and neutrophilia. This is competence without comprehension, which is entirely justifiable, as it represents powerful, data-driven medicine. Would the identification of particular metabolites or their fragments by GC-MS in exhaled air by itself qualify for unraveling the critical pathobiological pathways in relation to eosinophilic or neutrophilic inflammation? This is unlikely, as the "big brothers" of this technology, such as transcriptomics and proteomics, are much closer to the mechanistic networks and are delivering at present (3, 4).

The prospect of using GC-MS in this context is therefore twofold. First, when associating the present VOCs with accompanying RNA and protein profiles, it might become feasible to indirectly establish any transcriptomic or proteomic fingerprints of asthma by noninvasive analysis of exhaled VOCs. Then breathomics is used for rapidly recognizing elaborate biological phenotypes, as has been done by Brinkman and colleagues for electronic nose (eNose) profiles against sputum transcriptomics profiles (8) (data in online supplement). Second, GC-MS data from the present study can also be used for tailoring cross-reactive sensors for eNoses toward their most discriminative and evidence-based combination for establishing eosinophilic or neutrophilic inflammation (9). Notably, eNoses have also been trained and validated in discriminating eosinophilic and neutrophilic inflammation with high accuracy, regardless of the clinical diagnosis of asthma or chronic obstructive pulmonary disease (8, 10). The advantage of the latter technology is that it can be linked to big online databases and cloud computing, providing real-time results in the doctor's office (www.breathbase.org).

The article by Schleich and colleagues (7) presents a landmark study on the validation of exhaled VOCs in the inflammatory profiling of asthma. This is needed for type 2 and increasingly also for non–type 2 asthma phenotypes. Ongoing clinical tailoring of breathomics is definitely bringing data-driven, precision medicine to the point of care. ■

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

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Seeing the Forest for the (Arterial) Tree: Vascular Pruning and the Chronic Obstructive Pulmonary Disease Pulmonary Vascular Phenotype

The clinical consequences of pulmonary hypertension (PH) in patients with chronic obstructive pulmonary disease (COPD) and the effect of right ventricular (RV) failure on prognosis has long been recognized. Mild to moderate PH is common in patients with severe COPD; however, severe PH (mean pulmonary arterial pressure [mPAP] $\geqslant$35 mm Hg or a mPAP $\geqslant$25 mm Hg with a cardiac index $<$2.0 $L \cdot min^{-1} \cdot m^{-2}$) is less frequent and, when present, is often associated with comorbid conditions such as left heart disease or chronic thromboembolic disease (1–3). More recently, however, it has been recognized that the pulmonary vasculature may be significantly compromised in some patients with mild to moderate COPD and minimal emphysema, the so-called "pulmonary vascular phenotype" (4). Often referred to as

Originally Published in Press as DOI: 10.1164/rccm.201901-0248ED on March 25, 2019

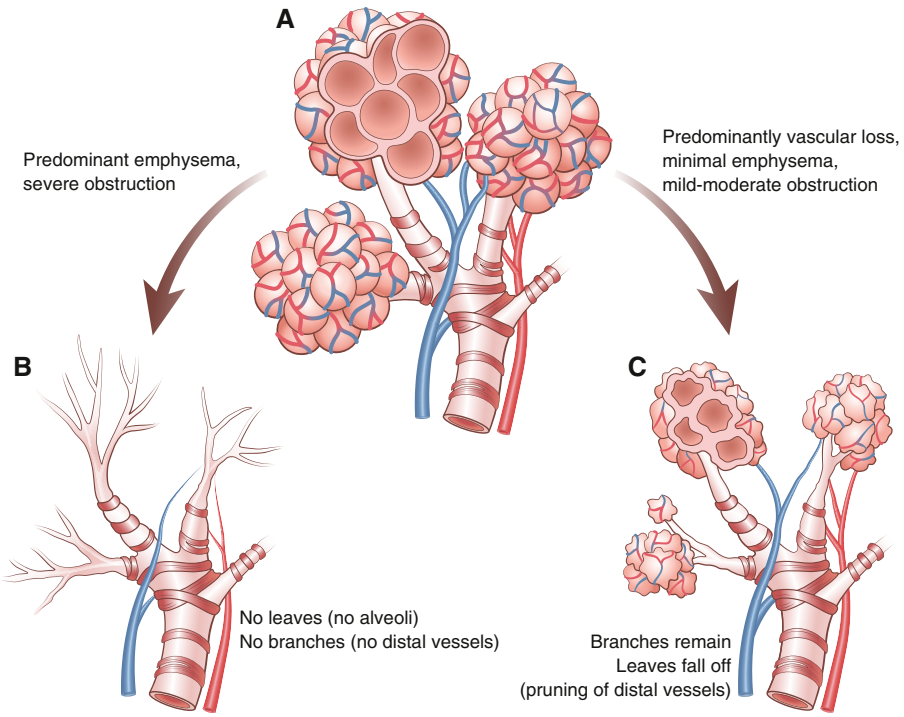

Figure 1. (*A*) A normal, healthy bronchovascular tree. Imagine the airways and alveoli are like branches on a tree with pulmonary arterial–capillary networks reflecting the individual leaves. (*B*) In most patients with chronic obstructive pulmonary disease, smoking-induced damage to the distal airways and alveolar destruction are the main mechanisms for loss of the pulmonary vascular bed and the consequent pulmonary hypertension. Dropout of the distal arteries and capillaries (leaves) is congruent with the degree of damage to the branches (i.e., emphysema and severe airflow obstruction). (*C*) In patients with chronic obstructive pulmonary disease with a pulmonary vascular phenotype, smoking-related vascular injury predominates. There may be primarily a loss of the distal arterial–capillary networks (pruning of the leaves) with relative preservation of the airways and alveoli (branches). Illustration by Patricia Ferrer Beals.

out-of-proportion PH in the past, these patients have severe PH in the setting of mild to moderate airflow obstruction, normal or low Pa_{CO_2}, low D_{LCO}, and circulatory, rather than ventilatory, limitation during exercise (4, 5).

In this issue of the *Journal*, Washko and colleagues (pp. 454–461) elegantly tease out supportive evidence for a pulmonary vascular phenotype in COPD by examining the relationships among distal pulmonary arterial pruning, emphysema, and RV size with exercise capacity and survival (6). Using volumetric computed tomography (CT) scans, they measured the percentage of emphysematous lung tissue, and performed morphologic assessment of distal pulmonary blood vessel volume (those with a cross-sectional area <5 mm^2 [BV5]) and RV epicardial volume (RV_{EV}) in >3,500 ever-smokers enrolled in the COPDGene study. The researchers found that RV_{EV} was smaller with progressively worsening airflow obstruction; that is, from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 to GOLD stage 4, the RV size actually decreased. The extent of emphysematous lung and arterial pruning, defined as lower arterial BV5, were both independently associated with larger RVs, such that for any degree of emphysema, a 10-ml decrease in arterial BV5 gave a 1-ml increase in RV size. In stratified multivariable models, however, arterial vascular pruning was associated with RV enlargement only in patients in the mildest quartile of airflow obstruction ($FEV_1 > 73.6\%$ predicted) and in patients with <9.13% emphysema. Lending further support to the pulmonary vascular phenotype hypothesis was their finding that patients with milder COPD may have had pulmonary vascular and circulatory exercise limitation, as the RV_{EV} independently predicted 6-minute-walk distance only in the quartile of patients in the least amount of emphysema. RV enlargement was also associated with higher mortality, but this effect was modified by arterial BV5, such that mortality was 63% higher in patients with RV enlargement and arterial pruning, but there was no significant increased risk for death without pruning.

The results reported by Washko and colleagues illustrate a subgroup of patients with mild to moderate COPD and lesser degrees of emphysema who suffer from disproportionate arterial drop-out and have RV dilation and a worse prognosis. These patients with mild COPD with arterial vascular pruning are reminiscent of the "vanishing capillary syndrome," a recently proposed explanation for smoking-related pulmonary vasculopathy in patients otherwise diagnosed with idiopathic pulmonary arterial hypertension (IPAH) (7). In 2013, Trip and colleagues described a well-characterized group of patients with IPAH with a low D_{LCO} (<45% predicted) who were older and more often male, with a significant smoking history, and with 68% demonstrating mild to moderate emphysema on CT scan (8). Despite having similar hemodynamic severity as those with a higher D_{LCO}, 5-year survival was much lower in the low-D_{LCO} group (38% vs. 80%). More recently, Olsson and colleagues described a small group of patients with IPAH with a low D_{LCO} and no parenchymal lung disease on CT (9). PAH therapies were rather ineffective in these patients, with a mean decline in the 6-minute-walk distance of 10 m, and with only 1/22 patients improving functional class.

In the pulmonary vascular tree, distal arterial and capillary loss could be attributed to destruction of the "branches and leaves" from

emphysematous changes, or to direct smoking-induced injury to the small arteries and capillaries (pruning of the leaves; Figure 1). Indeed, endothelial injury and pulmonary vascular remodelling may occur in smokers before the development of airflow obstruction or emphysema (10–12). The mechanisms underlying preferential vascular injury over airway-predominant and emphysematous changes are incompletely understood, but may be related to inducible nitric oxide synthase from bone marrow–derived cells and are independent of hypoxia (10). Identification of the genetic and cellular mechanisms associated with arterial pruning could help identify those susceptible to smoking-induced pulmonary vasculopathy and development of severe PH.

It is important to note some limitations when interpreting the results of Washko and colleagues, as there were no right heart catheterization data to confirm the presence or mechanism of PH (i.e., precapillary vs postcapillary PH) in those with arterial pruning or an enlarged RV; thus, further invasive hemodynamic data to support these findings are necessary (6). Second, as acknowledged by the authors, noncardiac gated CT image acquisition is a limitation that precludes measurement of the RV wall thickness and may inaccurately reflect true RV volume. Furthermore, chronic thromboembolic disease and CT features of left heart disease, such as left atrial enlargement, were not systematically excluded in the patients with arterial pruning and large RV size. These are confounding causes of PH independent of emphysema or airflow obstruction; thus, their potential effects on CT measurements of RV_{EV}, vascular pruning, and prognosis are not clear. Last, D_{LCO} measurements were not available in this study, so any potential link between the phenotype of IPAH with a low D_{LCO} and patients with mild COPD with arterial pruning remains speculative.

We must properly define this phenotype with hemodynamic and imaging criteria before embarking further down the rabbit hole of PAH-targeted therapy trials in patients with arterial pruning and mild to moderate COPD. To date, trials of PAH therapies in COPD have shown mixed, but overall disappointing, results (5). Therefore, properly designed and adequately powered studies with meaningful clinical endpoints could be justified if enriched with patients with mild to moderate COPD with markers of pulmonary vascular disease, such as arterial pruning. Washko and colleagues take us one step forward in understanding the characteristics and importance of a pulmonary vascular phenotype in COPD. Although there are poor outcomes associated with this phenotype and there are currently limited specific treatment options, expectations for PAH therapies in this group should be cautious, in light of the disconcerting experience with patients with vanishing capillary syndrome IPAH (7, 9). A tree without leaves may not easily be unpruned. ■

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

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