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 (FEV1) to FVC (FEV1/FVC) < 70% were excluded from the study. We used the percentage of predicted maximal oxygen uptake (%VO2max) as an index of exercise capacity. The correlations between %VO2max and lung function and other factors known to be associated with impaired exercise capacity were then assessed.

Univariate analysis revealed %VO2max correlated significantly with percentage of predicted FEV1 (%FEV1), duration of type 2 diabetes, regular exercise habits, and systolic and diastolic blood pressures. In a multivariate analysis, %FEV1 and regular exercise habits were found to be independent determinants of %VO2max.

A mild reduction in %FEV1, 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 %FEV1 should be noted even when both %FVC and FEV1/FVC are within normal limits.

Key words: Exercise capacity, Lung function, %FEV1, 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. Despite there being no evidence that stress testing is routinely necessary before beginning an exercise program, 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. While there is evidence of a strong negative association between exercise capacity and mortality in patients with type 2 diabetes, it is also known that these patients benefit more from exercise training, with regard to oxygen uptake (VO2), than do healthy control subjects.

The reasons for exercise impairment in patients with type 2 diabetes remain unknown. Previous studies have shown that numerous factors are...
associated with impaired exercise capacity, such as high levels of glycosylated hemoglobin (HbA1C), 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)\(^1\)\(^{-13}\),\(^{20}\).

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 VO\(_2\) (\%VO\(_2\)max) correlated positively with \%FEV\(_1\)\(^4\). In contrast, Wasserman and colleagues reported that \%VO\(_2\)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 VO\(_2\) were significantly lower in patients with chronic heart failure than control subjects, with both \%FVC and \%FEV\(_1\) being correlated positively with peak VO\(_2\)\(^9\). 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 \(\geq 80\%\) and ratio of FEV\(_1\) to FVC (FEV\(_1\)/FVC) \(\geq 70\%\)].

**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 HbA1C 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 \(\mu\)g/mg-creatinine\(^2\) or a serum creatinine level >2 mg/dl\(^8\), and (8) using a \(\beta\)-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)\(^{9}\), TOSOH Co., Toyama, Japan) and UAE was measured by a turbidimetric immunoassay (TIA) (KITAS Micro ALB test kit\(^9\), Kinos Co., Tokyo, Japan). Spirometry was conducted in triplicate, with the patient in the standing position, using a portable spirometer (HI-701\(^\circ\) Chest Co., Tokyo, Japan) according to the guidelines of the American Thoracic Society\(^8\)). The predicted values of FVC and FEV\(_1\) were calculated using the formulas of Baldwin\(^5\) and Berglund\(^7\), respectively, as follows:

\[
\text{FVC (ml)} = \left[ 27.63 - 0.112 \times \text{Age (years)} \right] \times \text{height (cm)}
\]

\[
\text{FEV}_1 (\text{ml}) = \left[ 34.4 \times \text{height (cm)} - 33 \times \text{Age (years)} - 1000 \right]
\]

\%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\(^0\), Nihon Kohden Co., Tokyo, Japan) with an incremental ramp protocol. To ensure safety, the target heart rate was set at 210 - age (beats/min). VO\(_2\) and carbon dioxide production (VCO\(_2\)) were measured breath-by-breath using a computerized expired gas analyzing system (Aeromonitor AE-300RC\(^8\), 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
was 12.9 pg/ml (range: 4.0 to 43.0). Mean plasma BNP level at rest was 29.1 ± 4.4 ml/min/kg and mean %V̇O₂max 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 SpO₂ 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, %V̇O₂max correlated positively with %FEV₁ (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 %V̇O₂max and age, BMI, the Brinkmann index, FVC, %FVC, FEV₁, FEV₁/FVC, HbA1C, high-sensitivity CRP, plasma BNP levels at rest, UAE, lowest SpO₂, and appearance of ST changes (Table 2). %FEV₁ was correlated positively with age, duration of diabetes, FVC, %FVC, and FEV₁, and

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 %V̇O₂max and other variables, we performed Spearman’s rank correlation test. Multiple stepwise regression analysis was performed to investigate which variables were independent determinants of %V̇O₂max.

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 FEV₁, 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·creatinine²). Mean plasma BNP level at rest was 12.9 pg/ml (range: 4.0 to 43.0).

CPET

All subjects finished CPET safely. Mean V̇O₂max was 29.1 ± 4.4 ml/min/kg and mean %V̇O₂max 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 SpO₂ was 97.5 ± 1.3%. Perceived exertion was
Table 2. Univariate analyses showing the relationship between %VO₂max and clinical and spirometric variables

<table>
<thead>
<tr>
<th></th>
<th>rs</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.263</td>
<td>0.154</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.295</td>
<td>0.107</td>
</tr>
<tr>
<td>Smoking history (never/past)</td>
<td>0.166</td>
<td>0.373</td>
</tr>
<tr>
<td>Brinkmann index</td>
<td>0.042</td>
<td>0.824</td>
</tr>
<tr>
<td>Duration of type 2 diabetes</td>
<td>0.421</td>
<td>0.032†</td>
</tr>
<tr>
<td>Regular exercise habits</td>
<td>0.431</td>
<td>0.015†</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.377</td>
<td>0.036†</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.405</td>
<td>0.024†</td>
</tr>
<tr>
<td>FVC</td>
<td>0.078</td>
<td>0.677</td>
</tr>
<tr>
<td>%FVC</td>
<td>0.152</td>
<td>0.416</td>
</tr>
<tr>
<td>FEV₁</td>
<td>0.199</td>
<td>0.284</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.263</td>
<td>0.152</td>
</tr>
<tr>
<td>%FEV₁</td>
<td>0.413</td>
<td>0.021†</td>
</tr>
<tr>
<td>HbA₁C</td>
<td>-0.013</td>
<td>0.944</td>
</tr>
<tr>
<td>High-sensitivity CRP</td>
<td>-0.344</td>
<td>0.058</td>
</tr>
<tr>
<td>Plasma BNP levels</td>
<td>0.014</td>
<td>0.939</td>
</tr>
<tr>
<td>UAE</td>
<td>-0.011</td>
<td>0.953</td>
</tr>
<tr>
<td>Lowest SpO₂</td>
<td>-0.120</td>
<td>0.526</td>
</tr>
<tr>
<td>Appearance of ST change</td>
<td>-0.208</td>
<td>0.261</td>
</tr>
</tbody>
</table>

†p < 0.05 for Spearman's rank correlation test.
%VO₂max: percentage of predicted maximal oxygen uptake; BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; HbA₁C: glycosylated hemoglobin; CRP: C-reactive protein; BNP: brain natriuretic peptide; UAE: urinary albumin excretion; SpO₂: 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 (%FEV₁) and percentage of predicted maximal oxygen uptake (%VO₂max).

Inversely with UAE (Table 3). No correlation was found between HbA₁C and %FEV₁. HbA₁C 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 %VO₂max and/or %FEV₁ in order to determine which variables were independent determinants of %VO₂max. This analysis showed that %FEV₁ and regular exercise habits were independent determinants of %VO₂max (Table 4).

**DISCUSSION**

This study examined the association between clinical variables and %VO₂max, 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 %FEV₁, and also regular exercise habits, were independent determinants of %VO₂max. To our knowledge, this is the first report illustrating an influence of lung function on exercise capacity in patients with type 2 diabetes. Although %FEV₁ has been used as a determinant of COPD severity,\(^{22}\) this index is usually not considered in subjects with FEV₁/FVC of ≥ 70%. Even under such conditions, this study indicated that a value of %FEV₁ has clinical significance, at least in patients with type 2 diabetes.

Regular exercise habits were found to be an independent determinant of high %VO₂max. 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 VO₂ 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.\(^{20}\) 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.
We were unable to clarify the precise mechanism by which %FEV₁ influences exercise capacity in diabetic patients. In the study by Babb and colleagues, %FEV₁ correlated positively with %VO₂max and inversely with end-expiratory lung volume (EELV) at maximal exercise. An increase in EELV leads to a decrease in inspiratory capacity and dynamic hyperinflation during exercise in patients with even mild COPD. It is also known there is competition between respiratory and locomotor muscles for the supply of energy. If this association between %FEV₁ and EELV is applicable to our subjects, after taking into account that the subjects in the study by Babb and colleagues had %FEV₁ varying from mild chronic airflow limitation to above normal, whereas our subjects were all above normal, we speculate that even a mild reduction in %FEV₁ 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 %VO₂max.

Because of its high affinity for oxygen, an increase in HbA₁C is known to impair oxygen transport, resulting in decreased exercise capacity. A previous study in diabetic patients showed that HbA₁C correlated inversely with exercise capacity, and positively with skeletal muscle reoxygenation time during recovery after exercise. However, in our study, HbA₁C 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. The severity of UAE is known to be closely linked with left microvascular diabetic complications, such as UAE and the existence of retinopathy. The severity of UAE is known to be closely linked with left microvascular diabetic complications, such as UAE and the existence of retinopathy.
ventricular dysfunction in these patients. As diabetic microvascular complications result from poor glycemic control, both high HbA1c and microvascular disease may cause abnormal skeletal muscle oxygenation during exercise in diabetic patients.

In our study, UAE was not correlated with \%VO2,max but showed an inverse correlation with \%FEV1. However, as we excluded patients with overt albuminuria from the study, we cannot conclude from our results that \%FEV1 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. We speculate that another possible mechanism may explain the correlation between \%FEV1 and \%VO2,max in these patients: the decrease in \%FEV1 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 \%FEV1 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 \%FEV1 and exercise capacity in patients with type 2 diabetes. When evaluating spirometric values in patients with type 2 diabetes, a reduction in \%FEV1 should be noted even when both \%FVC and FEV1/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.

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**REFERENCES**