serum incubations because of the presence of various angiotensinsases in blood. A preferred method to minimize peptide metabolism is to use an inhibitor cocktail, preventing metabolism (and clotting of blood), and solid-phase extraction (C18, C8, or phenyl matrix) of the plasma fraction to concentrate the peptides and remove interfering substances prior to assay using radioimmunoassays (10). Previous pilot studies using this technique reported circulating levels of AngII in the 20 pM range (20 pg/mL) among patients negative or positive for COVID-19 with moderate and severe respiratory failure (8). In contrast, Gerard and colleagues found AngII undetectable (<0.3 pg/mL) in the majority of their serum samples for both control and COVID-19 groups, perhaps reflecting *ex vivo* metabolism of AngII in the serum samples.

Their findings, if further validated, have several implications for both COVID-19–related and non–COVID-19–related ARDS. First, although cellular entry and destruction of ACE2 has been implicated in COVID-19–related ARDS, its contributions to non–COVID-19–related ARDS have been thought to be less relevant. However, if ACE2 plays a key role in non–COVID-19–related ARDS, therapeutic approaches in patients with COVID-19–related ARDS may have similar efficacy in non–COVID-19–related ARDS. Second, it would be important to carefully evaluate ACE2 expression in the lung compartment (early versus late after symptom onset) and how serial measurements of angiotensins and peptidases change over time as well as before and after therapy in patients hospitalized with COVID-19–related ARDS. These investigations may shed light on the interplay of clinical severity, the time course of illness, and response to treatment. Using therapies from successful COVID-19 clinical trials and applying them to non–COVID-19 ARDS would be a tremendous downstream impact from clinical trials conducted during the pandemic. These data from Gerard and colleagues are an important step in uncovering the role of the RAAS in COVID-19 and ARDS. ■

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References

1. Uhal BD, Li X, Piasecki CC, Molina-Molina M. Angiotensin signalling in pulmonary fibrosis. *Int J Biochem Cell Biol* 2012;44:465–468.
2. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, *et al.* Acute respiratory distress syndrome. *Nat Rev Dis Primers* 2019;5:18.
3. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319–323.
4. Wilson JG, Calfee CS. ARDS subphenotypes: understanding a heterogeneous syndrome. *Crit Care* 2020;24:102.
5. Ware LB. Physiological and biological heterogeneity in COVID-19-associated acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:1163–1165.
6. Gerard L, Lecocq M, Bouzin C, Hoton D, Schmit G, Pereira JP, *et al.* Increased angiotensin-converting enzyme 2 and loss of alveolar type II cells in COVID-19–related acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021;204:1024–1034.
7. Olajuyin AM, Zhang X, Ji HL. Alveolar type 2 progenitor cells for lung injury repair. *Cell Death Discov* 2019;5:63.
8. Files DC, Gibbs KW, Schaich CL, Collins SP, Gwathmey TM, Casey JD, *et al.* A pilot study to assess the circulating renin-angiotensin system in COVID-19 acute respiratory failure. *Am J Physiol Lung Cell Mol Physiol* 2021;321:L213–L218.
9. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–128.
10. Chappell MC, Pirro NT, South AM, Gwathmey TM. Concerns on the specificity of commercial ELISAs for the measurement of angiotensin (1-7) and angiotensin II in human plasma. *Hypertension* 2021;77:e29–e31.

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Metabolic Risk Factors and the Development of World Trade Center Lung Disease

Longitudinal epidemiologic studies have shown that long-term exposure to particulate matter (PM) air pollution can be associated with steeper loss of lung function over time (1). Metabolic syndrome (MetSyn), which is characterized by a combination of metabolic risk factors such as dyslipidemia, hypertension, large abdominal girth, and poor glycemic control (2), has also been associated with lower lung volumes, more rapid function decline, and developing asthma (3–5). Less is known, however, about how PM exposure and metabolic risk factors longitudinally synergize in causing respiratory disease. This is an important public health question given the overwhelming prevalence of obesity and MetSyn and the wide population exposure

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to PM pollution. Although not a model of chronic PM exposure, World Trade Center (WTC) cohort studies do provide a unique opportunity to understand the adverse health impacts of an acute massive PM exposure and how the risk of subsequently developing lung disease can potentially be modified by metabolic factors. This was initially studied in a nested case-control study of workers from the Fire Department of New York, in which abnormal baseline high-density lipoprotein and triglycerides were an independent risk factor of greater susceptibility to lung function impairment after September 11 (6); however, this study was limited by a single point in time metabolic biomarker assessment.

To further understand the temporal relationship of MetSyn, exposure intensity, and lung dysfunction, in this issue of the *Journal*, Kwon and colleagues (pp. 1035–1047) used data from 5,738 rescue and recovery active workers who were part of the baseline WTC cohort and had spirometry testing within 180 days of September 11. Over 52,000 pulmonary function tests (on average 9.1/subject; SD, 2.6) measured from September 11 until August 2017 were used for this analysis (7). To assess the temporality associations between lung function and MetSyn, spirometry measurements were aligned to all other clinical measurements within 180 days to best measure concurrent associations. Clinical parameters including weight, blood pressure, glucose, and lipid panel were measured at WTC entry and repeated at longitudinal follow-up times. Exposure intensity was obtained from questionnaires and defined by the time of arrival at September 11 and subsequent working months at the WTC site. The investigators proposed a multidimensional analytic approach to adequately capture the complex interplay between MetSyn components, comorbidities, and the study outcomes, which included having at least one FEV_1% predicted <lower limit of normal as primary (WTC–lung injury [LI]) and the FVC% predicted <lower limit of normal, FEV_1/FVC as secondary. At baseline, those with WTC-LI were more likely to have lower FEV_1% predicted and meet criteria for MetSyn. Longitudinally, increasing body mass index categories or having additional MetSyn criteria were associated in a dose–response fashion with the primary outcome. When investigating the temporal associations of MetSyn with WTC-LI, elevated triglycerides had the highest hazard ratio, followed by low high-density lipoprotein and obesity. The intensity of PM exposure was a significant factor, and of greater magnitude than smoking, in all the time to event models.

These results are consistent with prior cohort studies and certainly contribute to strengthening the causality between metabolic dysregulation and subsequent lung impairment. Some of the more exciting and novel results from this study included: *1*) the use of a partially linear single index hazards model to develop a MetSyn single index to jointly estimate the relative contribution of its components, which showed that although a lower index moderately decreased the risk of WTC-LI, a positive one exponentially increased it; and *2*) dynamic risk profiling to estimate the rate of change of MetSyn on the onset time of disease to determine how MetSyn recovery reduces lung disease, which showed that improvements in hypertension, body mass index, and dyslipidemia were associated with a substantial risk reduction in WTC-LI. These results agree with a cohort study showing that improvements in MetSyn components after bariatric surgery can, independently of the amount of body weight lost, improve pulmonary outcomes (8).

There are several key takeaway points from this study. First, MetSyn components incrementally and exponentially augment the risk for developing lung impairment independently of other confounders and competing risks. Second, each MetSyn component, probably through independent and synergistic mechanisms (9), increases the risk for developing lung disease. Third, improving MetSyn could substantially reduce the risk of losing lung function.

There are important study limitations to consider, which potentially limit the external validity of these findings. This is a large cohort of exposed individuals with and without WTC-LI. It is therefore impossible to tease out the impact of MetSyn on lung function in individuals that were not massively exposed to PM during September 11. Given this important limitation, it is difficult to extrapolate whether MetSyn or its components would longitudinally interact with air pollution PM to induce lung disease; however, this possibility is supported by large cross-sectional studies (10, 11).

Taken together, despite limitations, the results from this large and well-done longitudinal study strongly support a causal relationship for metabolic dysregulations as risk factors for developing lung disease. The time has come to think of MetSyn not only as a cardiovascular risk factor but also as a modifiable pulmonary one as well. ■

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References

1. Götschi T, Heinrich J, Sunyer J, Künzli N. Long-term effects of ambient air pollution on lung function: a review. *Epidemiology* 2008;19:690–701.
2. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2010;375:181–183.
3. Forno E, Han YY, Muzumdar RH, Celedón JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *J Allergy Clin Immunol* 2015;136:304–11.e8.
4. Koo HK, Kim DK, Chung HS, Lee CH. Association between metabolic syndrome and rate of lung function decline: a longitudinal analysis. *Int J Tuberc Lung Dis* 2013;17:1507–1514.
5. Brumpton BM, Camargo CA Jr, Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J* 2013;42:1495–1502.
6. Naveed B, Weiden MD, Kwon S, Gracely EJ, Comfort AL, Ferrier N, *et al.* Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med* 2012;185: 392–399.
7. Kwon S, Lee M, Crowley G, Schwartz T, Zeig-Owens R, Prezant DJ, *et al.* Dynamic metabolic risk profiling of World Trade Center lung disease: a longitudinal cohort study. *Am J Respir Crit Care Med* 2021;204:1035–1047.
8. Forno E, Zhang P, Nouraie M, Courcoulas A, Mitchell JE, Wolfe BM, *et al.* The impact of bariatric surgery on asthma control differs among obese individuals with reported prior or current asthma, with or without metabolic syndrome. *PLoS One* 2019;14:e0214730.
9. Baffi CW, Wood L, Winnica D, Strollo PJ Jr, Gladwin MT, Que LG, *et al.* Metabolic syndrome and the lung. *Chest* 2016;149: 1525–1534.

10. Eze IC, Schaffner E, Foraster M, Imboden M, von Eckardstein A, Gerbase MW, *et al.* Long-term exposure to ambient air pollution and metabolic syndrome in adults. *PLoS One* 2015;10:e0130337.
11. Shamy M, Alghamdi M, Khoder MI, Mohorjy AM, Alkhatim AA, Alkhalaf AK, *et al.* Association between exposure to ambient air particulates and metabolic syndrome components in a Saudi Arabian population. *Int J Environ Res Public Health* 2017;15:27.

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Small Airways in Idiopathic Pulmonary Fibrosis: Quiet but Not Forgotten

The quiet zone, a term coined by Jere Mead in 1970 to reference small conducting airways in the lung, denotes the fact that disease can accumulate in this anatomical region while remaining clinically silent and undetectable by either patients or their clinicians (1). Although the role played by loss of small airways in chronic obstructive pulmonary disease is widely recognized, the importance of these airways in idiopathic pulmonary fibrosis (IPF) is less well appreciated.

The current pathogenic paradigm in IPF postulates that the disease arises because of premature senescence of alveolar epithelial cells following repetitive alveolar injury in genetically susceptible individuals (2). This gives rise to an aberrant wound healing response that favors accumulation of extracellular matrix and abnormal remodeling of the lung. The alveolus and the alveolar epithelium have long been center stage in the search for the initial site of injury in IPF. Ultrastructural studies consistently report damage, necrosis, and apoptosis of alveolar epithelial cells with associated denudation of the basement membrane (3). In animal models, the selective induction of apoptosis of type II alveolar epithelial cells triggers the development of fibrosis (4). Similarly, interfering with reepithelialization of the alveolus after acute lung injury results in an exaggerated fibrotic response (5). Clinically, the absence of airflow obstruction in IPF has been taken to infer that the disease is confined to the alveolus.

More recent data have called into question the primacy of alveolar injury and disruption of the alveolar epithelium as the initial lesion of IPF. Genetic studies have identified a gain-of-function polymorphism in the promotor region of the gene for MUC5B as the most commonly occurring risk allele for IPF (6). MUC5B encodes a mucin expressed by the epithelium lining respiratory bronchioles. Although the mechanism by which excessive mucin production gives rise to IPF is unknown, it has been proposed that that accumulation in distal respiratory bronchioles leads to retention of injurious particles, resulting in focal and persistent injury, repair, and regeneration at the bronchoalveolar junction (7). Further evidence for a role of small airways in IPF pathogenesis comes from studies of single-cell transcriptomics performed on explant lungs (8). These have shown marked changes in the expression profile of numerous epithelial cell types in the fibrotic lung in comparison to healthy control lungs and identification of two unique Club-cell populations.

A recent study by Verleden and colleagues used a variety of techniques to make a detailed assessment of the full bronchial tree in IPF explant lungs (9). The authors demonstrated that small airways <2 mm in diameter show increased visibility owing to airway wall thickening and distortion of the airway lumen. At the same time, micro–computed tomography (CT) demonstrated a 60% reduction in terminal bronchioles in IPF lungs compared with healthy control lungs. This reduction was equally evident in regions of minimal fibrosis and areas of dense established fibrosis. The extent of small airway loss was not affected by pack-year smoking history.

In the current issue of the *Journal*, Ikezoe and colleagues (pp. 1048–1059) publish a further exploration of the relationship between small airway loss and fibrosis in IPF (10). Using microCT and by undertaking a systematic uniform random sampling approach within whole explant lungs, the authors were able to assess the full spectrum of disease in lungs from donors with IPF. In keeping with the prior study, Ikezoe and colleagues demonstrate that in IPF lungs compared with age-matched controls, numbers of terminal bronchioles and respiratory transitional bronchioles are significantly reduced, and terminal bronchiole airway walls thickened even in regions lacking evidence of parenchymal fibrosis. In regions of fibrosis, the terminal bronchioles have thicker walls and dilated and distorted lumens, which lead to the formation of honeycomb cysts. Although the study was performed in end-stage explant lungs, the authors took advantage of the heterogeneity of fibrosis in IPF to postulate that small airway loss occurs early in the evolution of IPF and that it appears to precede the development of fibrosis.

The study does have a number of limitations, not least of which is that the authors had to rely on explant lungs to conduct their assessment of IPF lung tissue. This is understandable given that adequate samples of lung tissue are not generally available in any circumstance apart from after lung transplant. The number of lungs studied was small, but the authors ensured, as far as possible, that these were well matched. A lack of longitudinal sampling (again challenging given the techniques involved) raises the possibility that a loss of small airways in early life may predispose to IPF development rather than necessarily representing a step in the pathogenesis of the disease. It is to be hoped that technological improvements in the resolution of CT imaging will enable these questions to be addressed in the future.

Ikezoe and coworkers are to be congratulated on providing robust evidence for an important role of the small airways in the earliest stages of the development of IPF (10). Their study has a

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