inner-city hospital (4). From our reported study, we now provide Figure 1 for a representative participant with such findings. Magnetic resonance imaging ventilation is shown coregistered to the patient-specific CT airway tree, alongside oscillometry plots and pre- and post-bronchodilator pulmonary function measurements (1). In this participant with severe (Global Initiative for Asthma 5) asthma, CT total airway count was 129, which is approximately less than one-half of what is expected. FEV₁ and FVC were both normal and improved after bronchodilator, whereas FRC, residual volume, and TLC were not changed after bronchodilator. Oscillometry was also performed during the original study visit (1). Both resistance and reactance were abnormally elevated, and the frequency dependence of resistance and reactance suggested heterogeneously narrowed and stiffened small airways.

The substantially reduced CT total airway count and oscillometry evidence of small airways dysfunction may help explain the low FEV₁ and FVC with normal FEV₁/FVC in this participant with asthma. Because postmortem studies of such patients are exceedingly rare, *in vivo* physiologic tests such as oscillometry and multiple-breath nitrogen washout may help establish any potential relationships between reduced CT total airway count, spirometry evidence of restrictive lung disease and small airway dysfunction in patients with asthma. Prospective investigations of the relationships between CT total airway count and oscillometry are currently underway.

As Dr. Miller and colleagues suggest, total airway count may help explain low FVC and observations of rapid lung function decline in World Trade Center workers (3) and coal workers with lung disease (5). Truncated airway trees measured using CT imaging, concomitant with oscillometry evidence of small airway obstruction, challenge our understanding and assumptions about the role of airway disease in all patients with chronic lung disease. ■

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

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Lipid-Laden Macrophages Are Not Diagnostic of Pulmonary Alveolar Proteinosis Syndrome and Can Indicate Lung Injury

To the Editor:

We read with interest the recent case report by Israel and colleagues that describes a young woman that presented with acute hypoxemia, bilateral pulmonary infiltrates, and a history of e-cigarette use (1). The authors concluded that this was a case of pulmonary alveolar proteinosis (PAP) secondary to vaping-associated lung injury on the basis of the radiological and cytological findings presented. The case presented is undoubtedly interesting, and the report raises several important topical issues, including the spectrum of e-cigarette- or vaping-associated lung injury (EVALI) and the utility of lipid-laden macrophages in BAL fluid. However, we have some remarks regarding this case and the suggested association between EVALI and PAP.

PAP is a rare syndrome characterized by progressive alveolar surfactant accumulation and hypoxemic respiratory failure and is categorized as primary, secondary, or congenital. Primary PAP accounts for the vast majority of cases and is caused by the disruption of GM-CSF (granulocyte-macrophage colony-stimulating factor) signaling, by GM-CSF autoantibodies (autoimmune PAP, accounting for 90% of cases), or by genetic mutations involving the GM-CSF receptor. Secondary PAP occurs in various conditions that cause altered function or a reduced number of alveolar macrophages resulting in abnormal surfactant clearance in the lung (2).

The case presented by Israel and colleagues is not entirely convincing for secondary PAP, and we believe

it is more likely that either infection or EVALI was the principal issue for this patient. First, “crazy-paving” is not pathognomonic of PAP, and there are many other causes, including acute lung injury and lipoid pneumonia, both of which could be present as a result of EVALI in this case (3). Second, the presence of lipid-laden macrophages in BAL fluid is nonspecific, and although Oil-Red-O-positive cells are certainly a feature of PAP, they are present in many types of lung disease (4). Furthermore, the presence of periodic acid-Schiff-positive material again is not indicative of PAP alone and can be seen in a spectrum of pulmonary pathology (5). In this case, no biopsy was performed, and a label of secondary PAP was made on the basis of BAL and computed tomography findings. This is not the current best practice; indeed, all patients should have GM-CSF autoantibodies checked when PAP is suspected, and if there is no known secondary cause of PAP and GM-CSF signaling is intact, then a lung biopsy is needed to truly determine the presence of PAP syndrome (2). Finally, the rapid response to antibiotics and steroids, neither of which are effective therapies for primary or secondary PAP, go against this being a case of secondary PAP. Moreover, it would take several months for the alveolar macrophage pool to replenish/repair and export accumulated lipids, which is evidenced by the delayed response to inhaled GM-CSF seen in cases of autoimmune PAP (6). We conclude that this case more likely represents either infectious or inflammatory acute lung injury possibly related to EVALI, but the paucity of evidence cannot confirm secondary PAP.

Although we disagree that this is a case of secondary PAP, it highlights the importance of carefully interpreting the presence of lipid-laden macrophages in the lung. It has been demonstrated that in a mouse model of EVALI, there was altered surfactant phospholipid homeostasis and foamy macrophages but no evidence histologically of PAP lung disease (7). There have been numerous reports of Oil-Red-O macrophages in EVALI (8), but this likely represents lung injury resulting in abnormal surfactant production from type II pneumocytes or from altered macrophage function resulting in lipid accumulation. Hence, the interpretation of lipid-laden macrophages must be treated cautiously. With the increased recognition of EVALI as a novel pulmonary condition, there has been renewed focus on lipid-laden macrophages, but we conclude that foamy macrophages in EVALI likely indicate lung injury, and caution should be given to using this finding as a diagnostic marker (9). ■

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Originally Published in Press as DOI: 10.1164/rccm.202005-1880LE on July 16, 2020