Insulin Improves Alveolar-Capillary Membrane Gas Conductance in Type 2 Diabetes

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OBJECTIVE — In type 1 diabetes, lung diffusing capacity for carbon monoxide (DL_{CO}) may be impaired, and insulin has been shown to be beneficial in cases in which near-normal metabolic control is achieved. An influence of insulin, per se, on the alveolar-capillary membrane conductance is unexplored. We aimed at testing this possibility.

RESEARCH DESIGN AND METHODS — We studied 19 life-long nonsmoking, asymptomatic patients with type 2 diabetes and normal cardiac function, whose GHb averaged 6.2 ± 0.3% with diet and hypoglycemic drugs. DL_{CO} and its subcomponents (alveolar capillary membrane conductance [D_M] and pulmonary capillary blood volume available for gas exchange [Vc]), vital capacity (VC), forced expiratory volume 1 s (FEV_1), cardiac output (CO), ejection fraction (EF), pulmonary wedge pressure (WPP), and pulmonary arteriolar resistance (PAR) were determined before and within 60 min after infusion of 50 ml saline + 10 IU of regular insulin or after saline alone on 2 consecutive days (random block design). Glycemia was kept at baseline levels during experiments by dextrose infusion.

RESULTS — Percent of normal predicted DL_{CO} averaged 84.2 ± 7.9% and in 14 patients was <100%. Insulin infusion, not saline alone, improved ($P < 0.01$) DL_{CO} (12%) and D_M (14%) and raised DL_{CO} to 98% of the normal predicted value. There were no variations in VC, FEV_1, CO, EF, WPP, or PAR, suggesting that the influences of the hormone on gas transfer were not mediated by changes in spirometry, volumes, and hemodynamics of the lung.

CONCLUSIONS — Several cases of type 2 diabetes present with increased impedance to gas transfer across the alveolar-capillary membrane, and hypoglycemic drugs do not prevent this inconvenience. Insulin, independently of the metabolic effects, acutely improves gas exchange, possibly through a facilitation of the alveolar-capillary interface conductance.

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A defective pulmonary function in asymptomatic diabetic patients is more prevalent than generally recognized, involving ~60% of adult cases (1–3). A reduced alveolar-capillary membrane lung diffusing capacity for carbon monoxide (DL_{CO}) has been described in type 1 diabetes (2–7). Patients with this type of diabetes, whose GHb was chronically maintained at levels near normal with intensive therapy by insulin pump, consistently showed normal or less impairment in DL_{CO} than patients treated with conventional therapy who sustained chronically elevated GHb (5,6). The conclusion was that in type 1 diabetes, chronic maintenance of near-normoglycemia is associated with improved lung diffusing capacity. However, it is unclear whether the degree of glycemic control is the only factor involved in the amelioration of gas transfer or whether insulin, per se, facilitates the conductance of the alveolar-capillary membrane in diabetes. Patients with type 2 diabetes with near-normal glycemic control by oral antidiabetic treatment were investigated. In these patients, DL_{CO} was measured before and after acute insulin infusion, and glycemia was maintained at the baseline level during the experiment. A study such as this can also provide information on frequency and extent of pulmonary gas transfer impairment in type 2 diabetes (8) and elucidate whether hypoglycemic drugs can prevent deterioration of the alveolar capillary membrane function in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population. A total of 19 hospital-admitted patients (Institute of Cardiology, University of Milan) with type 2 diabetes were investigated. They had mild untreated primary hypertension (6 cases) or atypical chest pain (13 cases) with normal coronary angiography. Among these patients there was no history of heart or lung diseases—physical examination, chest X-ray, electrocardiogram, and echocardiogram were normal. Only patients who were life-long nonsmokers were enrolled. Their carboxyhemoglobin concentration was <2%, a value compatible with that of nonsmoking urban dwellers. Hyperglycemia was controlled by diet plus sulfonylurea in 8 cases or metformin in 11 cases. The mean GHb level on therapy was 6.2 ± 0.3%, and the average duration of diabetes (from diagnosis) was 8 years. They had no clinical signs of distal symmetric neuropathy, autonomic insufficiency (measured by variations in RR intervals with cycled breathing and by the presence of a >20 mmHg decrease in upright blood pressure without a change in heart rate), or renal disease (proteinuria

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Abbreviations: CO, cardiac output; CV, coefficient of variation; DL_{CO}, lung diffusing capacity for carbon monoxide; D_M, alveolar capillary membrane conductance; EF, ejection fraction; FEV_1, forced expiratory volume 1 s; SVR, systemic vascular resistance; PAR, pulmonary arteriolar resistance; Va, alveolar volume; Vc, pulmonary capillary blood volume available for gas exchange; VC, vital capacity, WPP, pulmonary wedge pressure.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of the study patients*

n	19
Sex (M/F)	11/8
Age (years)	59.9 ± 6.2
Weight (kg)	75.8 ± 6.9
Body surface area (M^2)	1.72 ± 0.15
Blood pressure (mmHg)	
Systolic	132.8 ± 10.8
Diastolic	88.6 ± 12.3
Fasting glucose (mg/dl)	128 ± 12
Cholesterol (mg/dl)	236 ± 14
Triglyceride (mg/dl)	172 ± 17
GHb, %	6.2 ± 0.3
Vital capacity (% predicted)	92.2 ± 8.5
FEV_1 (% predicted)	96.1 ± 9.3
DL_{CO} (% predicted)	84.2 ± 7.9
DL_{CO}/Va (% predicted)	82.2 ± 9.5

Data are means ± SD.

or serum creatinine >1.5 mg/dl). In these patients, vital capacity (VC) and forced expiratory volume 1 s (FEV_1) were 92.2 ± 8.5 and 96.1 ± 9.3% of the normal predicted value, respectively. Sixteen patients had no diabetic retinopathy, three had simple diabetic retinopathy, and none had a proliferative diabetic form. No drug treatment was prescribed except hypoglycemic drugs. All patients voluntarily gave their written consent to the procedures after the nature of the test had been explained. The study was approved by the ethical review committee of the hospital.

Tests of pulmonary function. VC, FEV_1, and DL_{CO} were assessed by Sensor Medics 2,200 Pulmonary Function Test System (Anaheim, CA). These data were expressed in absolute values and as a percent of predicted normal values. Reference equations were used in these analyses when values were expressed as percentage of normal predicted (9–11). DL_{CO} was measured with a standard single-breath technique (10) in duplicate (the average was taken as the final result), with washout intervals of at least 4 min, and with correction for the subject's hemoglobin concentration. Measurements of the alveolar capillary membrane conductance (D_M) and of the pulmonary capillary blood volume available for gas exchange (Vc), i.e., the DL_{CO} subdivisions, were performed in all patients at low and high oxygen concentrations, according to the classic Roughton and Forster method (11,12). There was a high level of agreement between consecutive measurements of $1/D_M$, with a correlation coefficient of 0.92 and a coefficient of variation (CV) <7%. Under study protocols similar to this (13), we have found no evidence of significant carbon monoxide back-tension effects on serial DL_{CO}, D_M, and Vc measurements. The single-breath alveolar volume (Va) was derived by methane dilution, and the alveolar-capillary membrane transfer coefficient (D_M/Va) was calculated.

Laboratory methods. Background evaluations were made after an overnight fast. Plasma glucose concentration was determined with autoanalyzer using a glucose oxidase method. Serum cholesterol and triglyceride concentrations were obtained with standard enzymatic methods. Glycohemoglobin level was measured by high-performance liquid chromatography. Insulin was measured by solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA). In our laboratory this method has an intra-assay CV of 5.5% and an interassay CV of 8.7%.

Hemodynamics. Cardiac output and pulmonary pressures were measured with a thermodilution, balloon-tipped catheter. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were calculated in dyn · s^{-1} · cm^{-5} from the following formula: SVR = MAP − MRAP × 1,332 × 60/CO and PAR = MPP − MWPP × 1,332 × 60/CO where MAP, MRAP, MPP, and MWPP are mean systemic arterial pressure, mean right atrial pressure, mean pulmonary arterial pressure, and mean pulmonary

Table 2—*Plasma glucose and insulin concentrations and hemodynamic and respiratory values in the baseline and within 60 min after regular insulin (10 IU) or saline infusions*

	n	Baseline	Saline	Insulin
Plasma insulin (μu/ml)	14	11.9 ± 4.1	12.3 ± 5.2 (a) 12.6 ± 4.7 (b)	409.2 ± 139 (a)* 78.3 ± 14.7 (b)*
Plasma glucose (mg/dl)	19	128 ± 12	129 ± 14	126 ± 11
CO (ml/min)	19	5400 ± 220	5490 ± 175	5720 ± 245
SVR (dyn · s^{-1} · cm^{-5})	19	1410 ± 153	1480 ± 172	1290 ± 193
Left ventric EF (%)	19	65.7 ± 2.3	63.9 ± 2.6	67.2 ± 3.1
Wedge pulmonary pressure (mmHg)	19	16.1 ± 2.3	15.3 ± 3.1	15.6 ± 2.4
PAR (dyn · s^{-1} · cm^{-5})	19	19 ± 14	21 ± 15	18 ± 18
VC (l)	19	4.1 ± 0.4	4.3 ± 0.5	4.2 ± 0.3
FEV_1 (l)	19	3.25 ± 0.40	3.10 ± 0.41	3.29 ± 0.36
DL_{CO} (ml · min^{-1} · $mmHg^{-1}$)	19	23.8 ± 4.3	23.5 ± 3.9	27.1 ± 3.7*
D_M (ml · min^{-1} · $mmHg^{-1}$)	19	38.6 ± 5.2	38.9 ± 4.8	44.8 ± 5.3*
DL_{CO}/Va (ml · min^{-1} · $mmHg^{-1}$ · l^{-1})	19	3.7 ± 1.3	3.9 ± 1.1	4.8 ± 0.9*
D_M/Va (ml · min^{-1} · $mmHg^{-1}$ · l^{-1})	19	6.2 ± 1.2	5.9 ± 1.1	7.4 ± 1.3*
DL_{CO}/D_M (%)	19	61.7 ± 6.9	60.4 ± 6.3	60.5 ± 6.8
Vc (ml)	19	86.2 ± 24.9	83.3 ± 28.5	80.4 ± 25.6
Vc/Va (ml/l)	19	18.3 ± 2.5	18.9 ± 2.7	19.1 ± 2.8

Data are means ± SD. *$P < 0.01$ vs. baseline. a, end of infusion; b, 30 min after infusion (immediately before pulmonary function reassessment).

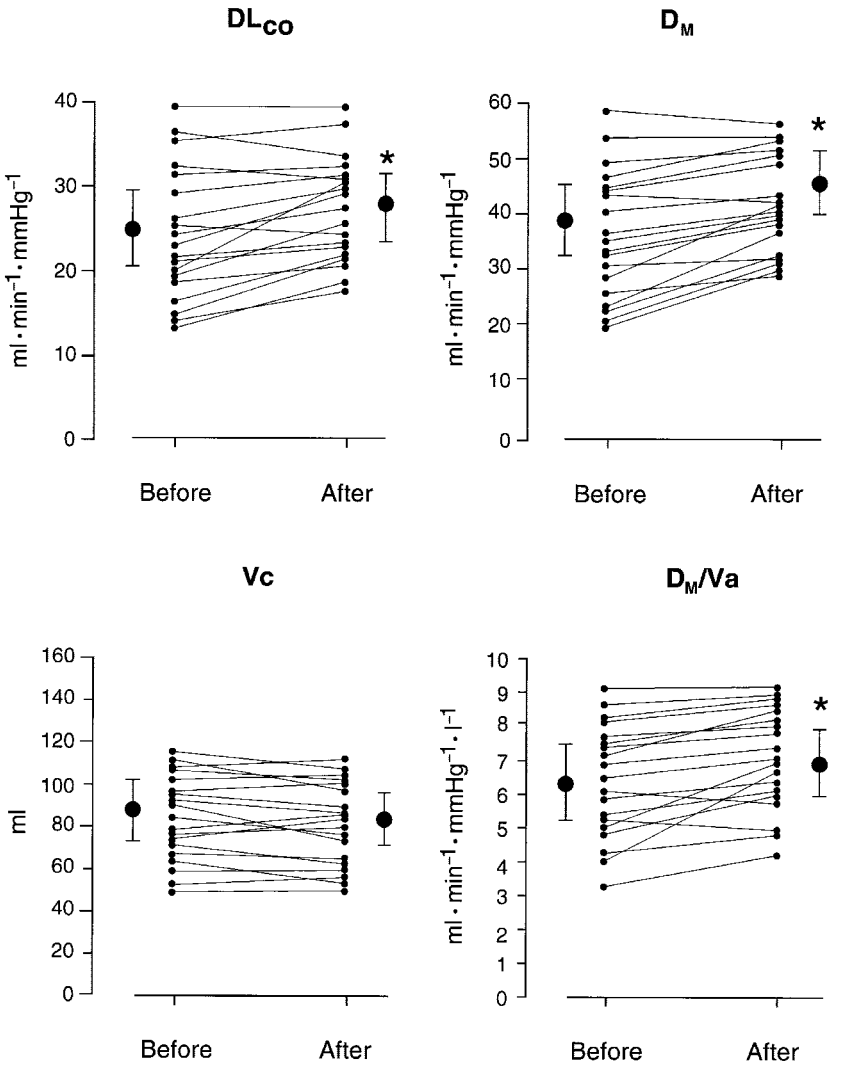

Figure 1—*Individual responses of the pulmonary gas exchange capacity to the infusion of insulin. Large ●, means ± SD. *P < 0.01 vs. before.*

wedge pressure, respectively, and CO is cardiac output.

Study protocol. These patients were admitted to the hospital and were fed a weight-maintaining diet, of which the caloric content was similarly distributed in each patient as carbohydrate, fat, and protein. They were withdrawn from their hypoglycemic drugs for 24 h before insulin studies.

Experiments were began at 8:00 A.M. and carried out after 12-h overnight fast in a quiet room at a constant temperature of 23°C. A 5F catheter was introduced percutaneously into an antecubital vein, advanced to a central venous position, and used for infusions. It was floated, when necessary, to the pulmonary artery or to the wedge position for hemodynamic measurements. A catheter needle inserted into a brachial artery was used for pressure monitoring. Baseline two-dimensional echocardiography (14) for left ventricular volume and ejection fraction (EF) (Simpson's rule), hemodynamics, pulmonary volumes, and gas exchange capacity were tested after 30 min rest. Five minutes later, 50 ml normal saline that either contained or did not contain 10 IU of regular insulin (Humulin; Eli Lilly) was infused through the venous catheter at a rate of 1.0 ml/min. Pulmonary, hemodynamic, and ultrasound measurements (in that order) were carried out within 30–60 min after infusion. On the following morning, the same procedures were performed again while patients were switched to insulin or inactive solution infusion, according to a random block design. Insulin levels were determined in 14 patients at rest at the end of infusions and 30 min later, immediately before pulmonary function reassessment. In five patients, we did not have the opportunity of performing insulin assay. Blood glucose was kept at the baseline level (between 117 and 153 mg/dl) for the duration of the experiment by administering intravenous 20% dextrose solution at a variable rate according to glycemia. The supplemented dextrose solution volume ranged between 20 and 110 ml. Serum potassium levels remained >3.7 mEq/l in each patient. Glucose plasma levels were obtained at baseline, at 10-min intervals during infusions, and before assessing lung function after infusions.

Statistical analysis. Data are presented as the means ± SD. Data were analyzed using two-way repeated measure ANOVA and Newman Keuls multiple comparison procedure. A P value <0.05 was considered significant.

RESULTS — As shown in Tables 1 and 2, baseline CO, EF, wedge pulmonary pressure, PAR, VC, and FEV_1 were within normal limits in these patients. Blood pressure, fasting glucose, insulin, cholesterol, triglyceride levels, and GHb concentrations were mildly or moderately augmented. DL_{CO} was moderately reduced (84.2% of normal predicted value). We did not find a correlation of DL_{CO} with age, degree of retinopathy, or time from diabetes diagnosis.

Infusion of saline alone was not associated with any variations in the gas-exchanging capacity. On the contrary, measurements performed between 30 and 60 min after insulin infusion documented a significant improvement of DL_{CO}, D_M, DL_{CO}/Va, and D_M/Va, without variations in lung volumes or in cardiac and pulmonary hemodynamics. Insulin levels (Table 2) were definitely augmented at the end of the hyperinsulinemic-glycemic clamp and were still significantly raised from baseline when pulmonary function was reassessed. Figure 1 depicts, in absolute values, the individual responses of the gas exchange capacity to the intravenous infusion of insulin. Of 19 patients, 15 (79%) showed an improvement of DL_{CO} and D_M that resulted in a mean increase from baseline by 12 and 14%, respectively. The transfer co-

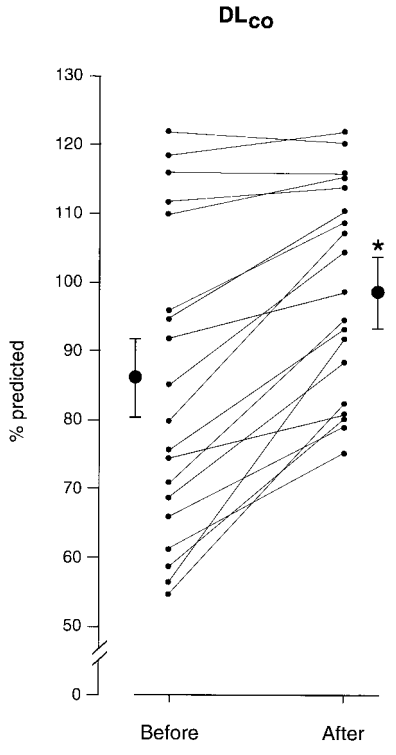

Figure 2—*Individual percentages of predicted normal values of the DL_{CO} before and after insulin. Large ●, means ± SD. *P < 0.01 vs. before.*

efficient (D_M/Va) augmented by 16.5%. Vc showed an insignificant average fall from baseline of 6 ml. These changes were not present 24 h later at measurements before the infusion of saline alone in patients who had received insulin the day before.

The individual values of DL_{CO} before and after insulin reported in Fig. 2 are percent of predicted normal values—before insulin, DL_{CO} averaged 84.2% of normal predicted value, and 14 of 19 cases had a value <100% of the predicted value; after insulin, DL_{CO} averaged 98% of normal predicted value, and 10 of 19 cases had a value <100%.

CONCLUSIONS

Lung diffusing capacity in type 2 diabetes. While lung diffusing capacity in type 1 diabetes has been the subject of several reports (1,3–7), there has not been any systematic investigation of alveolar-capillary membrane conductance in type 2 diabetes or its relationship with glycemic control. Our population consisted of 19 subjects with type 2 diabetes, whose blood GHb was maintained at near-normal levels with diet and hypoglycemic drugs. Although they had no respiratory disease, and VC and FEV_1 were within normal limits, baseline DL_{CO} averaged 83% of the predicted normal value, and in 14 cases it was <100% of the predicted normal value. A link between diabetes and impedance to gas exchange was not contradicted by smoking (patients had never smoked, and carboxyhemoglobin concentration was <2% in all patients), cardiac dysfunction (8,15,16) (there was no history or clinical, chest X-ray, echocardiographic signs of heart failure; CO, left ventricular EF, diastolic volume, and wedge pulmonary pressure at rest were all within normal limits); or age (there was no correlation between age and DL_{CO}). Yet, mild primary hypertension in six patients was not a confounding factor, because these patients were not prescribed any antihypertensive treatment, and DL_{CO} at rest was comparable with that in the normotensive patients. There was no correlation between DL_{CO} and time from diabetes diagnosis. Therefore, it appears that some impairment in gas transfer may affect a significant number of asymptomatic type 2 diabetic patients. This is in contrast with the report of Minette et al. (7), who failed to show any gas exchange abnormalities in diabetes. In this study, however, patients were purposely selected who were insulin-dependent for the previous 5 years. In the hypothesis of a benefit of insulin on gas exchange capacity, Minette's findings do not detract from our results but indeed reinforce them. Yet, oral hypoglycemic drugs and maintenance of near-normal GHb in type 2 diabetes do not seem to fully prevent the development of alveolar-capillary membrane conductance impairment. Whether in this patient category a greater elevation of GHb would be associated with a greater reduction of DL_{CO} at rest, remains an open question.

Response to insulin and underlying mechanisms. After insulin, not after saline, the efficiency of CO diffusion augmented significantly, as shown by an improvement of the alveolar-capillary interface conductance, D_M, and the transfer coefficient, D_M/Va. As to the mechanisms involved, some preliminary possibilities should be considered. Insulin and glucose delivery through the cava site may have led to high concentrations of these substances into the pulmonary circulation and influenced the conductance properties at the air-blood interface; this effect, however, would probably be very short lasting and undetectable by the methods used. Insulin may affect the pulmonary capillary caliber/blood flow, which would influence CO diffusion—there were, however, no changes in pulmonary capillary volume and CO with insulin. Insulin might increase the affinity of hemoglobin for CO. However, the significant correlation observed between improvement of DL_{CO} with insulin and enhancement of exercise oxygen uptake and ventilatory efficiency in patients with type 2 diabetes (M.G., G. Tuminello, M.D.G., unpublished observations) is in favor of an important physiological improvement in gas exchange, not of an artifact of measurement, suggesting that in otherwise asymptomatic type 2 diabetes, a gaseous diffusion "defect" may have clinical significance and can be transiently corrected by administration of exogenous insulin.

Increase in CO, the opening or distension of pulmonary capillaries, and improvement in uniformity of blood distribution can increase respiratory gas diffusion capacity during physiological conditions such as exercise (17,18). Mechanisms like these were probably not involved in the response to insulin, because CO, EF, pulmonary wedge pressure, arteriolar resistance, VC, FEV_1, and Va were not affected. A significant participation of an acute reduction of glycemia is also excludable because blood glucose levels were kept constant during the experiments.

These considerations all point in the direction of a modulation of the alveolar-capillary gas conductance by insulin. Alveolar epithelial and endothelial capillary basal laminae in autopsied patients having diabetes were found to be significantly thicker than in control subjects (7) and were considered to underlie the excessive impedance to gas exchange in some diabetic patients. The acuteness of the response, however, is not consistent with thinning of the basal laminae as a mechanism for the improved gas transfer with insulin. More consistent with the characteristics of the respiratory response is an activation of a molecular transporter for gas diffusion, or an enhanced release of endothelium-derived nitric oxide (19–21) and of vasodilating prostaglandins (22), which, in parallel with reduced vascular tone and augmented permeability (23), might facilitate gas transfer. Other

possibilities are an upregulation of the alveolar epithelial fluid transport (24) by a β-agonistic activity (25), or a potentiation of the glucose-sodium cotransport (26,27) through the alveolar epithelium, thus lowering the resistance to the transfer of oxygen from the alveolus to its uptake by hemoglobin. Diabetes, in fact, may impact the regulation of Na^+-glucose transport, and alteration of expression may be due to either hyperglycemia, or reduced insulin levels or insulin resistance (28).

All of these possibilities imply that the diffusion defect results from a relative insulin deficiency that can be transiently overcome by administration of the hormone. Because type 2 diabetes is often characterized by insulin resistance that is associated with elevated insulin levels, giving insulin to a patient with hyperinsulinemia might seem to be paradoxical. However, much of the endogenous insulin may be redundant in view of the degree of insulin resistance, and additional exogenous insulin may successfully improve the deficiency that leads to alveolar-capillary membrane dysfunction.

In conclusion, this study documents that in a significant number of patients, type 2 diabetes is associated with some degree of impedance to the alveolar-capillary membrane gas transfer, despite the prescription of hypoglycemic drugs and a satisfactory metabolic control. Insulin produces an acute reduction of impedance that is unrelated or not exclusively related with changes in glycemia and consists of a direct facilitation of the interface conductance.

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