Hiroshima J. Med. Sci.
Vol. 59, No. 1, 7~13, March, 2010
HIJM 59–2

The Influence of Lung Function on Exercise Capacity in Patients with Type 2 Diabetes

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ABSTRACT

Patients with type 2 diabetes have impaired exercise capacity. While numerous factors are known to contribute to impaired exercise capacity, the role of lung function remains unclear. We conducted the present study to investigate the influence of lung function on exercise capacity in patients with type 2 diabetes.

Cardiopulmonary exercise testing was carried out in 31 male patients with type 2 diabetes without diabetic complications or cardiopulmonary diseases. Patients with abnormal spirometry results such as a percentage of predicted forced vital capacity (%FVC) < 80% and/or a ratio of forced expiratory volume in one second (FEV_1) to FVC (FEV_1/FVC) < 70% were excluded from the study. We used the percentage of predicted maximal oxygen uptake (%$\dot{V}O_2$max) as an index of exercise capacity. The correlations between %$\dot{V}O_2$max and lung function and other factors known to be associated with impaired exercise capacity were then assessed.

Univariate analysis revealed %$\dot{V}O_2$max correlated significantly with percentage of predicted FEV_1 (%FEV_1), duration of type 2 diabetes, regular exercise habits, and systolic and diastolic blood pressures. In a multivariate analysis, %FEV_1 and regular exercise habits were found to be independent determinants of %$\dot{V}O_2$max.

A mild reduction in %FEV_1, which may be a complication of diabetes, is associated with impaired exercise capacity in patients with type 2 diabetes. When evaluating spirometric values in patients with type 2 diabetes, a reduction in %FEV_1 should be noted even when both %FVC and FEV_1/FVC are within normal limits.

Key words: *Exercise capacity, Lung function, %FEV_1, Type 2 diabetes*

Exercise training is an important strategy for improving glycemic control in patients with type 2 diabetes and also for preventing development of the disorder in subjects with impaired glucose tolerance[17,26)]. Despite there being no evidence that stress testing is routinely necessary before beginning an exercise program[25)], we consider cardiopulmonary exercise testing (CPET) is useful for evaluating exercise capacity and prescribing the appropriate intensity of exercise in patients with diabetes.

Even when no obvious cardiovascular complications are present, patients with type 2 diabetes have a significantly reduced exercise capacity compared to normal subjects[8,14)]. While there is evidence of a strong negative association between exercise capacity and mortality in patients with type 2 diabetes[28)], it is also known that these patients benefit more from exercise training, with regard to oxygen uptake ($\dot{V}O_2$), than do healthy control subjects[8)].

The reasons for exercise impairment in patients with type 2 diabetes remain unknown. Previous studies have shown that numerous factors are

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associated with impaired exercise capacity, such as high levels of glycosylated hemoglobin (HbA_{1C}), old age, increased body mass index (BMI), female gender, raised systolic blood pressure, high pack-years smoking, African-American ethnicity, the presence of retinopathy, increased urinary albumin excretion (UAE), and increased levels of high-sensitivity C-reactive protein (CRP)[11-13,20].

Recent cross-sectional and epidemiological follow-up studies suggest the lung may be a target organ in type 2 diabetes, leading to a deterioration in lung function measurements, such as forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1)[6,10,31]. On the other hand, recent prospective studies have suggested that impaired lung function may be associated with subsequent development of type 2 diabetes[30]. These findings imply that impairment in lung function may not only be a complication of type 2 diabetes, but also a risk factor for development of the disorder.

Previous studies have focused on the relationships between exercise capacity and lung function in patients with either chronic obstructive pulmonary disease (COPD) or chronic heart failure and have produced inconsistent results[4,9,27]. In a study by Babb and colleagues, lung function of subjects varied from mild chronic airflow limitation to above normal [percentage of predicted FEV_1 (%FEV_1); 61 to 114%], while percentage of predicted maximal $\dot{V}O_2$ (%$\dot{V}O_2$max) correlated positively with %FEV_1[4]. In contrast, Wassserman and colleagues reported that %$\dot{V}O_2$max was not correlated with %FEV_1 in patients with COPD[27]. In a study by Clark and colleagues, percentage of predicted FVC(%FVC), %FEV_1, and peak $\dot{V}O_2$ were significantly lower in patients with chronic heart failure than control subjects, with both %FVC and %FEV_1 being correlated positively with peak $\dot{V}O_2$[9]. However, the influence of lung function on exercise capacity in patients with type 2 diabetes remains unknown despite the close relationship between type 2 diabetes and deterioration in lung function. We therefore carried out the present study to examine the influence of lung function variables on exercise capacity in patients with the disorder. The patients were selected for the study if they had type 2 diabetes with no obvious cardiac or respiratory diseases, as evidenced by normal brain natriuretic peptide (BNP) levels and normal lung function tests [i.e., %FVC $\geqq$ 80% and ratio of FEV_1 to FVC (FEV_1/FVC) $\geqq$ 70%].

MATERIALS AND METHODS

Subjects

Male patients with type 2 diabetes were recruited for this study between January 2003 and October 2003. The study protocol was approved by the ethics committee of Hiroshima University and all patients gave informed consent prior to commencement of the study. Exclusion criteria included the following conditions: (1) poorly controlled diabetes with an HbA_{1C} level > 10%[11], (2) insulin therapy, (3) current smoker[19], (4) history of any respiratory or cardiovascular disease, (5) FEV_1/FVC < 70% or %FVC < 80% on spirometry, (6) the presence of retinopathy or distal symmetrical neuropathy[12], (7) overt albuminuria > 300 μg/mg·creatinine[2] or a serum creatinine level >2 mg/dl[8], and (8) using a ß-blocker. We checked each patient's smoking habits by means of a questionnaire and also by measuring venous carboxyhemoglobin (CO-Hb) concentration (%). Subjects who continued smoking cigarettes at entry or whose CO-Hb was > 3% were classified as current smokers[19]. Subjects were asked about their physical activity and were considered to have regular exercise habits if they undertook aerobic exercises for longer than 30 min more than once a week. Venous blood was withdrawn and a random urine sample was collected after 20 min of rest in the supine position. In this study, plasma BNP levels were measured using an immuno-enzymometric assay (E test 「TOSOH」 II (BNP)®, TOSOH Co., Toyama, Japan) and UAE was measured by a turbidimetric immunoassay (TIA) (KITAS Micro ALB test kit®, Kinos Co., Tokyo, Japan). Spirometry was conducted in triplicate, with the patient in the standing position, using a portable spirometer (HI-701® Chest Co., Tokyo, Japan) according to the guidelines of the American Thoracic Society[3]. The predicted values of FVC and FEV_1 were calculated using the formulas of Baldwin[5] and Berglund[7], respectively, as follows:

FVC (ml) =
[27.63 – 0.112 × Age (years)] × height (cm)

FEV_1 (ml) =
34.4 × height (cm) – 33 × Age (years) – 1000

%FVC was calculated as the ratio of FVC to predicted FVC, and %FEV_1 as the ratio of FEV_1 to predicted FEV_1.

CPET

All eligible subjects were instructed to consume a light meal and take their medications at least 3 hr before CPET. CPET was conducted using an electrically braked cycle ergometer (STB-2400®, Nihon Kohden Co., Tokyo, Japan) with an incremental ramp protocol. To ensure safety, the target heart rate was set at 210 - age (beats/min). $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were measured breath-by-breath using a computerized expired gas analyzing system (Aeromonitor AE-300RC®, Minato Medical Science Inc., Osaka, Japan). During CPET, blood pressure, heart rate, percutaneous arterial oxygen saturation (SpO_2) and a 12-lead electrocardiogram(ECG) were monitored continuously. After a 3 min resting period and a 1 min warm-up period at 10 watts per min

(W/min), the workload was increased at a rate of 20 W/min. The subjects were instructed to maintain 50 to 60 revolutions per minute (rpm). CPET was terminated when one of the following criteria was observed: (1) inability to maintain 50 rpm as a result of any symptom, (2) reaching the target heart rate, (3) desaturation with an SpO_2 < 90%, (4) appearance of ischemic changes or severe arrhythmia on the ECG. An ischemic response was defined as a J point depression of 1 mm or greater, with a flat or down slope ST-segment depression during exercise. The degrees of chest discomfort and leg fatigue were evaluated by the modified Borg scale[16]. $\dot{V}O_2$ at the time of CPET termination was defined as $\dot{V}O_2$max. We used %$\dot{V}O_2$max as an index of individualized exercise capacity, calculated as the ratio of $\dot{V}O_2$max to predicted $\dot{V}O_2$max. In this study, the predicted value of $\dot{V}O_2$max was calculated using the following formula:

$\dot{V}O_2$max (ml/min/kg) =

$$51.445 - 0.331 \times \text{Age (years)}^{29)}.$$

Statistical analysis

All statistical analyses were performed with the statistical program SPSS for Windows (version 11.0, SPSS Japan Inc., Chicago, IL, USA). The data were expressed as mean ± standard deviation (SD). To investigate the correlation between %$\dot{V}O_2$max and other variables, we performed Spearman's rank correlation test. Multiple stepwise regression analysis was performed to investigate which variables were independent determinants of %$\dot{V}O_2$max.

A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Thirty-one male patients with type 2 diabetes met the inclusion criteria and were recruited in the study. Table 1 summarizes the baseline characteristics of these patients and shows that the spirometric values, mean FVC and FEV_1, were greater than 100% of predicted values. The age range of the study participants was 35 to 74 years, while mean UAE was 32.4 μg/mg·creatinine (range: 2.4 to 179.3), a level marginally higher than the criterion for microalbuminuria of 30 μg/mg·creatinine[2]. Mean plasma BNP level at rest was 12.9 pg/ml (range: 4.0 to 43.0).

CPET

All subjects finished CPET safely. Mean $\dot{V}O_2$max was 29.1 ± 4.4 ml/min/kg and mean %$\dot{V}O_2$max was 88.8 ± 14.0%. Mean heart rate at the time of CPET termination was 146.8 ± 1.7 beats/min (95.3 ± 7.0% of predicted value), while mean lowest SpO_2 was 97.5 ± 1.3%. Perceived exertion was moderate on the modified Borg scale for chest discomfort and leg fatigue at peak exercise, being 5.0 ± 2.2 and 5.5 ± 2.6, respectively. Although significant ischemic changes were found in ten subjects, no patient complained of chest pain.

Correlations between exercise capacity and other variables

On univariate analysis, %$\dot{V}O_2$max correlated positively with %FEV_1 (Fig. 1), duration of type 2 diabetes, and regular exercise habits, and inversely with both systolic and diastolic blood pressure (Table 2). No correlation was found between %$\dot{V}O_2$max and age, BMI, the Brinkmann index, FVC, %FVC, FEV_1, FEV_1/FVC, HbA_{1C}, high-sensitivity CRP, plasma BNP levels at rest, UAE, lowest SpO_2, and appearance of ST changes (Table 2). %FEV_1 was correlated positively with age, duration of diabetes, FVC, %FVC, and FEV_1, and

Table 1. Clinical and spirometric characteristics of the patients in the study*

Variables	
Demographics	
Age, yr	56.0 ± 8.8
BMI, kg/m^2	24.2 ± 3.6
Duration of diabetes, yr	5.4 ± 4.2
Smoking history, No.	
Never / Past	11 / 20
Brinkmann index	266.8 ± 289.5
Regular exercise, No.	
Yes / No	18 / 13
Systolic blood pressure, mmHg	138.4 ± 17.9
Diastolic blood pressure, mmHg	83.5 ± 10.0
HbA_{1C}, %	6.7 ± 0.9
High-sensitivity CRP, mg/dl	0.07 ± 0.09
BNP, pg/ml	12.9 ± 11.1
CO-Hb, %	1.4 ± 0.3
UAE, μg/mg·creatinine	32.4 ± 50.7
Spirometric parameters	
FVC, liter	4.0 ± 0.5
%FVC, %	111.9 ± 12.6
FEV_1, liter	3.1 ± 0.4
FEV_1/FVC, %	79.4 ± 4.0
%FEV_1, %	110.4 ± 13.2

*Data are expressed as mean ± standard deviation (S.D.).

BMI: body mass index; HbA_{1C}: glycosylated hemoglobin; CRP: C-reactive protein; BNP: brain natriuretic peptide; CO-Hb: carboxyhemoglobin; UAE: urinary albumin excretion; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second.

Table 2. Univariate analyses showing the relationship between %$\dot{V}O_2$max and clinical and spirometric variables

	rs	p value†
Age	0.263	0.154
BMI	-0.295	0.107
Smoking history (never/past)	0.166	0.373
Brinkmann index	0.042	0.824
Duration of type 2 diabetes	0.421	0.032†
Regular exercise habits	0.431	0.015†
Systolic blood pressure	-0.377	0.036†
Diastolic blood pressure	-0.405	0.024†
FVC	0.078	0.677
%FVC	0.152	0.416
FEV_1	0.199	0.284
FEV_1/FVC	0.263	0.152
%FEV_1	0.413	0.021†
HbA_{1C}	-0.013	0.944
High-sensitivity CRP	-0.344	0.058
Plasma BNP levels	0.014	0.939
UAE	-0.011	0.953
Lowest SpO_2	-0.120	0.526
Appearance of ST change	-0.208	0.261

†$p < 0.05$ for Spearman's rank correlation test.
%$\dot{V}O_2$max: percentage of predicted maximal oxygen uptake;
BMI: body mass index; FVC: forced vital capacity;
FEV_1: forced expiratory volume in one second;
HbA_{1C}: glycosylated hemoglobin; CRP: C-reactive protein;
BNP: brain natriuretic peptide; UAE: urinary albumin excretion;
SpO_2: percutaneous arterial oxygen saturation.

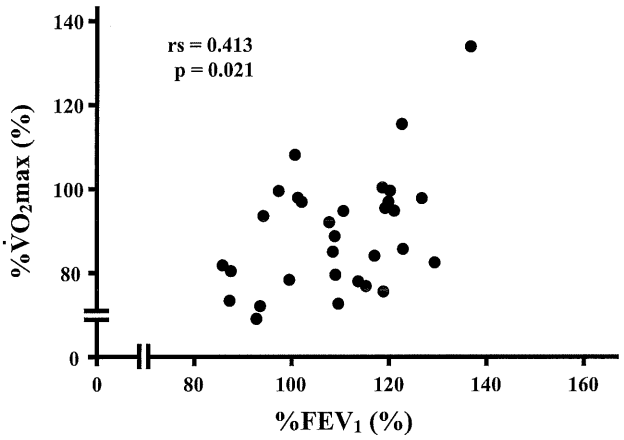

Fig. 1. Scattergram showing a positive correlation (rs = 0.413, p = 0.021) between percentage of predicted forced expiratory volume in one second (%FEV_1) and percentage of predicted maximal oxygen uptake (%$\dot{V}O_2$max).

inversely with UAE (Table 3). No correlation was found between HbA_{1C} and %FEV_1. HbA_{1C} was not correlated with duration of diabetes (data not shown).

Multiple stepwise regression analysis was performed using BMI and all the factors that correlated with %$\dot{V}O_2$max and/or %FEV_1 in order to determine which variables were independent determinants of %$\dot{V}O_2$max. This analysis showed that %FEV_1 and regular exercise habits were independent determinants of %$\dot{V}O_2$max (Table 4).

DISCUSSION

This study examined the association between clinical variables and %$\dot{V}O_2$max, an indicator of exercise capacity, in patients with type 2 diabetes and no obvious cardiopulmonary complications. The variables investigated included spirometric measures and factors known to be associated with impairment of exercise capacity in this patient group[11-13,20].

The major finding of this study was that lung function, specifically %FEV_1, and also regular exercise habits, were independent determinants of %$\dot{V}O_2$max. To our knowledge, this is the first report illustrating an influence of lung function on exercise capacity in patients with type 2 diabetes. Although %FEV_1 has been used as a determinant of COPD severity[22], this index is usually not considered in subjects with FEV_1/FVC of $\geqq$ 70%. Even under such conditions, this study indicated that a value of %FEV_1 has clinical significance, at least in patients with type 2 diabetes.

Regular exercise habits were found to be an independent determinant of high %$\dot{V}O_2$max. This result is consistent with a previous report that showed patients with type 2 diabetes benefit more from exercise training with regard to improvement in $\dot{V}O_2$ than do healthy control subjects[8]. A recent study that incorporated 25 years of follow-up also demonstrated a relationship between higher levels of physical activity and a slower decline in lung function in healthy subjects[23]. Physical activity is considered to counteract the loss of elastic recoil that leads to premature airway closure and airway trapping during forced expiration[23]. Biochemical changes in connective tissue, particularly collagen and elastin, which result from non-enzymatic glycosylation of proteins induced by chronic hyperglycemia, are considered to be a possible mechanism for the rapid decline in lung function that may develop in diabetic patients[18]. It is therefore possible that regular exercise may delay the decline in lung function seen in diabetic subjects, not only as a direct consequence, but also indirectly by improving hyperglycemia.

Table 3. Univariate analyses showing the relationship between %FEV_1 and clinical and spirometric variables

	rs	p value†
Age	0.483	0.006†
BMI	-0.153	0.412
Smoking history (never/past)	-0.098	0.600
Brinkmann index	-0.106	0.569
Duration of type 2 diabetes	0.453	0.020†
Regular exercise habits	0.080	0.667
Systolic blood pressure	-0.166	0.372
Diastolic blood pressure	-0.206	0.267
FVC	0.428	0.016†
%FVC	0.718	<0.001†
FEV_1	0.512	0.003†
FEV_1/FVC	-0.018	0.925
HbA_{1C}	0.002	0.993
High-sensitivity CRP	-0.320	0.080
Plasma BNP levels	0.222	0.239
UAE	-0.378	0.040†
Lowest SpO_2	-0.073	0.702
Appearance of ST change	0.008	0.967

†$p < 0.05$ for Spearman's rank correlation test.
FEV_1: forced expiratory volume in one second;
BMI: body mass index; FVC: forced vital capacity;
HbA_{1C}: glycosylated hemoglobin; CRP: C-reactive protein;
BNP: brain natriuretic peptide; UAE: urinary albumin excretion; SpO_2: percutaneous arterial oxygen saturation.

Table 4. Multivariate analyses showing the relationship between %$\dot{V}O_2$max and clinical and spirometric variables

$R^2 = 0.412$	ß	p value†
Age	0.020	0.923
BMI	-0.244	0.175
Duration of type 2 diabetes	0.282	0.151
Regular exercise habits	0.427	0.016†
Systolic blood pressure	-0.247	0.162
Diastolic blood pressure	-0.281	0.115
FVC	-0.219	0.229
%FVC	-0.333	0.146
FEV_1	-0.096	0.631
%FEV_1	0.470	0.009†
HbA_{1C}	0.093	0.606
High-sensitivity CRP	-0.088	0.639
UAE	0.027	0.883

†$p < 0.05$ for multiple stepwise regression.
%$\dot{V}O_2$ max: percentage of predicted maximal oxygen uptake;
BMI: body mass index; FVC: forced vital capacity;
FEV_1: forced expiratory volume in one second;
HbA_{1C}: glycosylated hemoglobin; CRP: C-reactive protein;
BNP: brain natriuretic peptide.

We were unable to clarify the precise mechanism by which %FEV_1 influences exercise capacity in diabetic patients. In the study by Babb and colleagues, %FEV_1 correlated positively with %$\dot{V}O_2$max and inversely with end-expiratory lung volume (EELV) at maximal exercise[4]. An increase in EELV leads to a decrease in inspiratory capacity and dynamic hyperinflation during exercise in patients with even mild COPD[21]. It is also known there is competition between respiratory and locomotor muscles for the supply of energy[1]. If this association between % FEV_1 and EELV is applicable to our subjects, after taking into account that the subjects in the study by Babb and colleagues had %FEV_1 varying from mild chronic airflow limitation to above normal, whereas our subjects were all above normal, we speculate that even a mild reduction in %FEV_1 may increase EELV during maximal exercise. This in turn would be expected to lead to an increase in work involved in breathing, thereby resulting in a decrease in energy supply to locomotor muscles and a subsequent decrease in %$\dot{V}O_2$max.

Because of its high affinity for oxygen, an increase in HbA_{1C} is known to impair oxygen transport, resulting in decreased exercise capacity[11]. A previous study in diabetic patients showed that HbA_{1C} correlated inversely with exercise capacity, and positively with skeletal muscle reoxygenation time during recovery after exercise[24]. However, in our study, HbA_{1C} did not correlate with exercise capacity, nor was there any significant association between exercise capacity and smoking history, UAE, or high-sensitivity CRP level, factors which have all been shown to correlate with exercise capacity in diabetic patients[11-13,20]. In addition, contrary to the result of the Atherosclerosis Risk in Communities study[31], HbA_{1C} was not found to correlate with %FEV_1. These different results may possibly be explained by the selection criteria used for patients in our study, where subjects with a high HbA_{1C} were excluded from entry.

Microvascular diabetic complications, such as UAE and the existence of retinopathy have been shown to be independent determinants of exercise capacity in diabetic patients[12]. The severity of UAE is known to be closely linked with left

ventricular dysfunction in these patients[15]. As diabetic microvascular complications result from poor glycemic control, both high HbA_{1C} and microvascular disease may cause abnormal skeletal muscle oxygenation during exercise in diabetic patients[24].

In our study, UAE was not correlated with $\%\dot{V}O_2max$, but showed an inverse correlation with $\%FEV_1$. However, as we excluded patients with overt albuminuria from the study, we cannot conclude from our results that $\%FEV_1$ is more closely associated with exercise capacity than UAE in diabetic patients.

In diabetic patients, poor glycemic control would be expected to result in a deterioration in both lung function and diabetic complications[2,31]. We speculate that another possible mechanism may explain the correlation between $\%FEV_1$ and $\%\dot{V}O_2max$ in these patients: the decrease in $\%FEV_1$ may be associated with an increase in UAE and hence left ventricular dysfunction. Further studies are needed to clarify this possibility.

The present study had a limitation that due to recruitment difficulties there was a lack of control subjects without diabetes. Therefore, whether or not the association between $\%FEV_1$ and exercise capacity is restricted only to patients with diabetes is yet to be elucidated. As all the subjects in our study had normal spirometric values, our results may also be applicable to normal subjects. However, additional studies are necessary to examine this possibility.

In conclusion, we found a significant association between $\%FEV_1$ and exercise capacity in patients with type 2 diabetes. When evaluating spirometric values in patients with type 2 diabetes, a reduction in $\%FEV_1$ should be noted even when both %FVC and FEV_1/FVC are within normal limits. The lung is one of the target organs affected by type 2 diabetes and therefore strategies to slow the decline in lung function are essential. Our results have clinical implications in terms of early identification of patients with low exercise capacity and also raise the possibility of early intervention to improve the lifestyle of patients with type 2 diabetes.

Conflict of interest statement

Yoshihiro Kitahara, Noboru Hattori, Akihito Yokoyama, Kiminori Yamane, Kiyokazu Sekikawa, Tsutomu Inamizu, and Nobuoki Kohno have no conflicts of interest to disclose.

ACKNOWLEDGMENTS

The authors thank Mitsuru Tabusadani, PT, PhD for his assistance in performing CPET.

(Received July 16, 2009)
(Accepted March 9, 2010)

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