Lung Dysfunction in Diabetes

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Clear decrements in lung function have been reported in patients with diabetes over the past 2 decades, and many reports have suggested plausible pathophysiological mechanisms. However, at the present time, there are no reports of functional limitations of activities of daily living ascribable to pulmonary disease in patients with diabetes. Accordingly, this review is directed toward a description of the nature of reported lung dysfunction in diabetes, with an emphasis on the emerging potential clinical implications of such dysfunction.

More than a quarter-century ago, Schuyler et al. (1) investigated lung function in 11 young (21–28 years old) patients with type 1 diabetes and age-matched normal control subjects. This classic study was the first to report measurements of nearly all the available tests of lung function, including lung elasticity, capacity to transfer carbon monoxide (CO, a surrogate for oxygen transfer capacity), absolute thoracic gas volumes, airflow resistance, and maximal forced spirometric pulmonary function tests (PFTs). As their subjects were lifelong nonsmokers without allergies or lung disease, their finding that lung elastic recoil was decreased in these young patients with diabetes was interpreted to reflect effects of diabetes on lung elastic proteins. This was the first suggestion in the literature that the lung may be a target organ of diabetes. Because the elastic structure of the lung supports the intrathoracic airways and helps to maintain their patency, the authors suggested that patients with diabetes were at risk for developing chronic airflow obstruction. While small changes in lung elastic recoil do not have direct clinical implications, subsequent development of chronic airflow obstruction could incur significant disability due to mechanical dysfunction of the lungs and airways.

Scherthaner et al. (2) could not confirm the findings of Schuyler et al. in patients with type 1 diabetes. However Sandler et al. (3) did find decreased lung elasticity. In addition, they found decreased CO transfer capacity with decreased pulmonary capillary blood volume in 40 patients (15–60 years of age) with insulin-dependent diabetes compared with age-matched control subjects, all lifelong nonsmokers. Lung CO transfer capacity is significantly affected by the integrity of lung capillary endothelium and, therefore, the findings of Sandler et al. focused attention on pulmonary vascular changes. The concept of the lung as a target organ for diabetic microangiopathy received continuing attention. Reports of lung function tests in patients with diabetes over the next 15 years have focused largely on pulmonary microangiopathy with relatively few studies of pulmonary mechanical function. Lung function tests relating specifically to pulmonary microangiopathy include CO transfer capacity and pulmonary capillary blood volume.

In patients with type 1 diabetes, decreased lung transfer capacity for CO has been documented in association with evidence of other diabetic microangiopathy (4–6). Decreased CO transfer capacity has also been correlated with the prevalence and/or severity of retinopathy and renal microangiopathy in patients with type 2 diabetes (7–11), supporting the concept of the lung as a target organ for diabetic microangiopathy. Sandler (12) concluded that the lung should be considered a target organ in diabetes, but noted that the documented physiological abnormalities were modest in degree, and clinical implications of those findings were not clearly defined in terms of respiratory disease at that time. Subsequent studies demonstrated further evidence of pulmonary microangiopathy, including thickening in alveolar capillary and pulmonary arteriolar walls in human postmortem studies of patients with diabetes (13) and decreased lung capillary blood volume in patients with type 1 diabetes (14).

In contrast to the substantial evidence supporting the concept of the lung as a target organ for diabetic microangiopathy, reports of lung mechanical abnormalities in diabetes have been less convincing. Tests relating to lung mechanical function include lung elasticity (particularly dynamic breathing changes in lung elasticity), airflow resistance, and maximal forced spirometric PFTs. Most reports of lung mechanical function have utilized spirometric PFTs, which are commonly interpreted as indicative of airflow obstruction. In practice, however, PFTs are influenced by a wide variety of factors: they are physically demanding, maximally forced, coordinated efforts that are subject to deterioration with any debilitating disease, aging, loss of muscle strength from any cause, and obesity.

An early study (7) showed decreased spirometric PFTs in patients with diabetes and this was confirmed by Schnack et al. (6), who also documented a clear relationship between spirometric PFTs and long-term metabolic control. However, spirometric PFTs in other studies failed to show significant differences between patients with diabetes and normal control subjects, differences from normal population-predicted values, or a relationship with diabetes control or duration of disease (8,14–16). Recent large epidemiologic studies (17–20) have used associations between simple spirometric PFTs and either complications or duration of diabetes to determine statistical significance after controlling for height, sex, age, BMI, and cigarette smoking. Davis et al. (17) found reduced spirometric pulmo-
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Pulmonary function (in comparison with normal population-predicted values) in patients with type 2 diabetes. Obesity, vascular disease, and duration of diabetes also contributed significantly to a reduction in lung function, but current and ex-smokers approached clinically significant chronic airflow obstruction. Klein et al. (18,19) measured peak expiratory flow (PEF) during brief, 1- to 2-s maximal forced expiratory efforts. They found no association of PEF with progression of retinopathy, incidence of proliferative retinopathy, macular edema, lower extremity amputation or ulcers, or self-reported cardiovascular disease in univariate analyses. However, a multivariate model allowed adjustment for the leading contributions to the model related to sex, age, and BMI and showed an association of PEF with a history of cardiovascular disease, pulse rate, glycosylated hemoglobin, end-stage renal disease, lower extremity amputation/ulcer, and subsequent 6-year survival. Engstrom et al. (20) reported an association between lower values of spirometric PFTs and the incidence of diabetes in middle-aged men.

Conclusions about pulmonary function are affected by methodological sensitivity. Thus, early conflicting reports of CO transfer capacity in patients with diabetes and correlation with other diabetic microangiopathy were soon resolved by using more sensitive methods, including the measurement of pulmonary capillary blood volume (3). Fusco et al. (14) reported even more subtle pulmonary capillary blood volume abnormalities in patients with type 1 diabetes using tests of CO transfer capacity and capillary blood volume in both the seated and supine positions. Patients with normal CO transfer capacity in the seated posture showed decreased capillary volume in the supine posture relative to normal control subjects. The authors suggested seated and supine measures of CO transfer capacity to diagnose early pulmonary vascular damage in diabetes. Accordingly, Ozmen et al. (15) noted that their failure to show a relationship between CO transfer capacity and microalbuminuria, diabetes duration, or glycemic control was most likely due to relative insensitivity of the usual clinical method of measuring CO transfer capacity.

In an analogous manner, most reports of lung mechanical function in diabetes must be viewed with circumspection in view of the many extraneous factors known to affect spirometric PFTs. More sensitive tests of lung mechanical function document abnormal dynamic lung elastic pressure changes during breathing in patients with type 1 diabetes, parameters known as “reduced dynamic lung compliance” (4,21–23), which are characteristic of peripheral airway obstruction (24,25). They also occur in asymptomatic cigarette smokers with normal spirometric PFTs. While they reflect early peripheral airway disease, their clinical implications in patients with diabetes have not been elucidated.

Thus, routine clinical lung function tests may not detect the presence of modest lung function abnormalities in diabetes, either early pulmonary microangiopathy or early peripheral airway disease. While more sensitive tests reveal such abnormalities, there is no clear evidence at the present time of clinically significant lung disease in patients with diabetes who have modest lung function abnormalities. However, another more important issue has yet to be addressed, namely the increased deterioration of lung function over time in patients with diabetes, particularly with respect to the impact of inhalational delivery of pharmacological agents.

The lungs have a very large surface area that, along with the ability to transfer large amounts of oxygen from the air to blood, presents a convenient portal for entry of therapeutic agents. Two preliminary reports have described declines in spirometric PFTs and CO transfer capacity associated with the use of inhaled insulin (INH) in patient cohorts followed for 0.5–2 years (26,27). These reports have not been confirmed by standardized testing and quality assurance procedures, and differences between subjects treated with INH and subcutaneous insulin (SC) were modest, with unproven clinical significance (27). However, even when no statistically significant differences between INH and SC occurred, the absolute rate of decline of spirometric PFTs in patients taking either INH or SC was two to three times as large as expected in normal nonsmoking subjects (28). This reinforces concerns about abnormal lung function in patients treated with SC, and regarding the greater rate of decline over time than that manifested in normal subjects.

A further concern in patients with diabetes is the presence of systemic inflammation. Systemic inflammation is associated with endothelial dysfunction in patients with diabetes (29–31). In addition, it may contribute independently to airflow obstruction, in a manner analogous to that by which peripheral airway inflammation leads to airflow obstruction in asthma (32). Two approaches may be used in its assessment, including a sensitive method of measuring airflow obstruction (“forced oscillation”) and measurements of inflammatory markers in exhaled breath condensate (EBC).

Forced oscillation is the noninvasive equivalent of dynamic lung compliance. It measures respiratory resistance during resting breathing, and has been primarily validated over the past 25 years in Western Europe (33–37). It is sensitive enough to detect early inflammatory peripheral airway disease in asymptomatic cigarette smokers (33–35). Forced oscillation provides a sensitive index of peripheral airway dysfunction that may be more easily applied to larger groups of patients with diabetes than dynamic lung compliance (4,23).

Direct measurements of inflammatory markers in lung epithelial lining fluid are now feasible by analysis of EBC (38–40) during normal resting breathing. One report documented a fourfold increase in leukotriene B4 in subjects with chronic obstructive pulmonary disease (COPD) who also had diabetes, compared with COPD patients and asthmatics without diabetes (40). Other inflammatory indexes may also be measured in EBC, and they may be increased in subjects with diabetes if the chronic inflammation associated with diabetes is manifest in lung lining fluid. Anecdotal reports of salutary effects of thiazolidinediones on PFTs in patients with both asthma and diabetes have suggested that activation of peroxisome proliferator-activated receptor-γ, and the stabilization of mast cells may result in decreased release of inflammatory cytokines (41).

Finally, the effects of cigarette smoking in diabetic subjects may relate to possible pulmonary inflammation, by extrapolation from what is known about asthma. Cigarette smoking and asthma both cause peripheral airway inflammation and dysfunction. In most nonasthmatic cigarette smokers, many years of exposure are required to cause clinically significant chronic airflow obstruction. In contrast, subjects with chronic asthmatic
peripheral airway inflammation develop much more severe airflow obstruction when combined with cigarette smoking. If the systemic inflammation of diabetes is importantly expressed in the lung, it is likely that cigarette smoking will wreak similar havoc in the lungs of patients with diabetes as it does in asthmatic subjects. Davis et al. (17) found that a smoking history was the most influential variable related to spirometric PFTs other than age and duration of diabetes. Even previous smoking had more influence than diabetes duration. Thus, even if diabetic patients were to quit smoking, they may still have significant peripheral airway dysfunction, and this may lead to adverse responses to inhaled medications.

Summary
Early investigations of lung function in type 1 diabetes suggested that the lung is a target organ for diabetes. Subsequent reports of lung transfer capacity for CO and postmortem histopathological studies support the notion that the lung is indeed a target organ for diabetic microangiopathy, in both type 1 and type 2 diabetes. Additional evidence documents peripheral airway dysfunction in type 1 diabetes in the absence of cigarette consumption, allergies, or other common causes of airflow obstruction. Common simple lung function tests alone are likely to underestimate the prevalence and degree of lung dysfunction in diabetes, but newer noninvasive tests of lung mechanical function provide a more sensitive assessment of peripheral airway function. Questions related to inhalational delivery of medications add to the motivation to explore these issues in more detail. It appears useful to remain circumspect toward conclusions drawn from the use of hitherto routine clinical lung function tests; this may be especially important in further studies of INH. However, the clinical impact of measured decrements in lung function is still unproven, and will be defined only with long-term monitoring of pulmonary function changes in association with the presence or absence of overt lung disease.

A major unresolved question about lung dysfunction in diabetes concerns the issue of a possible inflammatory pulmonary infrastructure and whether this increases the risk of adverse reactions to otherwise innocuous vehicles or agents. It appears that cigarette smoking in patients with diabetes poses an increased risk of chronic obstructive lung disease, as compared with nondiabetic subjects. Does cigarette smoking in diabetic patients increase the risk of adverse pulmonary responses from any inhaled medication? Such questions relate importantly to future development of inhaled drug delivery systems. Before proceeding further with clinical trials of other inhaled medications in patients with diabetes, it would seem prudent to assess whether the lung is a target organ for the chronic systemic inflammation of diabetes. New technology appears to offer considerable promise for noninvasive evaluation of inflammatory mediators in lung lining fluids.

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