

# Lung Function Changes Related to Diabetes Mellitus

CONNIE C.W. HSIA, M.D. and PHILIP RASKIN, M.D.

## ABSTRACT

Diabetic microangiopathy targets the lung as it does other organs. Even though respiratory dysfunction in most patients with diabetes is subclinical and rarely the presenting complaint, there are several reasons why pulmonary assessment is important: (1) Pulmonary function testing noninvasively quantifies physiological reserves in a large microvascular bed that is not clinically devastated by diabetes. (2) Subclinical loss of pulmonary reserves becomes overtly debilitating under conditions of stress, such as with aging, chronic hypoxia due to lung disease or high altitude exposure, or volume overload secondary to cardiac and renal failure. (3) Unlike myocardial or skeletal muscle function, pulmonary indices are largely independent of physical fitness. (4) Interpretation of pulmonary function indices is not complicated by secondary sequelae of diabetic end-organ failure or prior therapy. Lung function could provide useful measures of the progression of systemic microangiopathy. (5) Chronic use of inhaled insulin may affect long-term pulmonary function, while preexisting pulmonary dysfunction may alter the absorption and bioavailability of inhaled insulin. This review will discuss the changes in lung function observed in diabetes, their underlying mechanisms, and their physiological and clinical implications.

## WHY ASSESS LUNG FUNCTION IN DIABETES MELLITUS?

**C**HRONIC HYPERGLYCEMIA leads to widespread nonenzymatic protein glycosylation and macro- and microvascular end-organ dysfunction.<sup>1-3</sup> Pulmonary involvement in diabetes has been sporadically reported for many decades, including a predisposition to infections, aspiration, pulmonary edema, bronchomotor dysregulation, disordered breathing during sleep, and central hypoventilation as well as abnormal lung mechanics and gas exchange.<sup>4</sup> However, general recognition of the lung as a major organ targeted by diabetes is a recent phenomenon with the advent of inhaled

insulin. Even though respiratory dysfunction in most patients with diabetes is subclinical and rarely the presenting complaint, there are several reasons why pulmonary assessment is important: (1) Pulmonary function testing noninvasively quantifies physiological reserves in a large microvascular bed that is not clinically devastated by diabetes. (2) Subclinical loss of pulmonary reserves becomes overtly debilitating under conditions of stress, such as with aging, chronic hypoxia due to parenchymal lung disease or high altitude exposure, or volume overload secondary to cardiac and renal failure. (3) Unlike myocardial or skeletal muscle function, pulmonary indices are largely independent of physical fitness. (4) Interpretation

of pulmonary function indices is not complicated by secondary sequelae of diabetes end-organ failure or prior therapy. Evaluation of therapeutic response and reversibility of established end-organ dysfunction is often difficult using conventional end points once an organ becomes clinically ravaged by diabetes. For example, nephrotic syndrome once established can progress because of hypertension associated with renal insufficiency, or because of direct tubular toxicity of albuminuria independent of the inciting insult from the diabetes state. Repeated laser treatment alters retinal perfusion pattern independent of diabetic retinopathy. Physical deconditioning can exacerbate skeletal muscle weakness and cardiac dysfunction independent of diabetic myopathy. The alveolar-capillary network, by virtue of its large size, is protected against overt respiratory complications at a given level of systemic microvascular destruction. Hence, lung function could provide useful measures of the progression of systemic microangiopathy. (5) Chronic use of inhaled insulin may affect long-term pulmonary function. Conversely, preexisting pulmonary dysfunction may alter the absorption and bioavailability of inhaled insulin. This review will discuss the changes in pulmonary dysfunction observed in diabetes and their underlying mechanisms as well as physiological and clinical implications.

### LUNG FUNCTION IN DIABETES MELLITUS

#### *Respiratory autonomic neuropathy*

An abnormal ventilatory response in diabetes is characterized by depressed cholinergic bronchomotor tone and neuroadrenergic denervation in the lung. Up to one-third of subjects with diabetes<sup>5</sup> showed abnormal ventilatory response to hypoxia, hypercapnia, or exercise consistent with autonomic neuropathy. A subset showed excessively high tidal volumes during exercise resembling changes after vagotomy. The ventilatory response during submaximal exercise<sup>6</sup> and acute isocapnic hypoxia<sup>7</sup> was blunted in type 2 diabetes. Patients with diabetes demonstrate diminished ability

to perceive inspiratory resistive loads.<sup>8</sup> In a small study using *m*-[<sup>123</sup>I]iodobenzylguanidine ([<sup>123</sup>I]MIBG) ventilatory scintigraphy to assess neuroadrenergic bronchial innervation,<sup>9</sup> [<sup>123</sup>I]MIBG clearance declined significantly during 5 years of follow-up in patients with diabetes with and without autonomic neuropathy, suggesting progressive neuroadrenergic denervation, the rate of which was inversely related to the severity of baseline autonomic dysfunction. In these patients forced expiratory volume in 1 s (FEV<sub>1</sub>) declined at twice the physiological rate regardless of the presence of documented autonomic neuropathy. However, longitudinal [<sup>123</sup>I]MIBG clearance in subjects without diabetes was not assessed in this study<sup>9</sup> so appropriate control data are not available. Further investigation is needed to define impairment in ventilatory control with respect to glycemia. The greater breathlessness perceived by patients with diabetes during hypoxia exposure is associated with a disproportionate increase in inspiratory effort and a smaller increase in tidal volume relative to subjects without diabetes,<sup>10</sup> a pattern more consistent with mechanical restriction of the ventilatory pump than blunting of central drive. Abnormal ventilatory control in diabetes would likely be exaggerated by association with obesity and could translate into greater difficulties during acclimatization to high altitude or during chronic adaptation to hypoxia.

#### *Lung restriction*

Patients with diabetes without a smoking history or clinical lung disease consistently demonstrate a modest restrictive ventilatory defect with proportional (8–20%) reductions in lung volume, forced vital capacity (FVC), FEV<sub>1</sub>, and forced expiratory flow in the midrange of vital capacity compared to subjects without diabetes<sup>11–17</sup> and in relation to glycemic control.<sup>14,18</sup> Total lung capacity, lung elastic recoil, and dynamic lung compliance were abnormally reduced in type 1 diabetes.<sup>15</sup> Small airway obstruction has been observed with an increased ratio of residual volume to total lung capacity,<sup>19–21</sup> which probably resulted from diminished lung recoil and parenchymal tethering of peripheral airways. Reduced lung vol-

ume without airflow limitation or respiratory muscle weakness in diabetes has been associated with limited joint mobility and attributed to stiffness of the skin and connective tissue of the chest wall.<sup>16</sup> The consequence of abnormal lung and thoracic mechanics in diabetes is an excessively increased work of breathing during heavy exercise.<sup>14</sup> The changes in lung mechanics resemble accelerated aging with generalized derangement in connective tissue metabolism as well as irreversible collagen cross-linking in thoracic and lung tissue.<sup>22,23</sup> Compared to control lungs from individuals without diabetes, lungs from individuals with diabetes show accumulation of collagen and elastin with retarded connective tissue breakdown.<sup>24</sup> Parenchymal changes noted at autopsy include congestion, histiocytosis, septal interstitial and smooth muscle hypertrophy, type 2 pneumocyte hyperplasia, thickened basement membrane, areas of fibrosis, and septal obliteration, summarized by Hsia and Raskin.<sup>25</sup> Most post-mortem reports consist of a small number of subjects, and comparisons to lungs from individuals without diabetes are largely qualitative or uncontrolled.

An elevated fasting blood glucose alone is associated with reduced lung function,<sup>18</sup> and a predisposition to diabetes is associated with restrictive ventilatory defect prior to onset of overt diabetes. In the Normative Aging Study,<sup>26</sup> lung function data from adult men before, at, and after being diagnosed with diabetes were analyzed. Men who developed type 2 diabetes had lower FEV<sub>1</sub> and FVC at all time points after adjustment for age, height, weight, and smoking. A cross-sectional study in British women confirms the inverse association of FEV<sub>1</sub> and FVC with insulin resistance and prevalence of type 2 diabetes.<sup>27</sup> In the prospective Atherosclerosis Risk in Communities Study, a low baseline FVC in middle-aged adults without diabetes was independently associated with insulin resistance and predicted incident type 2 diabetes in both genders after adjustment for age, race, adiposity, smoking, physical activity, and study center.<sup>28</sup> During prospective follow-up in the Normative Aging Study,<sup>26</sup> there were no significant differences in adjusted rates of longitudinal change between subjects with and without diabetes, while in the

Fremantle Diabetes Study<sup>17</sup> declining spirometry and lung volume indices were directly related to poor glycemic control, and a decreased FEV<sub>1</sub> was a predictor of mortality in type 2 diabetes after adjusting for other recognized risk factors. In the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, the presence of baseline restrictive ventilatory defect predicted the development of insulin resistance and type 2 diabetes,<sup>29</sup> while in another study a low peak expiratory flow rate predicted clinical complications and mortality in type 1 diabetes.<sup>30</sup> Although shared risk factors such as obesity could not be entirely excluded, these large-scale epidemiological studies clearly demonstrate a relationship between hyperglycemia and spirometry results.

The mechanisms underlying prediabetes lung restriction are not clear. It is possible that lung growth and insulin resistance are co-influenced by shared exposures during somatic maturation. Alternatively, insulin resistance could alter lung volume and mechanical function directly or via mediators such as leptin. Leptin is produced by adipose tissue and circulates to the hypothalamus to induce satiety. Leptin also modulates lung cell growth and function<sup>31</sup> as well as central respiratory control<sup>32</sup> via receptor-mediated mechanisms. Serum leptin levels are variably elevated in morbidly obesity,<sup>32</sup> associated with small lung volumes, abnormal respiratory mechanics, and depressed respiratory control that manifest as central hypoventilation or obstructive sleep apnea. In nonobese normal subjects serum leptin levels are inversely related to FEV<sub>1</sub>,<sup>33</sup> suggesting the possibility that leptin deficiency or leptin resistance could be involved in the pathogenesis of pulmonary dysfunction.

#### *Reduced lung diffusing capacity*

Lung diffusing capacity for carbon monoxide (DL<sub>CO</sub>) (in mL/min/mm Hg) is a measure of gas conductance across alveolar tissue membrane into capillary erythrocytes and subsequent chemical binding to hemoglobin. According to the classical Roughton-Forster relationship,<sup>34,35</sup> DL<sub>CO</sub> is composed of two conductance arranged in series: membrane (DM<sub>CO</sub>) and blood ( $\Theta \cdot V_c$ ), where V<sub>c</sub> is pul-

monary capillary blood volume and  $\Theta$  the empirical rate of carbon monoxide uptake by whole blood, a function of capillary hemoglobin concentration and alveolar oxygen tension:

$$\frac{1}{DL_{CO}} = \frac{1}{DM_{CO}} + \frac{1}{\Theta \cdot Vc} \quad (1)$$

Modest but significant (10–30%) reductions in  $DL_{CO}$  develop in nonsmoking patients with diabetes.<sup>11,13,14,36</sup> In type 1 diabetes the lower  $DL_{CO}$  is predominantly due to a low  $DM_{CO}$ .<sup>14</sup> In type 2 diabetes both  $DM_{CO}$  and  $Vc$  are reduced.<sup>37</sup> The reduction in resting  $DL_{CO}$  correlates with diabetic retinopathy and disease duration.<sup>38,39</sup> Reductions in  $DL_{CO}$  and  $DM_{CO}$  during exercise are directly related to glycemic control and prevalence of extrapulmonary end-organ complications.<sup>14,37</sup> In addition,  $DL_{CO}$  and  $Vc$  normally increase from sitting to supine postures owing to alveolar-capillary recruitment caused by an increase in central blood volume. The posture-related increases are lost in patients with type 1 diabetes,<sup>40</sup> signifying an abnormal microvascular recruitment pattern and perhaps anatomical loss of alveolar capillaries. Diffusion impairment in lungs from individuals with diabetes parallels a similar impairment in skeletal muscle from diabetic rats estimated from the permeability–surface area product for small solutes.<sup>41</sup> The diffusion defect in muscle from diabetic animals is reported to have two major components: reduced microvascular surface area and greater perfusion heterogeneity.<sup>41</sup> Available evidence also suggests analogous anatomical and physiological mechanisms for the pulmonary diffusion defect, discussed below.

### *Lung morphology*

The anatomical determinants of membrane conductance are alveolar-capillary surface area and mean harmonic thickness of tissue-plasma diffusion barrier:

*Membrane conductance* =

$$D \cdot \frac{\text{Surface area}}{\text{Harmonic mean barrier thickness}} \quad (2)$$

where  $D$  is the diffusion constant, a function of gas permeability in tissue and plasma.<sup>42</sup> Gas

conductance estimated from lung ultrastructure is about twice that measured physiologically at rest but correlate strongly with physiological conductance measured at heavy exercise,<sup>43</sup> indicating that the structural capacity for gas transport is not fully utilized except at peak exercise. The difference between diffusing capacity estimated at rest and at peak exercise represents functional reserves available for recruitment. Postmortem observations in lungs from individuals with diabetes have noted thickening of alveolar epithelial and endothelial basement membranes,<sup>44</sup> emphysema-like airspace changes, and obliteration of alveolar capillaries as well as pleural arterioles.<sup>45</sup> Alveolar-capillary surface area and anatomical  $Vc$  have not been systematically quantified in lungs from those with diabetes, but the observed microangiopathic features parallel changes in the retina, kidney, peripheral nerve, and skeletal muscle,<sup>1,46–49</sup> consistent with shared pathology that increases diffusive resistance of the alveolar membrane.

Thickening of alveolar epithelial and endothelial diffusion barrier in diabetes begins with increased vascular endothelial permeability to macromolecules,<sup>50</sup> which is associated with intensified transendothelial vesicular transport, accumulation of caveolae, and overexpression of endothelial caveolin-1.<sup>51</sup> Later stages are marked by barrier remodeling with accumulation of type IV collagen and laminin as well as advanced glycation end products.<sup>52</sup> Altered surfactant metabolism in type 2 pneumocytes could also modulate the effective surface area for gas exchange. In lungs from rats with diabetes type 2 pneumocytes show increased glycogen granules and reduced lamellar bodies, accompanied by ultrastructural abnormalities in endoplasmic reticulum and Golgi apparatus<sup>53</sup> as well as differentially altered surfactant protein mRNA expression.<sup>54</sup> A thickened alveolar diffusion barrier, including the interstitium and basement membranes, also develops in chronic heart failure as a result of remodeling induced by hydrostatic stress<sup>55,56</sup>; these morphological effects are synergistic with that caused by diabetes. Diabetes exacerbates existing impairment of  $DL_{CO}$  and  $DM_{CO}$  caused by chronic heart failure, resulting in a further reduction of ventilatory efficiency, a

higher dead space-to-tidal volume ratio, and significantly worse exercise tolerance compared to heart failure alone.<sup>57,58</sup>

#### *Physiologic action of insulin*

In asymptomatic patients with type 2 diabetes with normal or impaired cardiac function, insulin infusion at a constant glycemic level acutely improves  $DL_{CO}$  and  $DM_{CO}$  without changing spirometry, volumes, and pulmonary hemodynamics.<sup>58,59</sup> This observation suggests the existence of physiological mechanisms for the reduction in  $DL_{CO}$  and  $DM_{CO}$  related to a glycemia-independent action of insulin. Insulin prevents cell apoptosis, protects against ischemia-reperfusion injury, suppresses production of pro-inflammatory cytokines and free radicals, enhances the synthesis of anti-inflammatory cytokines, and causes peripheral vasodilatation.<sup>60</sup> A key mediator of glycemia-independent insulin action is nitric oxide (NO). Insulin up-regulates endothelial NO production and induces pulmonary vascular dilatation in vitro,<sup>61</sup> while insulin resistance blunts micro- and macrovascular reactivity, activates multiple markers of endothelial dysfunction,<sup>62</sup> and predisposes to pulmonary arterial hypertension in individuals at risk of developing type 2 diabetes even at a stage when normal glucose tolerance exists.<sup>63</sup> NO-mediated insulin action could cause redistribution of pulmonary blood flow and improve regional diffusion-perfusion matching in the lung, thereby directly enhancing alveolar-capillary gas uptake in the absence of overt changes in hemodynamics, cardiac output, or  $V_c$ .

In addition to vasodilatation, insulin also induces airway epithelium to release NO and to inhibit smooth muscle contraction,<sup>64</sup> an observation that could potentially explain the small airway obstruction reported in some patients with diabetes.

Glycosylated hemoglobin ( $HbA_{1c}$ ) is reported to exhibit slightly higher in vitro affinity for carbon monoxide and oxygen (slightly lower standard  $P_{50}$  of oxyhemoglobin dissociation curve).<sup>65,66</sup> We did not find a significant correlation between standard  $P_{50}$  corrected for carboxyhemoglobin concentration and  $HbA_{1c}$

level in 61 subjects with diabetes; furthermore,  $P_{50}$  did not differ between subjects with and without diabetes (authors' unpublished data). It is very unlikely that the oxygen binding affinity of  $HbA_{1c}$  could explain the observed reductions in  $DL_{CO}$  or its components in diabetes.

#### *Physical fitness*

Variable physical fitness often confounds the assessment of cardiovascular and muscular function in diabetes.<sup>67,68</sup> Adaptation to physical training is similar among subjects with and without diabetes.<sup>69</sup> Patients with diabetes studied before and after physical training show modestly improved exercise tolerance, maximal oxygen uptake, and heightened insulin sensitivity but no improvement in metabolic control of diabetes.<sup>69-71</sup> Regular exercise per se may or may not improve glycemic control.<sup>72,73</sup> Physical activity level has no consistent effect on the risk of developing retinopathy.<sup>73</sup> However, glycemic control is best among patients who are motivated to participate in any kind of treatment program. In contrast to cardiac and muscular function, physical training has no effect on  $DL_{CO}$  measured at a given cardiac output,<sup>74</sup> but only extends the normal relationship of  $DL_{CO}$  with respect to cardiac output to a higher maximal cardiac output. Hence, physical fitness does not affect alveolar microvascular function, and variable physical fitness does not confound the interpretation of  $DL_{CO}$ .

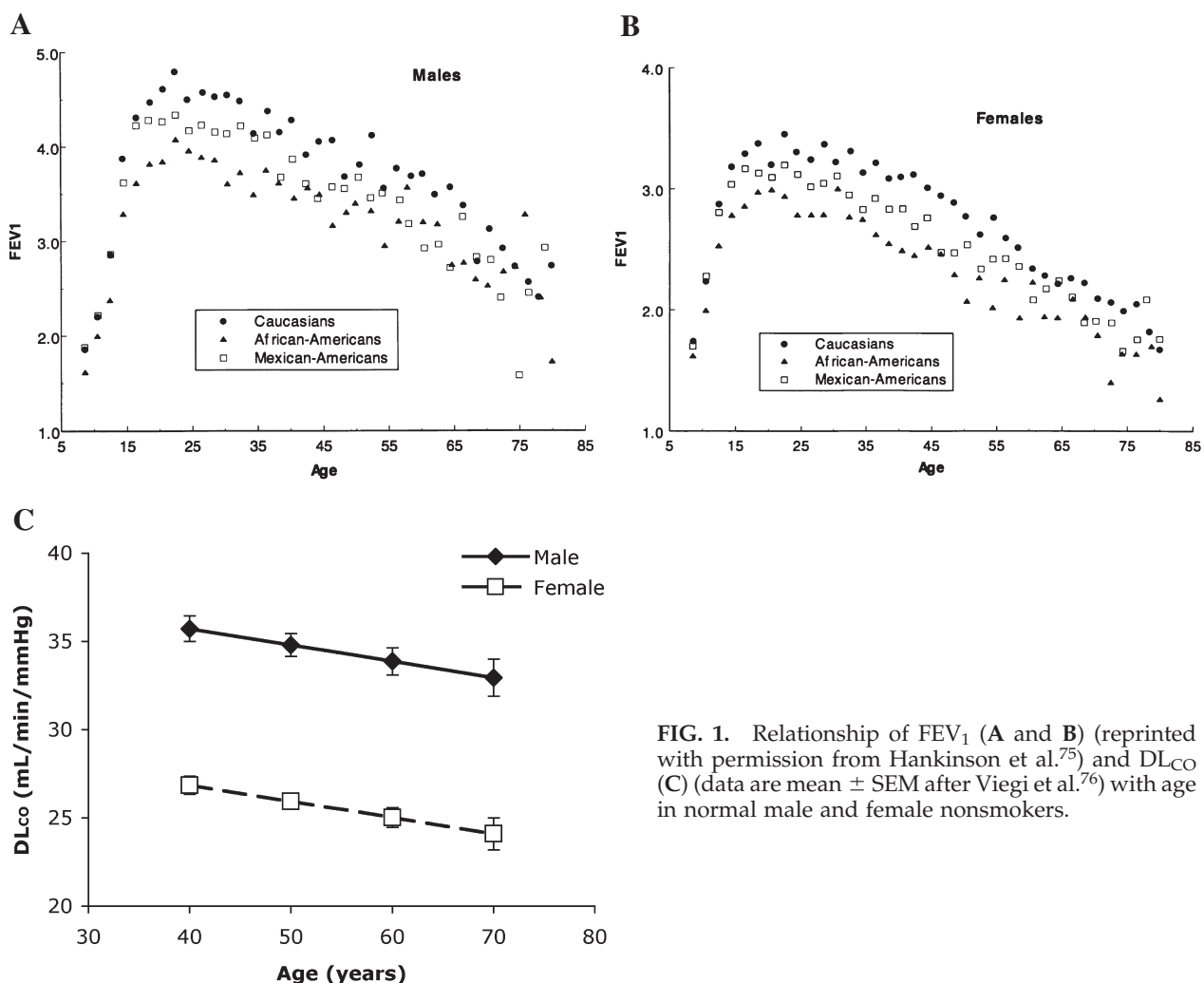
### PROGRESSION AND REVERSIBILITY

Lung function normally peaks around 20–30 years of age and decline steadily thereafter. Aging-related loss of parenchymal elastic fibers causes gradual diminution of lung elastic recoil and peripheral airway size. After about 55 years of age, respiratory muscles weaken, and the chest wall becomes stiffer. The greater outward recoil of a stiffer thorax combined with the reduced inward lung recoil results in increased end-expiratory and residual lung volumes, while total lung capacity remains fairly constant.  $FEV_1$  declines about 1–2% per year

(Fig. 1).<sup>75</sup> The decline is accelerated by overt respiratory disease and by cumulative inflammation or injury from environmental irritants, toxins, and allergens. In addition, adiposity negatively impacts lung function in the elderly.<sup>77</sup> The rate of DL<sub>CO</sub> decline averages about 1.3% per year in normal men and women, but accelerates with age after 40 years; by 70 years of age the rate of decline is four times that before 40 years of age regardless of gender, smoking status, or initial FEV<sub>1</sub> level.<sup>76</sup> DL<sub>CO</sub> declines with age as a result of cumulative loss of gas exchange surface area because of alveolar septal thickening and inflammation. As expected, chronic obstructive lung disease and asbestos exposure accelerate the rate of DL<sub>CO</sub> decline (2.7% and 2.2% per year, respectively).<sup>78</sup>

Epidemiological data have shown a modest increase in the annual rates of decline in FEV<sub>1</sub>

and FVC in those who develop diabetes in some studies<sup>17</sup> but not in others.<sup>12,26</sup> Further longitudinal investigation is clearly needed to clarify the relationship of lung function to aging in diabetes and in glucose intolerance states as well as in conjunction with environmental exposure and lung disease. For example, the adverse effect of diabetes or hyperglycemia on lung function is more pronounced in smokers than nonsmokers,<sup>18</sup> and interactions between hyperglycemia and tobacco may accelerate with age. The prevalence of diabetes and glucose intolerance in cystic fibrosis (CF) has risen dramatically as survival in CF has improved. In CF patients diabetes is caused primarily by pancreatic damage, but glucose tolerance may also be influenced by recurrent respiratory infections. CF patients with diabetes not only develop micro- and macroangiopathy, but also experience accelerated pulmonary function de-



**FIG. 1.** Relationship of FEV<sub>1</sub> (A and B) (reprinted with permission from Hankinson et al.<sup>75</sup>) and DL<sub>CO</sub> (C) (data are mean  $\pm$  SEM after Viegi et al.<sup>76</sup>) with age in normal male and female nonsmokers.

cline and increased mortality.<sup>79</sup> The co-existence of diabetes reduces survival of female CF patients by 16 years<sup>80</sup>; those patients with the lowest insulin production experience the highest rates of pulmonary decline.<sup>81</sup> For unknown reasons this relationship between diabetes and pulmonary decline was not observed in male CF patients.

Use of inhaled human insulin does not alter lung function acutely but causes a small decrement in FEV<sub>1</sub> after 2 weeks of therapy compared to subcutaneous insulin and is associated with higher levels of circulating insulin antibodies.<sup>82</sup> In a meta-analysis of 16 open-label trials in adult patients with diabetes,<sup>83</sup> inhaled insulin was associated with a progressive reduction in FEV<sub>1</sub> over the first 6 months compared to oral hypoglycemic agents or subcutaneous insulin in type 2 diabetes, and with a small decline in DL<sub>CO</sub> from baseline compared to subcutaneous insulin in type 1 diabetes. The decline in DL<sub>CO</sub> was largely reversible following discontinuation of inhaled insulin at least in short-term trials. In a randomized 2-year trial of supplemental inhaled insulin in adult patients with type 1 diabetes,<sup>84</sup> the estimated annual rate of decline in FEV<sub>1</sub> was 50% higher compared to subcutaneous insulin; the bulk of decline developed during the first 3 months of treatment. Over the 2 years, average annual rate of decline in DL<sub>CO</sub> was not significantly different between inhaled and subcutaneous insulin. The rate of decline or reversibility of decline after longer use is not known.

Limited data suggest that lung dysfunction in diabetes is potentially reversible. Among non-smoking patients with longstanding (>20 years) type 1 diabetes without cardiopulmonary symptoms, those who achieved near-normoglycemia for 6 years with intensive insulin therapy exhibited normal spirometry, DL<sub>CO</sub>, DM<sub>CO</sub>, and V<sub>c</sub> at any given cardiac output, while those with poor glycemic control during the same period exhibited significant impairment in pulmonary function.<sup>14</sup> The data indirectly suggest that a relatively short period of normoglycemia may retard the progression of pulmonary impairment. In another study of uremic patients with type 1 diabetes in whom spirometry and DL<sub>CO</sub> improved after simultaneous pancreas-kidney transplant compared to before, only spirometry improved

after kidney transplant alone.<sup>85</sup> This study provides direct support for the reversibility of pulmonary dysfunction following re-establishment of normoglycemia.

### CLINICAL SIGNIFICANCE AND FUTURE DIRECTION

It is now generally accepted that the respiratory system, like any other organ, is a target of diabetic microangiopathy. The pathogenesis is related to both a glycemia-dependent and a glycemia-independent action of insulin. Respiratory defects may predate the onset of diabetes and may have a reversible component. Owing to the large size of alveolar microvascular bed the microangiopathic effects on gas exchange are largely subclinical. Nonetheless, even a modest ventilatory defect can be assessed quantitatively using noninvasive methods, potentially allowing long-term tracking of microangiopathic progression independent of secondary sequelae of end-organ destruction. Diabetic angiopathy erodes pulmonary vascular reserves, thereby increasing susceptibility to complications induced by other pathological processes and by aging. A major area of active investigation is the interactions among obesity, diabetes, and aging of the lung. The large number of prospective studies currently underway should allow direct comparison of rates of microangiopathic progression in the lung to that in other organs. In parenchymal lung diseases concurrent diabetes appears to accelerate pulmonary decline; the spectrum and extent of this association require further delineation. Gender differences in lung function of patients with diabetes with and without primary lung disease may signal genetic or hormonal influences that are poorly understood. In addition, lung function could document reversibility of microangiopathy following strict glycemic control or definitive therapeutic intervention such as pancreatic transplantation or gene therapy.

### ACKNOWLEDGMENTS

This research was supported by grant R01 DK063242 from the National Institute of Dia-

betes and Digestive and Kidney Diseases. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or of the National Institutes of Health.

## REFERENCES

- Rosenstock J, Friberg T, Raskin P: Effect of glycemic control on microvascular complications in patients with Type I diabetes mellitus. *Am J Med* 1986;81:1012-1017.
- Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U: Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med* 1991;230:101-108.
- Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D: Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA* 1989;261:1155-1160.
- Hansen LA, Prakash UBS, Colby TV: Pulmonary complications in diabetes mellitus. *Mayo Clin Proc* 1989;64:791-799.
- Williams JG, Morris AI, Hayter RC, Ogilvie CM: Respiratory responses of diabetics to hypoxia, hypercapnia and exercise. *Thorax* 1984;39:529-534.
- Brassard P, Ferland A, Bogaty P, Desmeules M, Jobin J, Poirier P: Influence of glycemic control on pulmonary function and heart rate in response to exercise in subjects with type 2 diabetes mellitus. *Metabolism* 2006;55:1532-1537.
- Weisbrod CJ, Eastwood PR, O'Driscoll G, Green DJ: Abnormal ventilatory responses to hypoxia in Type 2 diabetes. *Diabet Med* 2005;22:563-568.
- O'Donnell CR, Friedman LS, Russomanno JH, Rose RM: Diminished perception of inspiratory-resistive loads in insulin-dependent diabetics. *N Engl J Med* 1988;319:1369-1373.
- Antonelli Incalzi R, Fuso L, Pitocco D, Basso S, Trove A, Longobardi A, Calcagni ML, Giordano A, Ghirlanda G: Decline of neuroadrenergic bronchial innervation and respiratory function in type 1 diabetes mellitus: a longitudinal study. *Diabetes Metab Res Rev* 2006;23:311-316.
- Scano G, Filippelli M, Romagnoli I, Mancini M, Misuri G, Duranti R, Rosi E: Hypoxic and hypercapnic breathlessness in patients with type I diabetes mellitus. *Chest* 2000;117:960-967.
- Sandler M, Bunn AE, Stewart RI: Pulmonary function in young insulin-dependent diabetic subjects. *Chest* 1986;90:670-675.
- Lange P, Parner J, Schnohr P, Jensen G: Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *Eur Respir J* 2002;20:1406-1412.
- Ramirez LC, Dal Nogare A, Hsia CCW, Arauz C, Strowig S, Schnurrbreen L, Raskin P: Relationship between diabetes control and pulmonary function in insulin dependent diabetes mellitus. *Am J Med* 1991;91:371-376.
- Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CCW: Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. *Am J Med* 1997;103:504-513.
- Schuyler MR, Niewoehner DE, Inkley SR, Kohn R: Abnormal lung elasticity in juvenile diabetes mellitus. *Am Rev Respir Dis* 1976;113:37-41.
- Schnapf BN, Banks RA, Silverstein JH, Rosenbloom AL, Chesrown SE, Loughlin GM: Pulmonary function in insulin-dependent diabetes mellitus with limited joint mobility. *Am Rev Respir Dis*, 1984;130:930-932.
- Davis WA, Knuiman M, Kendall P, Grange V, Davis TM: Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004;27:752-757.
- Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ: Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med* 2003;167:911-916.
- Zanen P, Folgering H, Lammers JW: Flow-volumes indices as means to discriminate between intra- and extrapulmonary restrictive disease. *Respir Med* 2005;99:825-829.
- van Gent R, Brackel HJ, de Vroede M, van der Ent CK: Lung function abnormalities in children with type I diabetes. *Respir Med* 2002;96:976-978.
- Mancini M, Filippelli M, Seghieri G, Iandelli I, Innocenti F, Duranti R, Scano G: Respiratory muscle function and hypoxic ventilatory control in patients with type I diabetes. *Chest* 1999;115:1553-1562.
- Brownlee M, Vlassara H, Cerami A: Nonenzymatic glycosylation and the pathogenesis of diabetic complications. *Ann Intern Med* 1984;101:527-537.
- Hamlin CR, Kohn RR, Luschin JH: Apparent accelerated aging of human collagen in diabetes mellitus. *Diabetes* 1975;24:902-904.
- Ofulue AF, Thurlbeck WM: Experimental diabetes and the lung. II. In vivo connective tissue metabolism. *Am Rev Respir Dis* 1988;138:284-289.
- Hsia CC, Raskin P: The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. *Am J Med* 2005;118:205-211.
- Litonjua AA, Lazarus R, Sparrow D, Demolles D, Weiss ST: Lung function in type 2 diabetes: the Normative Aging Study. *Respir Med* 2005;99:1583-1590.
- Lawlor DA, Ebrahim S, Smith GD: Associations of measures of lung function with insulin resistance and Type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;47:195-203.
- Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Brancati FL: Vital capacity as a predictor of incident type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 2005;28:1472-1479.

29. Ford ES, Mannino DM: Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;27:2966–2970.
30. Klein BE, Moss SE, Klein R, Cruickshanks KJ: Peak expiratory flow rate: relationship to risk variables and mortality: the Wisconsin Epidemiologic Study of diabetic retinopathy. *Diabetes Care* 2001;24:1967–1971.
31. Vlahakis NE, Hubmayr RD: Response of alveolar cells to mechanical stress. *Curr Opin Crit Care* 2003;9:2–8.
32. O'Donnell CP, Tankersley CG, Polotsky VP, Schwartz AR, Smith PL: Leptin, obesity, and respiratory function. *Respir Physiol* 2000;119:163–170.
33. Sin DD, Man SF: Impaired lung function and serum leptin in men and women with normal body weight: a population based study. *Thorax* 2003;58:695–698.
34. Roughton FJW, Forster RE: Relative importance of diffusion and chemical reaction rates in determining the rate of exchange of gases in the human lung, with special reference to true diffusing capacity of the pulmonary membrane and volume of blood in lung capillaries. *J Appl Physiol* 1957;11:290–302.
35. Hsia CCW: Recruitment of lung diffusing capacity: update of concept and application. *Chest* 2002;122:1774–1783.
36. Sandler M, Bunn AE, Stewart RI: Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223–229.
37. Chance WW, Rhee C, Dane DM, Merrikh A, Phansalkar AR, Yilmaz C, Pruneda ML, Raskin P, Hsia CCW: Impaired pulmonary function in patients with type-2 diabetes mellitus [abstract]. *Proc Am Thorac Soc* 2006;3:A721.
38. Asanuma Y, Fujiya S, Ide H, Agishi Y: Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract* 1985;1:95–101.
39. Weir DC, Jennings PE, Hendy MS, Barnett AH, Burge PS: Transfer factor for carbon monoxide in patients with diabetes with and without microangiopathy. *Thorax* 1988;43:725–726.
40. Fuso L, Cotroneo P, Basso S, De Rosa M, Manto A, Ghirlanda G, Pistelli R: Postural variations of pulmonary diffusing capacity in insulin-dependent diabetes mellitus. *Chest* 1996;110:1009–1013.
41. Sexton WL, Poole DC, Mathieu-Costello O: Microcirculatory structure-function relationships in skeletal muscle of diabetic rats. *Am J Physiol* 1994;266:H1502–H1511.
42. Weibel ER: Morphometric and stereological methods in respiratory physiology, including fixation techniques. In: Otis AB, ed. *Techniques in the Life Sciences, Respiratory Physiology*. New York: Elsevier, 1984:1–35.
43. Takeda S, Hsia CCW, Wagner E, Ramanathan M, Estrera AS, Weibel ER: Compensatory alveolar growth normalizes gas exchange function in immature dogs after pneumonectomy. *J Appl Physiol* 1999;86:1301–1310.
44. Vracko R, Thorning D, and Huang TW: Basal lamina of alveolar epithelium and capillaries: quantitative changes with aging and in diabetes mellitus. *Am Rev Respir Dis* 1979;120:973–983.
45. Kodolova IM, Lysenko LV, Saltykov BB: [Changes in the lungs in diabetes mellitus]. *Arkh Patol* 1982;44:35–40.
46. Camerini-Davalos RA, Velasco C, Glasser M, Bloodworth JM Jr: Drug-induced reversal of early diabetic microangiopathy. *N Engl J Med* 1983;309:1551–1556.
47. Siperstein MD, Unger RH, Madison LL: Studies of muscle capillary basement membranes in normal subjects, diabetic and prediabetic patients. *J Clin Invest* 1968;47:1973–1999.
48. Raskin P, Marks JF, Burns H Jr, Plumer ME, Siperstein MD: Capillary basement membrane width in diabetic children. *Am J Med* 1975;58:365–372.
49. Raskin P, Pietri AO, Unger R, Shannon WA Jr: The effect of diabetic control on the width of skeletal muscle capillary basement membrane in patients with type I diabetes mellitus. *N Engl J Med* 1983;309:1546–1550.
50. Popov D, Hasu M, Costache G, Stern D, Simionescu M: Capillary and aortic endothelia interact in situ with nonenzymatically glycosylated albumin and develop specific alterations in early experimental diabetes. *Acta Diabetol* 1997;34:285–293.
51. Pascariu M, Bendayan M, Ghitescu L: Correlated endothelial caveolin overexpression and increased transcytosis in experimental diabetes. *J Histochem Cytochem* 2004;52:65–76.
52. Brownlee M: Advanced protein glycosylation in diabetes and aging. *Annu Rev Med* 1995;46:223–234.
53. Sugahara K, Ushijima K, Morioka T, Usuku G: Studies of the lung in diabetes mellitus. I. Ultrastructural studies of the lungs in alloxan-induced diabetic rats. *Virchows Arch A Pathol Anat Histol* 1981;390:313–324.
54. Sugahara K, Iyama K, Sano K, Morioka T: Differential expressions of surfactant protein SP-A, SP-B, and SP-C mRNAs in rats with streptozotocin-induced diabetes demonstrated by in situ hybridization. *Am J Respir Cell Mol Biol* 1994;11:397–404.
55. Lee YS: Electron microscopic studies on the alveolar-capillary barrier in the patients of chronic pulmonary edema. *Jpn Circ J* 1979;43:945–954.
56. Townsley MI, Fu Z, Mathieu-Costello O, West JB: Pulmonary microvascular permeability. Responses to high vascular pressure after induction of pacing-induced heart failure in dogs. *Circ Res* 1995;77:317–325.
57. Guazzi M, Brambilla R, Pontone G, Agostoni P, Guazzi MD: Effect of non-insulin-dependent diabetes mellitus on pulmonary function and exercise tolerance in chronic congestive heart failure. *Am J Cardiol* 2002;89:191–197.
58. Guazzi M, Brambilla R, De Vita S, Guazzi MD: Diabetes worsens pulmonary diffusion in heart failure, and insulin counteracts this effect. *Am J Respir Crit Care Med* 2002;166:978–982.
59. Guazzi M, Oreglia I, Guazzi MD: Insulin improves alveolar-capillary membrane gas conductance in type 2 diabetes. *Diabetes Care* 2002;25:1802–1806.

60. Das UN: Insulin: an endogenous cardioprotector. *Curr Opin Crit Care* 2003;9:375-383.
61. Aye M, Sheedy W, Harrison R, Thompson JS, Morice AH, Masson EA: Pulmonary vasodilation in the rat by insulin in vitro could indicate potential hazard for inhaled insulin. *Diabetologia* 2003;46:1199-1202.
62. Lim SC, Caballero AE, Smakowski P, LoGerfo FW, Horton ES, Veves A: Soluble intercellular adhesion molecule, vascular cell adhesion molecule, and impaired microvascular reactivity are early markers of vasculopathy in type 2 diabetic individuals without microalbuminuria. *Diabetes Care* 1999;22:1865-1870.
63. Caballero AE, Arora S, Saouaf R, Lim SC, Smakowski P, Park JY, King GL, LoGerfo FW, Horton ES, Veves A: Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. *Diabetes* 1999;48:1856-1862.
64. Papayianni M, Gourgoulis KI, Molyvdas PA: Insulin NO-dependent action on airways smooth muscles. *Nitric Oxide* 2001;5:72-76.
65. Ditzel J: Oxygen transport impairment in diabetes. *Diabetes* 1976;25:832-838.
66. MacDonald MJ, Bleichman M, Bunn HF: Functional properties of the glycosylated minor components of human adult hemoglobin. *J Biol Chem* 1979;254:702-707.
67. Babalola RO, Ajayi AA: A cross-sectional study of echocardiographic indices, treadmill exercise capacity and microvascular complications in Nigerian patients with hypertension associated with diabetes mellitus. *Diabet Med* 1992;9:899-903.
68. Baraldi E, Monciotti C, Filippone M, Santuz P, Magagnin G, Zanconato S, Zacchello F: Gas exchange during exercise in diabetic children. *Pediatr Pulmonol* 1992;13:155-160.
69. Mandroukas K, Krotkiewski M, Holm G, Stromblad G, Grimby G, Lithell H, Wroblewski Z, Bjorntrop P: Muscle adaptations and glucose control after physical training in insulin-dependent diabetes mellitus. *Clin Physiol* 1986;6:39-52.
70. Huttunen NP, Lankela SL, Knip M, Lautala P, Kaar ML, Laasonen K, Puukka R: Effect of once-a-week training program on physical fitness and metabolic control in children with IDDM. *Diabetes Care* 1989;12:737-740.
71. Bernbaum M, Albert SG, Cohen JD, Drimmer A: Cardiovascular conditioning in individuals with diabetic retinopathy. *Diabetes Care* 1989;12:740-742.
72. Selam JL, Casassus P, Bruzzo F, Leroy C, Slama G: Exercise is not associated with better diabetes control in type 1 and type 2 diabetic subjects. *Acta Diabetol* 1992;29:11-13.
73. Cruickshanks KJ, Moss SE, Klein R, Klein BE: Physical activity and proliferative retinopathy in people diagnosed with diabetes before age 30 yr. *Diabetes Care* 1992;15:1267-1272.
74. Saltin B, Blomqvist G, Mitchell JH, Johnson RL Jr, Wildenthal K, Chapman CB: Response to exercise after bed rest and after training. *Circulation* 1968;37:38:1-78.
75. Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-187.
76. Viegi G, Sherrill DL, Carrozzi L, Di Pede F, Baldacci S, Pistelli F, Enright P: An 8-year follow-up of carbon monoxide diffusing capacity in a general population sample of northern Italy. *Chest* 2001;120:74-80.
77. Wannamethee SG, Shaper AG, Whincup PH: Body fat distribution, body composition, and respiratory function in elderly men. *Am J Clin Nutr* 2005;82:996-1003.
78. Alfonso HS, Fritsch L, de Klerk NH, Olsen N, Sleith J, Musk AB: Effects of asbestos and smoking on gas diffusion in people exposed to crocidolite. *Med J Aust* 2005;183:184-187.
79. Brennan AL, Geddes DM, Gyi KM, Baker EH: Clinical importance of cystic fibrosis-related diabetes. *J Cyst Fibros* 2004;3:209-222.
80. Milla CE, Billings J, Moran A: Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 2005;28:2141-2144.
81. Milla CE, Warwick WJ, Moran A: Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *Am J Respir Crit Care Med* 2000;162:891-895.
82. Teeter JG, Riese RJ: Dissociation of lung function changes with humoral immunity during inhaled human insulin therapy. *Am J Respir Crit Care Med* 2006;173:1194-1200.
83. Ceglia L, Lau J, Pittas AG: Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann Intern Med* 2006;145:665-675.
84. Skyler JS, Jovanovic L, Kliozie S, Reis J, Duggan W: Two-year safety and efficacy of inhaled human insulin (Exubera) in adult patients with type 1 diabetes. *Diabetes Care* 2007;30:579-585.
85. Dieterle CD, Schmauss S, Arbogast H, Domsch C, Huber RM, Landgraf R: Pulmonary function in patients with type 1 diabetes before and after simultaneous pancreas and kidney transplantation. *Transplantation* 2007;83:566-569.

Address reprint requests to:

*Connie C.W. Hsia, M.D.*

*Department of Internal Medicine*

*University of Texas Southwestern Medical Center*

*5323 Harry Hines Boulevard*

*Dallas, TX 75390-9034*

*E-mail: Connie.Hsia@utsouthwestern.edu*