GÜNTER OBERDÖRSTER, PH.D.
University of Rochester
Rochester, New York

DAVID E. NEWBY, M.D., PH.D.
The University of Edinburgh
Edinburgh, Scotland

References

1. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, *et al.* Air pollution and cardiovascular disease: a statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association. *Circulation* 2004;109:2655–2671.
2. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; 356:447–458.
3. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. *Lancet* 1995;345:176–178.
4. Donaldson K, Mills N, MacNee W, Robinson S, Newby D. Role of inflammation in cardiopulmonary health effects of PM. *Toxicol Appl Pharmacol* 2005;207:483–488.
5. Törnqvist H, Mills NL, Gonzalez M, Miller MR, Robinson SD, Megson IL, MacNee W, Donaldson K, Soderberg S, Newby DE, *et al.* Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med* 2007;176:395–400.
6. Mills NL, Törnqvist H, Robinson SD, Gonzalez M, Darnley K, MacNee W, Boon NA, Donaldson K, Blomberg A, Sandstrom T, *et al.* Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* 2005;112:3930–3936.
7. Nemmar A, Hoet PH, Dinsdale D, Vermylen J, Hoylaerts MF, Nemery B. Diesel exhaust particles in lung acutely enhance experimental peripheral thrombosis. *Circulation* 2003;107:1202–1208.
8. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 2005;113:823–839.
9. Brown JS, Zeman KL, Bennett WD. Ultrafine particle deposition and clearance in the healthy and obstructed lung. *Am J Respir Crit Care Med* 2002;166:1240–1247.
10. Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B. Passage of inhaled particles into the blood circulation in humans. *Circulation* 2002;105:411–414.
11. Mills NL, Amin N, Robinson SD, Anand A, Davies J, Patel D, de la Fuente JM, Cassee FR, Boon NA, MacNee W, *et al.* Do inhaled carbon nanoparticles translocate directly into the circulation in humans? *Am J Respir Crit Care Med* 2006;173:426–431.
12. Möller W, Felten K, Sommerer K, Scheuch G, Meyer G, Meyer P, Häussinger K, Kreyling WG. Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. *Am J Respir Crit Care Med* 2008;177:426–431.
13. Frampton MW, Utell MJ, Zareba W, Oberdorster G, Cox C, Huang LS, Morrow PE, Lee FE, Chalupa D, Frasier LM, *et al.* Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. *Res Rep Health Eff Inst* 2004;126: 1–63.
14. Mills NL, Törnqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S, Boon NA, Donaldson K, Sandström T, Blomberg A, *et al.* Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* 2007;357:1075–1082.
15. Bräuner EV, Forchhammer L, Møller P, Barregard L, Gunnarsen L, Afshari A, Wåhlin P, Glasius M, Dragsted LO, Basu S, *et al.* Indoor particles affect vascular function in the aged: an air filtration-based intervention study. *Am J Respir Crit Care Med* 2008;177:419–425.

DOI: 10.1164/rccm.200710-1527ED

High-Resolution Computed Tomography and the Many Faces of Idiopathic Pulmonary Fibrosis

The idiopathic interstitial pneumonias (IIPs) are a diverse group of parenchymal lung diseases with varied treatment approaches and prognoses (1). Of the IIPs, usual interstitial pneumonia (UIP), the histopathologic correlate of idiopathic pulmonary fibrosis (IPF), is the most common, and associated with the worst prognosis. The clinical course of patients with IPF is variable and can display long periods of stability, a steady gradual decline, and/or periods of acute deterioration (2, 3). This unpredictable nature of UIP/IPF highlights the importance of identifying factors that can help refine the prognosis for patients at the time of initial diagnosis.

In this issue of the *Journal* (pp. 433–439), Sumikawa and colleagues evaluated the relationship between high-resolution computed tomography (HRCT) findings and survival in 98 patients who had a confident diagnosis of UIP by surgical lung biopsy (4). A confident diagnosis of UIP required patchy involvement with clear evidence of chronic scarring/honeycombing, the presence of fibroblastic foci, and the absence of features against a diagnosis of UIP, such as granulomas (1). These 98 cases were selected from a larger group of patients initially diagnosed as UIP but discarded from this study due to the lack of a confident pathologic diagnosis (n = 51), or lack of HRCT (n = 14). A group of four radiologists, with knowledge of the pathologic diagnosis, subsequently scored HRCT features and classified the HRCT scans as definite UIP (honeycomb change in a peripheral, basal distribution; n = 33), consistent with UIP (reticular pattern in a predominantly peripheral/basal distribution, but no honeycombing; n = 36), suggestive of an alternative diagnosis (n = 21), or unclassified (n = 8). Although the investigators do not specify the specific criteria for "suggestive of an alternative diagnosis," it seemed to be most influenced by the presence of ground-glass opacity that led the authors to consider a diagnosis of nonspecific interstitial pneumonia (NSIP).

One of the most striking findings of this study is the variable HRCT appearance of UIP despite very rigid histopathologic criteria. This study excluded 51 cases that were previously called UIP based on the lack of a confident diagnosis of UIP at biopsy. I would have expected the rigid inclusion criteria to define a more homogeneous patient population with similar HRCT features. Interestingly, only approximately one-third of HRCTs showed definite IPF and approximately one-third suggested an alternative diagnosis, such as NSIP, or were unclassifiable! We also found a high prevalence of histopathologic UIP in patients with an HRCT appearance of indeterminate or NSIP (5). These studies highlight the critical importance of a surgical lung biopsy in making an accurate diagnosis in patients without definite HRCT appearance of UIP, even when an alternative diagnosis, such as NSIP, is suspected.

This study also sheds additional light on the role of HRCT in determining prognosis for patients with IPF/UIP. The survival of patients within each HRCT category was statistically similar, although the median survival was shortest for the definite UIP

group (35 mo), intermediate for the consistent with UIP group (43 mo), and longest for the alternative diagnosis group (112 mo). This is similar to previous findings that patients with IPF/UIP and a definite HRCT appearance of UIP have a shorter median survival (21 mo) compared with those with an indeterminate/NSIP-appearing HRCT (69 mo) (5). The lack of statistical significance in the current study could be due to limited sample size or selection bias either through the selection of cases for biopsy or due to the large number of patients previously diagnosed with UIP who were excluded (n = 65) (4). Investigators in the current study also performed a detailed, quantitative analysis of HRCT features. In multivariate modeling, the extent of traction bronchiectasis and quantity of fibrosis were significant predictors of subsequent mortality. The overall extent of fibrosis on HRCT has previously been associated with increased risk of subsequent mortality, although traction bronchiectasis was not evaluated (6). It is uncertain if knowledge of the histopathologic diagnosis by radiologists in the current study influenced the HRCT diagnosis and/or quantification of features. However, the similar trends in these studies (4, 6) support a conclusion that HRCT appearance and quantification of features, particularly fibrosis, can be useful to stratify the risk of subsequent mortality for patients with IPF/UIP.

The work by Sumikawa and colleagues highlights the variable appearance of IPF/UIP on HRCT as well as the ability of HRCT appearance and quantification of features to predict the risk of subsequent mortality. Further work is required to define how scoring of these HRCT features would fare in predicting mortality in community settings in which disagreement between academic physicians is likely to be present (7). Additional studies combining HRCT features with elements of pulmonary physiology, such as vital capacity, diffusing capacity for carbon monoxide, desaturation, and pulmonary hypertension are also needed.

***Conflict of Interest Statement*:** K.R.F. has served as a consultant for companies evaluating novel treatments for IPF including Genzyme, Intermune, and Boehringer Ingelheim.

KEVIN R. FLAHERTY, M.D., M.S.
University of Michigan Health System
Ann Arbor, Michigan

References

1. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
2. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176:636–643.
3. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, Flaherty KR, Schwartz DA, Noble PW, Raghu G, *et al.* The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;142:963–967.
4. Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, Kondoh Y, Ogura T, Arakawa H, Fujimoto K, *et al.* Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. *Am J Respir Crit Care Med* 2008;177:433–439.
5. Flaherty K, Thwaite E, Kazerooni E, Gross B, Toews G, Colby T, Travis W, Mumford J, Murray S, Flint A, *et al.* Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003;58: 143–148.
6. Lynch DA, David Godwin J, Safrin S, Starko KM, Hormel P, Brown KK, Raghu G, King TE Jr, Bradford WZ, Schwartz DA, *et al.* High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. *Am J Respir Crit Care Med* 2005;172: 488–493.
7. Flaherty KR, Andrei AC, King Jr TE, Raghu G, Colby TV, Wells A, Bassily N, Brown KK, du Bois R, Flint A, *et al.* Idiopathic interstitial pneumonia: do community and academic physicians agree on diagnosis? *Am J Respir Crit Care Med* 2007;175:1054–1060.

DOI: 10.1164/rccm.200711-1649ED