Diminished Alveolar Microvascular Reserves in Type 2 Diabetes Reflect Systemic Microangiopathy

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OBJECTIVE — Alveolar microvascular function is moderately impaired in type 1 diabetes, as manifested by restriction of lung volume and diffusing capacity (DLCO). We examined whether similar impairment develops in type 2 diabetes and defined the physiologic sources of impairment as well as the relationships to glycemia and systemic microangiopathy.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted at a university-affiliated diabetes treatment center and outpatient diabetes clinic, involving 69 non-smoking type 2 diabetic patients without overt cardiopulmonary disease. Lung volume, pulmonary blood flow (Q), DLCO, membrane diffusing capacity (measured from nitric oxide uptake [DLNO]), and pulmonary capillary blood volume (VC) were determined at rest and exercise for comparison with those in 45 healthy nonsmokers as well as with normal reference values.

RESULTS — In type 2 diabetic patients, peak levels of oxygen uptake, Q and DLCO, DLNO, and VC at exercise were 10–25% lower compared with those in control subjects. In nonobese patients (BMI <30 kg/m²), reductions in DLCO, DLNO, and VC were fully explained by the lower lung volume and peak Q, but these factors did not fully explain the impairment in obese patients (BMI >30 kg/m²). The slope of the increase in VC with respect to Q was reduced ~20% in patients regardless of BMI, consistent with impaired alveolar-capillary recruitment. Functional impairment was directly related to AIC level, retinopathy, neuropathy, and microalbuminuria in a sex-specific manner.

CONCLUSIONS — Alveolar microvascular reserves are reduced in type 2 diabetes, reflecting restriction of lung volume, alveolar perfusion, and capillary recruitment. This reduction correlates with glycemic control and extrapulmonary microangiopathy and is aggravated by obesity.

Diabetes Care 31:1596–1601, 2008

Diabetic microangiopathy can involve alveolar tissue and capillaries, the largest microvascular bed in the body, leading to restriction of lung volume and alveolar gas transport, as manifested by reduced diffusing capacity of the lung for carbon monoxide (DLCO), as well as its components: membrane diffusing capacity and pulmonary capillary blood volume (VC). Lung diffusing capacity is the gas conductance across the lung, modeled as diffusion across alveolar-capillary membrane barrier followed by chemical binding to capillary hemoglobin. In young nonsmokers with poorly controlled type 1 diabetes, DLCO and its components were reduced 15–30% at rest and exercise compared with age-matched nondiabetic subjects (1,2). In type 1 diabetic patients who maintained near-normoglycemia, these parameters are near normal, suggesting a relationship between alveolar function and systemic microangiopathy. Impaired alveolar gas transfer in type 1 diabetes signals erosion of microvascular reserves that could accelerate clinical decline in conjunction with primary lung disease, aging, or cardiorespiratory complications and affect long-term tolerance to the use of inhaled insulin.

Type 2 diabetes has also been linked to lower spirometric indexes (3,4) and resting DLCO (3,6). However, previous studies had not taken into account the dependence of DLCO on pulmonary blood flow (Q). Normally, DLCO and its components increase 40–60% in a linear relationship as Q increases up to peak exercise. The ability to augment DLCO and its indexes the recruitment of alveolar microvascular reserves via enlarged membrane surfaces, as well as increased mass and improved distribution of alveolar-capillary erythrocytes. Recruitment is essential for maintaining a normal diffusion-to-perfusion (D/Q) ratio and achieving adequate oxygenation of end-capillary blood leaving the lung (7). Conventional interpretation of DLCO implicitly assumes an unchanged Q; this assumption is unwarranted and can be misleading. For example, lower cardiac output associated with diabetic heart disease decreases apparent DLCO even when alveolar diffusion is normal. Conversely, elevated cardiac output associated with obesity increases apparent DLCO and could mask the impairment of alveolar diffusion. Thus, the adequacy of alveolar-capillary recruitment and gas transfer cannot be optimally assessed without knowledge of both DLCO and Q. We hypothesized that restriction of lung volume, DLCO, and microvascular recruitment develops in type 2 diabetes independent of Q and that abnormalities correlate with disease duration, glycemic control, and extrapulmonary microangiopathy and are compounded by obesity. We simultaneously measured lung volume, Q, DLCO, membrane diffusing capacity, and VC using a noninvasive rebreathing technique in type 2 diabetic
patients from rest to heavy exercise. Measurements were compared with reference values obtained in nondiabetic control subjects and adjusted for $Q$. Alveolar-capillary recruitment was assessed from the slopes of the increase in $DLCO$, diffusion capacity of the lung for nitric oxide ($DLNO$) and $V_c$ with respect to $Q$.

**RESEARCH DESIGN AND METHODS** — The institutional review board approved all protocols; written informed consent was obtained from all subjects. Nonsmoking type 2 diabetic patients ($n = 69$) without overt cardiopulmonary disease were recruited from the University of Texas Southwestern Diabetes Treatment Center. Thirty-seven patients were treated with insulin; $25$ were also taking an oral hypoglycemic agent. Thirty-one patients were taking oral agents only. Thirty subjects were taking antihypertensive medication, and $32$ were taking antihyperlipidemia medication. Five subjects were remote smokers ($\sim 10$ pack-years); the average time since smoking cessation was $14$ years. Forty-five healthy nondiabetic nonsmokers served as simultaneous control subjects. Adjusted reference values were derived from $75$ cumulative nonobese (BMI < $30$ kg/m$^2$) control subjects.

**Apparatus**

Standard spirometry was performed (Vmax229; Sensormedics, Yorba Linda, CA). Subjects exercised on a bicycle ergometer (Ergometrics-800; Sensormedics) while breathing through a respiratory valve (8500; Hans Rudolph, Kansas City, MO) and solenoid-controlled switching assembly (GH3315; Precision Dynamics, Aliso Viejo, CA). Oxygen and CO$_2$ concentrations were measured by mass spectrometry (MGA-1100; PerkinElmer). Electrocardiogram and transcutaneous oxygen saturation (N-180; Nelon, Carlsbad, CA) were monitored continuously.

**Rebreathing technique**

The technique is well established (8,9). The bag-in-a-box reservoir contained a mixture of $0.3\%$ methane, $0.3\%$ carbon monoxide (CO), $0.8\%$ acetylene, and either $30$ or $90\%$ oxygen in a balance of nitrogen. When needed, nitric oxide (NO) ($\sim 40$ ppm) was added immediately before testing. At a selected end-expiration the valves switched electronically, allowing the subject to inspire one bolus of test gas to total lung capacity and then rebreathe this bolus in and out of an anesthetic bag for $12–16$ s while gas concentrations at the mouth were monitored. Methane, acetylene, and CO concentrations were measured by an infrared analyzer (Sensors, Saline, MI); the NO concentration was measured by chemiluminescence (NOA280; Sievers Instruments, Boulder, CO).

**Systemic microangiopathy**

Retinopathy was assessed by funduscopic examination. The presence of microaneurysm, hemorrhage, exudate, or neovascularization or previous laser treatment was considered positive. Microalbuminuria was assessed from a nonfasting urine sample: $\geq 30$ $\mu$g/mg creatinine was considered abnormal. Nerve conduction was studied in the Electrodiagnostics Laboratory of University Diabetes Treatment Center. The ulnar sensory and peroneal motor nerves were stimulated, and the compound nerve or muscle action potential was recorded to assess conduction velocity, latency, and amplitude in comparison with established reference values (10). Individual nerves were abnormal if at least one of these parameters was outside the normal threshold. Neuropathy was conservatively defined as abnormalities in both motor and sensory nerves.

**Protocol**

On the first visit, medical history was reviewed and physical examination was performed. A venous blood sample was drawn to measure hematocrit, Hb, and A1C concentrations. A urine sample was collected, and nerve conduction was measured. Spirometry, maximal voluntary ventilation, and $DLCO$ at rest were measured. Maximal oxygen uptake was determined by an incremental protocol ($20–30$ W every $3$ min) until volitional termination.

On a second visit, studies were performed at rest and at $30$, $60$, and $90\%$ of the predetermined maximal workload, with each sustained for $3$ min followed by the rebreathing maneuver. Duplicate measurements were performed with the test gas containing $30$ or $90\%$ oxygen in balanced order. Before rebreathing the test gas containing $90\%$ oxygen, subjects prebreathed $100\%$ oxygen for $\sim 30$ s until alveolar oxygen tension ($P_{O_2}$) reached $\sim 600$ mmHg. Subjects rested between workloads until heart rate and ventilation returned to baseline. On a third visit, the exercise protocol was repeated but without NO in the test gas. The presence of NO in the test gas mixture does not alter the measurements during the brief ($12–16$ s) rebreathing period (11).

**Data analysis**

The analysis was established previously (8,9). Lung volume (body temperature and pressure saturated, in liters) was estimated by methane dilution. $Q$, $DLNO$, and $DLCO$ were determined from end-tidal disappearance of acetylene, NO, and CO, respectively. Conductance of membrane and hemoglobin binding contribute about equally to $DLCO$. $DLNO$ was used as a direct index of membrane diffusing capacity. Because NO is rapidly scavenged by hemoglobin, resistance to alveolar NO uptake resides mainly within the tissue/erythrocyte membrane, and $DLNO$ is directly related to diffusing capacity of alveolar membrane for carbon monoxide ($DMCO$) ($DLNO = 2.42$ $DMCO$) (9). From $DLCO$ and the $DMCO$ derived from $DLNO$, $V_c$ was calculated by the standard equation:

$$\frac{1}{DLCO} = \frac{1}{DMCO} + \frac{1}{\Theta_{CO} \cdot V_c}$$

where CO uptake by 1 ml of whole blood ($\Theta_{CO}$) is dependent on mean $P_{A\ O_2}$ and the Hb concentration:

$$\frac{1}{\Theta_{CO}} = (0.73 + 0.0058 \times P_{A\ O_2}) \times \frac{14.6}{[Hb]}$$

$DMCO$ and $V_c$ were used to express $DLCO$ at a constant Hb concentration (14.6 g/dl) and $P_{A\ O_2}$ (120 mmHg).

Duplicate measurements were averaged and expressed as absolute values and as percentages of reference values from nondiabetic control subjects. End-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV) were adjusted for sex, age, and height (men: EELV = $5.72 \times$ height + $0.02 \times$ age – $7.24$, EILV = $11.32 \times$ height – $13.23$; women: EELV = $3.45 \times$ height + $0.02 \times$ age – $3.84$, EILV = $4.89 \times$ height + $0.02 \times$ age – $3.79$). $DLCO$, $DLNO$, and $V_c$ were adjusted for sex, age, body surface area, and $Q$ using multivariate regression analysis (8,11). Individual $DLCO$, $DLNO$, and $V_c$ measurements were analyzed with
Alveolar function in type 2 diabetes

Table 1—Baseline and peak exercise data

|                         | Control subjects | Type 2 diabetic patients | Type 2 diabetic patients |
|------------------------|-----------------|--------------------------|--------------------------|
|                         | BMI <30 kg/m²    | BMI >30 kg/m²             |                          |
| n (% female)           | 45 (47)         | 32 (41)                  | 37 (49)                  |
| Age (years)            | 45 ± 13         | 49 ± 10                  | 45 ± 11                  |
| Height (cm)            | 171 ± 9         | 169 ± 14                 | 169 ± 10                 |
| BMI (kg/m²)            | 28.8 ± 5.1      | 27.4 ± 1.6               | 34.4 ± 3.8**             |
| Hemoglobin (g/dl)      | 13.7 ± 1.4      | 14.0 ± 1.6               | 13.4 ± 1.7               |
| Hematocrit (%)         | 42 ± 4          | 43.5 ± 5                 | 41 ± 4                   |
| A1C (%)                | 8.7 ± 1.9       | 8.0 ± 1.6                |                          |
| Time from diagnosis (years) | 8.5 ± 5.4     | 7.3 ± 6.3                |                          |
| Spirometry             |                 |                         |                          |
| FVC (liters)           | 4.2 ± 0.9       | 3.7 ± 1.2                | 3.6 ± 1.0*               |
| % predicted            | 101 ± 15        | 92 ± 14*                 | 89 ± 14*                 |
| FEV₁ (liters)          | 3.2 ± 0.6       | 3.1 ± 0.9                | 3.0 ± 0.8                |
| % predicted            | 98 ± 13         | 97 ± 16                  | 93 ± 13                  |
| FEV₁/FVC (%)           | 77 ± 7          | 82 ± 5*                  | 83 ± 5*                  |
| Maximum voluntary ventilation (liters/min) | 134 ± 29 | 134 ± 42                | 131 ± 34                |
| % predicted            | 98 ± 14         | 100 ± 18                 | 99 ± 19                  |
| Peak exercise          |                 |                         |                          |
| Workload (W)           | 155 ± 53        | 122 ± 51*                | 116 ± 30*                |
| Heart rate (beats/min) | 167 ± 19        | 152 ± 20*                | 150 ± 18*                |
| % predicted maximum    | 93 ± 9          | 86 ± 10*                 | 83 ± 9*                  |
| O₂ uptake (liters • min⁻¹) | 2.0 ± 0.6     | 1.5 ± 0.6*               | 1.6 ± 0.5*               |
| % predicted maximum    | 93 ± 19         | 74 ± 18*                 | 77 ± 13*                 |
| Respiratory exchange ratio | 1.3 ± 0.1    | 1.2 ± 0.2                | 1.3 ± 0.2                |
| Ventilation (liters • min⁻¹) | 85 ± 21       | 68 ± 27*                 | 71 ± 22*                 |
| Tidal volume (liters)  | 2.4 ± 0.6       | 1.9 ± 0.8*               | 1.9 ± 0.7*               |

Data are means ± SD. *P ≤ 0.05 vs. control by ANOVA. †P ≤ 0.05 vs. type 2 diabetes BMI <30 by ANOVA.

respect to Q̇; slope of the linear regression provides an index of alveolar-capillary recruitment (7). Data were compared by ANOVA with a post hoc test by Fisher’s protected least significant difference. Differences were significant at P ≤ 0.05.

RESULTS — In type 2 diabetic patients, the prevalence of retinopathy was 32%, the prevalence of microalbuminuria was 38%, and the prevalence of nerve conduction defects was 28%. A1C exceeded 8.0% in 54% of patients; average A1C was slightly lower in obese (BMI >30 kg/m²) than in nonobese patients (Table 1). Hematological indexes were normal. Forced vital capacity (FVC) was significantly (8–11%) lower regardless of BMI. Forced expiratory volume in 1 s (FEV₁), and maximal voluntary ventilation were normal. Peak heart rate exceeded 80% of the predicted maximum; peak workload and peak oxygen uptake were ~25% below the predicted maximum. Ventilation and tidal volume at peak exercise were ~20% lower in patients compared with control subjects.

Mixing efficiency during rebreathing and transcutaneous oxygen saturation was normal in all subjects. Mean alveolar NO concentration (5–7 ppb) was similar among groups. In patients, EELV and EILV were ~15% below normal regardless of BMI (Fig. 1A). At the highest sustained workload, Q̇ in patients was below normal (Table 2). Unadjusted DLCO, DLNO, and VC measured upon exercise were modestly lower in patients compared with control subjects (Table 2). When expressed as a percentage of reference values adjusted for Q̇, DLCO, DLNO, and VC were within the normal range in nonobese patients but remained significantly reduced (16–18%) in obese patients (Fig. 1B). The relationship between DLNO and DMCO was normal (not shown). The slopes of the linear increase in DLCO and DLNO with respect to Q̇ were similar among groups. The slope of the linear increase in VC with respect to Q̇ was 20–25% below normal in patients regardless of BMI (Table 2).

In male and female patients, A1C >8.0% correlated with significantly lower DLCO, DLNO, VC, and EILV (Fig. 2A), and microalbuminuria correlated with lower DLCO, DLNO, and EILV (Fig. 2B) compared with patients without these complications. In male but not female patients, the presence of neuropathy was associated with significantly lower DLCO, DLNO, VC, and EILV (Fig. 2C), whereas retinopathy correlated with a significantly lower DLNO (Fig. 2B). There was no significant correlation of lung function to age or to disease duration in either sex.

CONCLUSIONS — This is the first study to quantify pulmonary microvascular reserves in type 2 diabetes. The main findings were as follows. 1) Lung volume was moderately reduced regardless of sex or obesity. 2) Peak Q̇, DLCO, DLNO, and VC were reduced upon exercise. 3) Adjustment for sex, age, and Q̇ normalized DLCO, DLNO, and VC in nonobese type 2 diabetic patients, but the adjusted parameters remained reduced in obese patients. 4) The slope of the increase in VC with respect to Q̇ was reduced regardless of obesity, consistent with diminished recruitment of alveolar capillaries. These results highlight the need to consider Q̇ when interpreting DLCO, and its components. 5) Alveolar microvascular indexes were significantly related to glycemic control and extrapulmonary microangiopathy in a sex-specific manner.

Lung volume

Hyperglycemia and insulin resistance are associated with lower FVC and FEV₁ (4,12). A restrictive pattern in middle-aged nondiabetic adults is predictive of subsequent type 2 diabetes (13). Some studies do not show differences in adjusted rates of longitudinal change in spirometry between diabetic and nondiabetic subjects (4), whereas others found that declining FEV₁ and lung volume are directly related to glycemic control and mortality (3). In type 1 diabetes, a lower lung volume is associated with abnormal elastic recoil (14) and elevated work of breathing at exercise (2). A stiff chest wall with limited joint mobility (15) may be caused by abnormal connective tissue metabolism as well as collagen cross-linking in thoracic and lung tissue. Autonomic neuropathy involving respiratory muscles may impair thoracic mobility. A similar pathogenesis may cause volume restriction in type 2 diabetes. In elderly men, adiposity and metabolic syndrome are associated with a restrictive spirometric pattern (16). Mechanical loading of the thorax due to adiposity could exacerbate lung volume restriction. Abnormal fat in-
obesity-associated increase in cardiac output (18). These results highlight the need to consider perfusion when interpreting lung diffusion. The magnitude of diffusion impairment in type 2 diabetes is milder than that observed in type 1 diabetes (1,2); differences could relate to longer disease duration in our earlier type 1 diabetes study (>15 years) compared with that for type 2 diabetes (~8 years) in this study. **True disease duration is often uncertain in type 2 diabetes, and we did not observe a significant relationship between type 2 diabetes duration and lung function. Also, type 1 diabetes is uniformly severe, whereas the severity of type 2 diabetes is heterogeneous. Nonetheless, a consistent inverse relationship between lung function and glycemia emerged in type 2 diabetes as in type 1 diabetes (2).**

In moderate/localized lung disease, DL\textsubscript{CO}, DL\textsubscript{NO}, and VC are reduced at a given Q, but the ability to recruit the remaining alveolar microvasculature is preserved; recruitment mitigates the reduction in DL\textsubscript{CO} to maintain arterial oxygen saturation (9,19). In contrast, few lung units are recruitable in diffuse pulmonary fibrosis: DL\textsubscript{CO} and its components are not only reduced at rest but fail to rise as Q increases (19); inadequate recruitment causes the diffusion-to-perfusion (D/Q) ratio to fall with exercise.

**Figure 1**—A: EELV and EILV expressed as percentages of the reference values adjusted for sex, age (years), and height (meters) were significantly lower in type 2 diabetic patients regardless of obesity (BMI >30 kg/m\textsuperscript{2}). Data are means ± SD. *P ≤ 0.05 versus nondiabetic control subjects. B: After adjustment for sex, age, body surface area, and pulmonary blood flow, DL\textsubscript{CO}, DL\textsubscript{NO}, and VC expressed as percentages of the reference values were not significantly different from normal in nonobese type 2 diabetic patients (BMI <30 kg/m\textsuperscript{2}) but remained significantly reduced in obese patients (BMI >30). Data are means ± SD. *P ≤ 0.05 versus normal subjects; †P ≤ 0.05 versus type 2 diabetic patients with BMI <30 kg/m\textsuperscript{2}.

**Diffusion and alveolar-capillary recruitment**

Normally, lung volume and Q are the major determinants of DL\textsubscript{CO}, DL\textsubscript{NO}, and VC (8,11). Upon exercise, DL\textsubscript{CO}, DL\textsubscript{NO}, and VC increase 40–60% in a linear relationship with respect to perfusion (7). In nonobese patients, the lower lung volume and lower Q at exercise fully explain the 10–25% reduction in measured DL\textsubscript{CO}, DL\textsubscript{NO}, and VC in obese patients after adjustment for Q (18). These results highlight the need to consider perfusion when interpreting lung diffusion. The magnitude of diffusion impairment in type 2 diabetes is milder than that observed in type 1 diabetes (1,2); differences could relate to longer disease duration in our earlier type 1 diabetes study (>15 years) compared with that for type 2 diabetes (~8 years) in this study. True disease duration is often uncertain in type 2 diabetes, and we did not observe a significant relationship between type 2 diabetes duration and lung function. Also, type 1 diabetes is uniformly severe, whereas the severity of type 2 diabetes is heterogeneous. Nonetheless, a consistent inverse relationship between lung function and glycemia emerged in type 2 diabetes as in type 1 diabetes (2).

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**Table 2—Unadjusted rebreathing data**

|                     | Type 2 diabetes                  |
|---------------------|----------------------------------|
|                     | Control subjects | BMI <30 kg/m\textsuperscript{2} | BMI >30 kg/m\textsuperscript{2} |
| EELV (liters)       |                    |                                  |
| Rest                | 3.5 ± 1.0          | 2.9 ± 1.0*                     | 2.9 ± 0.9*                    |
| Exercise            | 3.3 ± 1.0          | 2.9 ± 1.0                      | 2.9 ± 0.9                     |
| EILV (liters)       |                    |                                  |
| Rest                | 6.0 ± 1.4          | 5.6 ± 1.6                      | 5.4 ± 1.3                     |
| Exercise            | 6.0 ± 1.3          | 5.5 ± 1.5                      | 5.4 ± 1.2*                    |
| Q (liters · min\textsuperscript{-1}) |                |                                  |
| Rest                | 6.0 ± 1.4          | 5.5 ± 1.1                      | 6.1 ± 1.4                     |
| Exercise            | 14.5 ± 1.4         | 11.8 ± 3.4*                    | 12.8 ± 3.3*                   |
| DL\textsubscript{CO} (mL · [min · mmHg]\textsuperscript{-1}) | |                                  |
| Rest                | 25.9 ± 6.5         | 23.1 ± 6.2                     | 24.1 ± 5.7                    |
| Exercise            | 35.3 ± 9.2         | 30.6 ± 8.6*                    | 31.5 ± 7.2*                   |
| DL\textsubscript{NO} (mL · [min · mmHg]\textsuperscript{-1}) | |                                  |
| Rest                | 120 ± 33           | 99 ± 34*                       | 105 ± 32                      |
| Exercise            | 141 ± 43           | 114 ± 38*                      | 120 ± 35*                     |
| VC (ml)             |                    |                                  |
| Rest                | 78 ± 22            | 69 ± 23                        | 71 ± 21                       |
| Exercise            | 127 ± 45           | 98 ± 34*                       | 100 ± 30*                     |

Slope of relationship with respect to pulmonary blood flow (liters/min)

|                     | Type 2 diabetes                  |
|---------------------|----------------------------------|
|                     | Control subjects | BMI <30 kg/m\textsuperscript{2} | BMI >30 kg/m\textsuperscript{2} |
| DL\textsubscript{CO} |                    |                                  |
| Rest                | 1.5 ± 0.4          | 1.4 ± 0.3                       | 1.3 ± 0.2†                    |
| Exercise            | 2.8 ± 1.7          | 2.4 ± 1.5                       | 2.3 ± 1.3                     |
| DL\textsubscript{NO} |                    |                                  |
| Rest                | 6.4 ± 3.3          | 4.7 ± 1.7*                      | 4.4 ± 1.9*                    |

Data are means ± SD. Exercise data were obtained at 90% peak workload. *P ≤ 0.05 vs. control by ANOVA. †P ≤ 0.05 vs. type 2 diabetes BMI <30 by ANOVA.
leading to severe arterial hypoxemia (7). Thus, multivariate analysis of lung diffusion should include simultaneously measured Q as a dynamic determinant. Impairment of alveolar-capillary recruitment in type 2 diabetes regardless of obesity suggests parenchymal changes that impede opening or distention of alveolar capillaries, possibly caused by connective tissue deposition within alveolar walls that has been observed in experimental diabetes (17); obesity may exaggerate these changes.

Relation to systemic microangiopathy
Lung function in type 2 diabetes is worse in a sex-specific manner in the presence of extrapulmonary end-organ complications, suggesting that nonenzymatic protein glycation, which predicts long-term progression of retinopathy and nephropathy, also predisposes to lung restriction. Sex-specific susceptibility to diabetes complications is well known. For example, diabetic foot lesion has a poorer prognosis in men than in women (20). The DNA polymorphism that promotes angiotensinogen gene expression increases the risk of nephropathy in diabetic men but not women (21). The risk of cardiovascular disease is higher in diabetic women than in men (22). Diabetes-related oxidative stress and reduction in antioxidant activity is greater in women than in men (23). Lifestyle, genetics, sex hormones, vascular endothelial function, advanced glycation end products, and intrinsic sex differences in lung structure may influence sex susceptibility to complications.

Clinical implications
Unlike the smaller microvasculature in the retina, heart, or peripheral nervous system, alveolar microvasculature is extensive. The oxygen transport capacity of the lung is twice that of the cardiovascular system or skeletal muscle. In chronic lung disease, lung volume and DLCO could decline ~50% without an individual incurring dyspnea at rest. Because of the large physiological reserves and because peak cardiac output is concurrently reduced, diabetic pulmonary dysfunction remains “subclinical.” Nonetheless, a modest loss of alveolar-capillary reserves can be quantified by noninvasive methods independent of physical fitness and correlates with glycemia as well as systemic microangiopathy. It remains to be determined whether alveolar microvascular indexes track longitudinal microangiopathy in a “clean” organ that is not ravaged by diabetes or its treatment. Loss of alveolar reserves could exaggerate aging-related functional decline (5) and predispose to overt sequelae in conjunction with renal and heart failure or primary lung disease. For example, diabetes significantly increases mortality in women with cystic fibrosis (24). Residence at high altitude where alveolar hypoxia imposes the primary limitation to oxygen transport is associated with higher

Figure 2—Relations of lung function to glycemia and microangiopathy. A: In male and female patients, A1C >8.0% was associated with lower EILV (liters), DLCO and DLNO (both milliliters per minute per millimeter of mercury), and VC (milliliters) measured at 90% peak exercise. Data are means ± SEM. B: In male and female patients, an elevated urinary microalbumin level (micrograms per milligram of creatinine) was associated with lower DLCO, DLNO, and EILV at 90% peak exercise. C: In male patients, the presence of neuropathy was associated with lower EILV, DLCO, DLNO, and VC at 90% peak exercise. D: In male patients, the presence of retinopathy was associated with a lower DLNO at 90% peak exercise. Data are means ± SEM. *P ≤ 0.05 versus nondiabetic control subjects; †P ≤ 0.05 versus patients with A1C <8.0% or patients without complications. T2DM, type 2 diabetes.
prevalence of diabetic end-organ complications (25). These issues regarding physiological reserves are also important for the chronic use of inhaled insulin, which causes an early reduction in lung function (26). Finally, these data suggest that weight loss in obese type 2 diabetic patients could improve alveolar microvascular function.

Acknowledgment — This study is supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant R01 DK063242. We also acknowledge support of the General Clinical Research Center, M01 RR00633. We thank the staff of the University Diabetes Treatment Center for patient liaison and Brenda Brightman for performing nerve conduction studies.

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