EDITORIAL (SEE YEH ET AL., P. 741)

Lung Involvement in Diabetes

Does it matter?

Dyspnea upon exertion in a diabetic patient readily arouses suspicion of cardiovascular disease and/or physical deconditioning. As reviewed in our previous publications (1), a solid body of literature in the 1980s and 1990s established the occurrence of ventilatory restriction in type 1 diabetes; however, diabetic lung involvement did not gain wide recognition among internists until two recent developments helped change that perception. The first development is the cumulative data that demonstrate a pattern of modest lung restriction in type 2 diabetes qualitatively similar to that in type 1 diabetes, with proportional decreases in forced vital capacity (FVC) and forced expiratory flow in 1 s (FEV_1) that are directly related to glycemia (2–5) and a corresponding reduction in lung diffusing capacity (DL_{CO}) (6,7), the primary noninvasive measure of alveolar gas exchange capacity. As the prevalence of type 2 diabetes approaches epidemic proportions and pulmonary function emerges as an independent predictor of incident diabetes (8), pathophysiology of lung involvement also assumes greater relevance. The second development was the finding that chronic use of inhaled insulin could potentially trigger or exacerbate pulmonary dysfunction. Though shown to be efficacious and well tolerated, inhaled insulin has also been reported to cause a small early drop in spirometry and DL_{CO} at rest that did not progress during 2 years of follow-up (9). Its effects over longer duration of use and in the presence of primary lung disease, inflammation, or tobacco exposure are not clear. As inhaled insulin products continue to be developed, the spectacular collapse of Exubera notwithstanding, the issue of their potential impact on lung function will linger.

Owing to normally large physiological reserves that allow alveolar oxygen uptake to increase in accordance with metabolic demand, exertional dyspnea may not develop until 40–50% of alveolar gas-exchange capacity is lost, hence the chronic chain-smoker who claims immunity to the effects of tobacco or who presents with severe emphysema only after apparently recent onset of symptoms. Diabetic lung involvement is best characterized as a loss of physiological reserves (10) since in most reports the measured indexes fall well within 80% of the reference value, i.e., within the normal range of clinical testing that ordinarily would not prompt further diagnostic evaluation. Of greater importance is the long-term progression of subclinical dysfunction, its interaction with normal aging and cumulative microvascular injury, and its effect in combination with other stressors that either increase oxygen demand or reduce oxygen flux across the alveolar-capillary barrier (e.g., exercise and ambient hypoxia, respectively) and in secondary end-organ complications such as cardiac or renal failure that independently compromise alveolar gas exchange.

Against this background, Yeh et al.'s article (11) essentially confirms previous findings by Davis et al. (3), Litonja et al. (2), Lange et al. (4), and data from our own laboratory (12) of mild spirometric impairment in patients with type 2 diabetes who are free of overt cardiopulmonary disease. Compared with those in type 1 diabetes (13), spirometric reductions are generally milder in type 2 diabetes; the difference could be due to the fact that type 1 diabetes is intrinsically more severe or that most earlier studies of type 1 diabetes involved fewer subjects at a time when euglycemia was less strictly promoted and, consequently, glycemic control tended to be poorer. Yeh et al. also demonstrated a small but significantly higher annual rate of FVC decline in the diabetic (64 ml) compared with the nondiabetic (58 ml) population during 3 years of prospective follow-up. If we extrapolate the annual decline from 50 to 80 years of age, the nondiabetic subject would on average lose 1,740 ml in vital capacity while the diabetic subject would lose 1,920 ml, or 10%, more. Because lung capacity declines steadily after ~25 years of age regardless of physical fitness (14), the average healthy 80-year-old nonsmoker has whittled away about 30% of his/her lung capacity at early adulthood, and the extra loss due to diabetes could deplete reserves beyond the minimal threshold needed to increase alveolar oxygen uptake in response to metabolic stress, thereby exacerbating tissue hypoxia and heightening the risks of adverse clinical outcome should the elderly individual develop pneumonia, heart failure, volume overload, or vascular complications. These estimates may be conservative since, according to Hankinson et al. (14), the normal decline tends to accelerate after about age 55 years, and according to Yeh et al., the annual FVC decline tends to accelerate with longer diabetes duration (57, 63, and 68 ml/year for ≤5, 6–9, and ≥10 years, respectively). Primary cardiopulmonary disease further erodes the remaining reserves.

Of course, the above extrapolation is valid only if Yeh et al.'s finding of accelerated decline is corroborated. In fact, their conclusion is opposite that reached by Litonja et al. in American veterans (2) and by Lange et al. in Danish urban dwellers (4) that mild spirometric reductions in type 2 diabetes do not progress over more than 10 years of follow-up. Reasons for the discrepancy are not clear. The larger sample size in the study by Yeh et al. is a strength that perhaps facilitated the detection of longitudinal differences within a short follow-up period. There are also a few weaknesses, such as their inclusion of significantly more African Americans in the diabetic than the nondiabetic population. Average FVC and FEV_1 are lower in African Americans than in Caucasians after adjustment for sex, age, and height (14). Although Yeh et al. stated that race was included in the prediction of spirometry results, the reference equations they used (15) were based on Caucasian adults exclusively. The confounding influence of ethnic differences cannot be discounted. The diabetic population in Yeh's study is significantly more obese than the nondiabetic population. Adiposity independently impairs lung function, and we were not given any data on the changes in adiposity or in glycemic control during follow-up; thus, differences in these factors could also have contributed to the accelerated decline they observed.

Restriction of vital capacity becomes physiologically significant when it impairs alveolar gas exchange; the latter is

commonly indexed by DL_{CO}, a composite conductance parameter (in milliliters of gas transferred per min per mmHg of alveolar pressure gradient) that reflects cardiopulmonary interactions among alveolar air and capillary blood and their distribution and recruitment with respect to ventilation and perfusion (10). DL_{CO} was not measured in the study by Yeh et al., a common deficiency in epidemiological studies designed primarily to examine cardiovascular risk factors rather than pulmonary risk factors. Lung restriction in diabetes could result from chronic low-grade tissue inflammation, microangiopathy, and/or accumulation of advanced glycation end products; Yeh et al.'s data cannot distinguish involvement of the chest wall from lung parenchyma. Spirometry partly addresses the restriction of ventilation, but its physiological consequences must be defined within the context of dynamic cardiopulmonary interactions; i.e., alveolar gas exchange depends on the appropriate matching of ventilation to perfusion and perfusion to diffusion. The various components of vital capacity and chest wall and lung mechanics should be assessed and the effects of diabetes separated from those of obesity. Factors that might exacerbate or alleviate functional impairment, such as smoking and weight loss, also deserve further examination.

The study by Yeh et al. serves to further enhance recognition of the lung as a target of diabetic injury. Why should this issue matter to patients and physicians? Think of the lung as a crime victim who unwittingly abets the perpetrator to hasten the demise of the host. Cumulative loss of pulmonary reserves eventually aggravates tissue hypoxia associated with any form of angiopathy in distant organs that ultimately underlies diabetic morbidity and mortality. The data of Yeh et al. lend support to this hypothesis, but proving the charges beyond reasonable doubt remains a daunting challenge.

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P.R. is a member of a scientific advisory board for Novo Nordisk and has received research grants and/or honoria from Novo Nordisk, Pfizer, and MannKind.

Abbreviations: DL_{CO}, lung diffusing capacity; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity.

DOI: 10.2337/dc08-0103

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