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Cigarette Smoking Decreases Dynamic Inspiratory Capacity during Maximal Exercise in Patients with Type 2 Diabetes

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ABSTRACT

To investigate the influence of cigarette smoking on exercise capacity, respiratory responses and dynamic changes in lung volume during exercise in patients with type 2 diabetes.

Forty-one men with type 2 diabetes without cardiopulmonary disease were recruited and divided into 28 non-current smokers and 13 current smokers. All subjects received lung function tests and cardiopulmonary exercise testing using tracings of the flow-volume loop. Exercise capacity was compared using the percentage of predicted oxygen uptake at maximal workload (%$\dot{V}O_2$max). Respiratory variables and inspiratory capacity (IC) were compared between the two groups at rest and at 20%, 40%, 60%, 80% and 100% of maximum workload.

Although there was no significant difference in lung function tests between the two groups, venous carboxyhemoglobin (CO-Hb) levels were significantly higher in current smokers. %$\dot{V}O_2$max was inversely correlated with CO-Hb levels. Changing patterns in respiratory rate, respiratory equivalent and IC were significantly different between the two groups. Current smokers had rapid breathing, a greater respiratory equivalent and a limited increase in IC during exercise.

Cigarette smoking diminishes the increase in dynamic IC in patients with type 2 diabetes. As this effect of smoking on dynamic changes in lung volume will exacerbate dynamic hyperinflation in cases complicated by chronic obstructive pulmonary disease, physicians should consider smoking habits and lung function when evaluating exercise capacity in patients with type 2 diabetes.

Key words: *Cardiopulmonary exercise testing, Cigarette smoking, Inspiratory capacity, Type 2 diabetes*

Previous epidemiological studies have demonstrated that there is a dose-response relationship between the number of cigarettes smoked per day and the incidence of type 2 diabetes, and that cessation of cigarette smoking diminishes the risk of developing this disease[27,31]. Large population-based studies have also shown that glycosylated hemoglobin (HbA_{1C}) levels were lowest in persons who had never smoked, intermediate in former smokers and highest in current smokers. These results suggest a close association between cigarette smoking and type 2 diabetes and emphasize the importance of smoking cessation for the prevention and management of type 2 diabetes[27,31]. However, in a practical clinical setting, physicians treat many diabetic patients who are unable to stop smoking.

Although aerobic exercise is an important strategy for controlling hyperglycemia in patients with type 2 diabetes[14,28,29], little is known about

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the influence of cigarette smoking on exercise capacity in these patients. In healthy subjects, cigarette smoking is known to impair exercise capacity, mainly due to an elevation in blood carboxyhemoglobin (CO-Hb) levels which reduce the oxygen carrying capacity of blood and lead to relative tissue hypoxia[7,8,12,17,19,25,26]. On the other hand, in the previous study which focused on HbA_{1C} and exercise capacity in diabetic patients, HbA_{1C} but not cigarette smoking was shown to affect exercise capacity, with HbA_{1C} levels being significantly higher in current smokers[5]. We therefore consider it is necessary to investigate precisely the influence of cigarette smoking on exercise capacity in diabetic patients.

Recent studies have demonstrated that dynamic changes in lung volume affect exercise capacity. In particular, dynamic hyperinflation in patients with chronic obstructive pulmonary disease (COPD) is considered to be a major reason for impaired exercise capacity and dyspnea on exertion[6,21,22]. Cigarette smoking increases pulmonary airway resistance leading to an increase in the oxygen cost of breathing during exercise. In addition, cigarette smoking causes mucosal swelling and bronchoconstriction, resulting in an increase in the diffusion distance of oxygen across alveolar walls and a decrease in arterial oxygen content[17,20]. Cigarette smoking therefore may have a considerable influence on respiratory responses and dynamic changes in lung volume during exercise.

On the basis of these observations, we hypothesized that cigarette smoking may affect exercise capacity in diabetic patients by influencing dynamic changes in lung volume during exercise. This study was conducted to clarify these points.

PATIENTS AND METHODS

Subject recruitment

Male patients with type 2 diabetes without diabetic complications were recruited between January and December 2004. In all subjects, HbA_{1C} was < 10% and no subject had a history of cardiopulmonary disease, such as bronchial asthma or chronic heart failure. Smoking habits were assessed by venous CO-Hb levels and responses to a questionnaire. Subjects with CO-Hb levels ≥ 3% who had continued cigarette smoking at study entry were classified as current smokers, while subjects with CO-Hb levels < 3% who had never smoked cigarettes or had stopped cigarette smoking for longer than 3 months prior to study entry were classified as non-current smokers. Subjects who had only stopped smoking within the 3-month period prior to the study were excluded from enrollment. The subjects were asked about their physical activity habits and were classified as regular exercisers if they undertook aerobic exercise continuously for longer than 30 min more than once a week.

The lung function tests were conducted in triplicate using a portable spirometer (SUPER SPIRO DISCOM-21 FXⅡ®; Chest Co., Tokyo, Japan) according to the guidelines of the American Thoracic Society[2]. The formulas developed by Baldwin[3] and Berglund[4] were used to calculate vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). Subjects with a ratio of FEV_1 to FVC (FEV_1/FVC) < 70% or a percentage of predicted VC or FVC (%VC or %FVC) < 80% were excluded from the study. All subjects were given informed consent information and the study protocol was approved by the ethics committee of Hiroshima University.

Cardiopulmonary exercise testing (CPET) and inspiratory capacity (IC) during exercise

All eligible subjects were instructed to consume a light meal and take 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. For safety, the target heart rate was set at 210-age (beats/min). Oxygen uptake ($\dot{V}O_2$) 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 a 3-min rest period, the subjects were instructed to perform an IC maneuver that consisted of deep breathing from resting expiratory level to maximal inspiratory level (Fig. 1). After a 1-min warm-up period at 10 watts per minute (W/min), the workload was increased at a slope of 20 W/min. The subjects were instructed to maintain 50 to 60 revolutions per minute (rpm). During CPET, the flow-volume loop was continuously traced breath by breath, while tidal volume (VT), respiratory rate (RR), minute ventilation ($\dot{V}E$), respiratory equivalent ($\dot{V}E/\dot{V}CO_2$), blood pressure, heart rate, percutaneous arterial oxygen saturation (SpO_2) and 12-lead electrocardiogram were recorded continuously. CPET was terminated when one of the following criteria was satisfied: 1) unable to maintain 50 rpm for any reason, 2) reached target heart rate, 3) desaturation defined as SpO_2 < 90% and 4) appearance of ischemic changes or severe arrhythmia on the electrocardiogram. Degrees of chest discomfort and leg fatigue were evaluated using the modified Borg scale[11]. Workload at the time of CPET termination was defined as maximal workload (Wmax), while $\dot{V}O_2$ at Wmax was defined as $\dot{V}O_2$max. We used the percentage of predicted $\dot{V}O_2$max (%$\dot{V}O_2$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.

Study subjects were not familiar with the IC

maneuver during incremental exercise: performing maximal breathing from the end-expiratory level. Since it is assumed that total lung capacity remains constant during exercise, we defined IC during CPET as the difference between end-expiratory level and resting maximal inspiratory level (Fig. 1)[6,21,22]. IC was calculated at 20%, 40%, 60%, 80% and 100% of Wmax and the average values of three breaths were defined as IC at each percentage of Wmax.

Statistical analysis

The data were analyzed using the SPSS for Windows statistical program (version 11.0; SPSS; Chicago, IL, USA). The data are presented as mean ± SEM. The characteristics of the two groups were compared using the Mann-Whitney U test. Repeated measure one-way analysis of variance was used to compare the responses of respiratory variables in the two groups. When there was a statistically significant difference in the responses of these respiratory variables between the groups, the Mann-Whitney U test was used to compare the difference in values at each time point. Relationships between variables were examined using Spearman's rank correlation test. A p-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Table 1 shows the baseline characteristics of the two groups. Current smokers tended to be younger than non-current smokers, although this difference was not statistically significant. There was no statistically significant difference in body mass index, duration of diabetes, exercise habits, HbA_{1C} or plasma brain natriuretic peptide levels between the groups. The Brinkmann index: average number of cigarettes smoked per day × the number of years smoked, and venous CO-Hb levels were significantly higher in current smokers.

Table 1. Patient characteristics

	Non-current smoker (n = 28)	Current smoker (n = 13)	p value
Age (years)	55.6 ± 1.6	50.3 ± 2.2	0.066
Body mass index (kg/m^2)	24.5 ± 0.7	25.5 ± 0.7	0.538
Duration of diabetes (years)	6.7 ± 0.9	7.2 ± 1.7	0.682
Regular exercise habit (yes/no)	21 / 7	9 / 4	0.772
Brinkmann index	224.8 ± 52.7	732.2 ± 97.6	<0.001
HbA_{1C} (%)	6.5 ± 0.2	6.8 ± 0.4	0.989
Brain natriuretic peptide (pg/mL)	15.4 ± 3.0	11.7 ± 3.2	0.271
Carboxyhemoglobin (%)	1.4 ± 0.1	4.9 ± 0.7	<0.001

Values are mean ± SEM.
HbA_{1C}; glycosylated hemoglobin

Lung function tests at rest

Table 2 shows the results of lung function tests at rest. The values of VC, FVC, FEV_1 and FEV_1/FVC were similar in the two groups. The values of %VC, %FVC, percentage of predicted FEV_1 (%FEV_1), expiratory flow rate at 50% of FVC ($\dot{V}_{50}$)

Table 2. Lung function test results at rest

	Non-current smoker (n = 28)	Current smoker (n = 13)	p value
VC (L)	4.1 ± 0.1	4.1 ± 0.2	0.978
%VC	116.1 ± 2.4	112.0 ± 3.9	0.385
FVC (L)	3.8 ± 0.1	3.7 ± 0.2	0.779
%FVC	107.9 ± 2.5	101.4 ± 3.5	0.085
FEV_1 (L)	3.1 ± 0.1	3.0 ± 0.2	0.758
FEV_1/FVC (%)	79.7 ± 0.9	80.2 ± 1.3	0.801
%FEV_1 (%)	106.9 ± 3.1	97.5 ± 3.1	0.098
%$\dot{V}_{50}$ (%)	83.6 ± 4.6	73.5 ± 5.8	0.327
%$\dot{V}_{25}$ (%)	54.5 ± 4.2	48.1 ± 4.9	0.385

Values are mean ± SEM.
VC; vital capacity, FVC; forced vital capacity, FEV_1; forced expiratory volume in one second, $\dot{V}_{50}$; expiratory flow rate at 50% of forced vital capacity, $\dot{V}_{25}$; expiratory flow rate at 25% of forced vital capacity

Table 3. Cardiopulmonary exercise test results at maximal workload

	Non-current smoker (n = 28)	Current smoker (n = 13)	p value
Workload (Watt)	149.5 ± 4.4	158.2 ± 6.3	0.408
$\dot{V}O_2$max (mL/kg/min)	28.8 ± 0.8	27.9 ± 0.7	0.538
%$\dot{V}O_2$max (%)	87.7 ± 2.9	80.5 ± 2.4	0.218
$\dot{V}CO_2$ (mL/min)	2229.4 ± 80.0	2322.6 ± 101.6	0.695
Heart rate (beats/min)	151.1 ± 2.9	155.3 ± 4.0	0.355
SpO_2 (%)	96.6 ± 0.4	97.2 ± 0.3	0.872
Lactate (mg/dL)	45.5 ± 3.4	45.3 ± 3.0	0.737
Borg scale			
Chest	5.0 ± 0.3	4.5 ± 0.6	0.953
Leg	5.1 ± 0.4	5.5 ± 0.5	0.518

Values are mean ± SEM.
$\dot{V}O_2$max; oxygen uptake at maximal workload, $\dot{V}CO_2$; carbon dioxide production, SpO_2; percutaneous arterial oxygen saturation

and expiratory flow rate at 25% of FVC ($\dot{V}_{25}$) were not significantly different between the groups.

CPET

Table 3 shows the results of CPET at Wmax. $\dot{V}O_2$max and %$\dot{V}O_2$max values were similar in the two groups. Workload, $\dot{V}CO_2$, heart rate, SpO_2, venous lactate levels and Borg scale at Wmax were not significantly different between the groups. Only one non-current smoker developed significant ischemic changes without chest pain.

Respiratory variables and IC during exercise

Figure 1 shows typical examples of flow-volume loop during CPET in non-current smokers and current smokers. Figure 2 shows the values of VT, RR, $\dot{V}E$, and $\dot{V}E/\dot{V}CO_2$ at each workload. VT was slightly, but not significantly higher, in the non-current smoker group during the entire exercise period (Fig. 2a). The response of RR was significantly different (Fig. 2b), with values at ≥ 40% of Wmax being significantly higher in the current smoker group. The magnitude of changes in RR from rest to Wmax (ΔRR) was significantly different between the groups (ΔRR; 16.6 ± 1.4 in non-current smokers and 24.3 ± 2.8 breaths/min in current smokers, p = 0.017). The response of $\dot{V}E$ was similar in the two groups (Fig. 2c), whereas that of $\dot{V}E/\dot{V}CO_2$ was significantly different, with the current smoker group having significantly higher $\dot{V}E/\dot{V}CO_2$ at Wmax (Fig. 2d).

Figure 3 shows the values of IC at rest and at each workload. IC values at rest were similar in the two groups: [2.5 ± 0.1 (L) in non-current smokers and 2.4 ± 0.1 (L) in current smokers, p = 0.801]. The response of IC was significantly different (Figs. 1 and 3), with IC at Wmax being significantly lower in the current smoker group. The magnitude of changes in IC from rest to Wmax (ΔIC) was significantly different between the groups (0.5 ± 0.1 L in non-current smokers and 0.2 ± 0.1 L in current smokers, p = 0.009).

Table 4. Relations between venous CO-Hb levels and respiratory variables at rest or maximal workload.

	At rest		At maximal workload		Δ each variable	
	r	p	r	p	r	p
VT	-0.135	0.399	-0.180	0.261	-0.112	0.484
RR	0.010	0.951	0.394	0.011†	0.383	0.013†
$\dot{V}E$	0.007	0.964	0.257	0.105	0.292	0.064
$\dot{V}E/\dot{V}CO_2$	0.196	0.219	0.526	<0.001†	0.082	0.608
IC	-0.076	0.636	-0.297	0.059	-0.221	0.165

†; p < 0.05
CO-Hb; carboxyhemoglobin, VT; tidal volume, RR; respiratory rate, $\dot{V}E$; minute ventilation, $\dot{V}CO_2$; carbon dioxide production, IC; inspiratory capacity, %$\dot{V}O_2$max; percent predicted of oxygen uptake at maximal workload

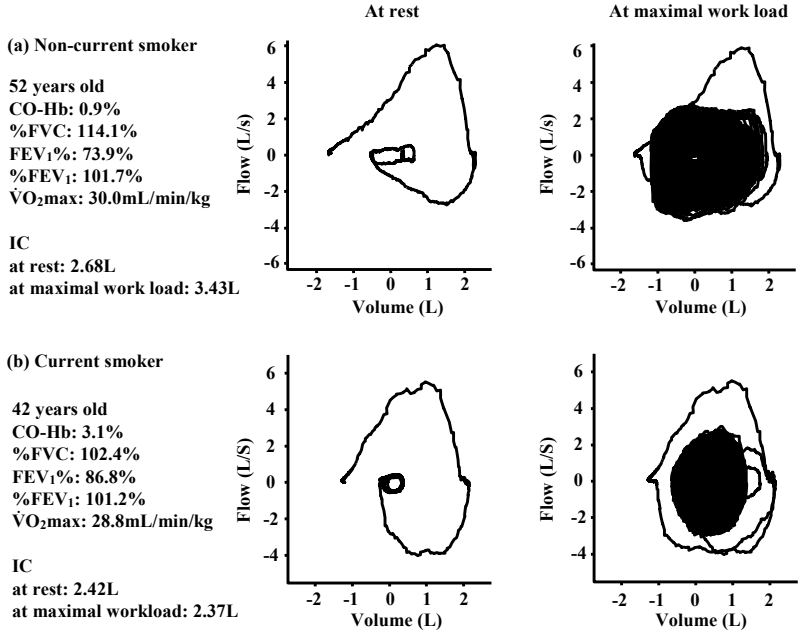

Fig. 1. Inspiratory capacity (IC) at rest and at maximal workload (Wmax) in non-current smokers (panel a) and current smokers (panel b).
A representative example of each group is shown. IC during cardiopulmonary exercise testing was defined as the difference between end-expiratory level and resting maximal inspiratory level. Current smokers had a limited increase in IC during exercise.

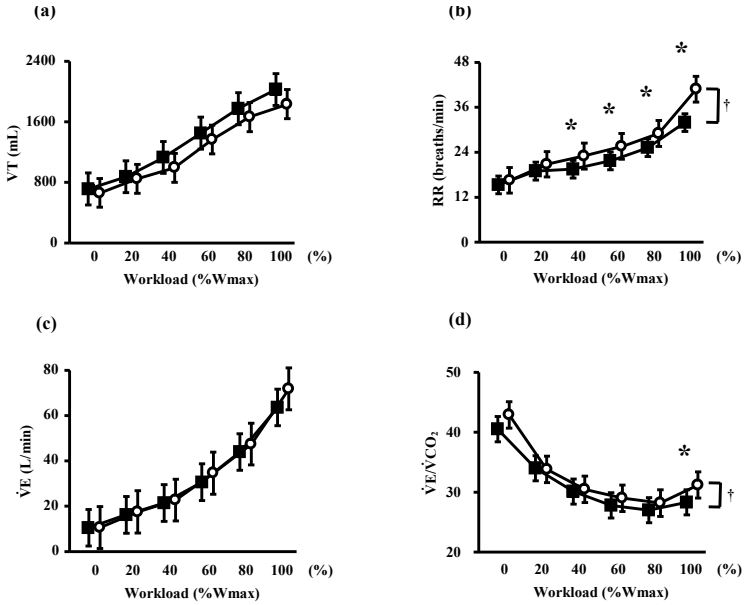

Fig. 2. The values of respiratory variables at different work loads during cardiopulmonary exercise testing (CPET) in non-current smokers (■) and current smokers (○).
Current smokers had significantly more rapid breathing (panel b; p = 0.005) and a significantly greater respiratory equivalent, suggesting a decrease in respiratory efficiency (panel d; p = 0.042).
VT, tidal volume; RR, respiratory rate; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production.
†; $p < 0.05$ in repeated measure one-way analysis of variance (ANOVA).
*; $p < 0.05$ in Mann-Whitney U test.

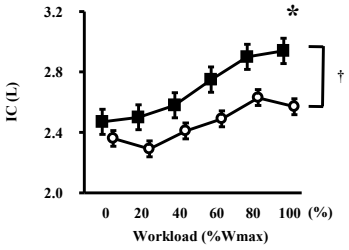

Fig. 3. The values of inspiratory capacity (IC) during cardiopulmonary exercise testing (CPET) at different work loads in non-current smokers (■) and current smokers (○). Current smokers had a limited increase in IC during exercise (p = 0.003).
†; $p < 0.05$ in repeated measure one-way analysis of variance (ANOVA).
*; $p < 0.05$ in Mann-Whitney U test.

At Wmax, there was positive correlation between $\dot{V}E/\dot{V}CO_2$ and RR, and an inverse correlation between RR and IC. IC tended to decrease with an increase in $\dot{V}E/\dot{V}CO_2$ (Figs. 4a-c).

Relationship between respiratory variables and exercise capacity and venous CO-Hb levels

We examined the correlation between venous CO-Hb levels and respiratory variables at rest and Wmax and also the magnitude of changes in these variables (Δ for each variable) (Table 4). No respiratory variable at rest correlated with CO-Hb levels. At Wmax, $\dot{V}E/\dot{V}CO_2$ and RR correlated positively with CO-Hb levels, with IC tending to decrease with increasing CO-Hb levels. There was a positive correlation between ΔRR and CO-Hb levels. $\Delta\dot{V}E$ tended to increase and ΔIC tended to

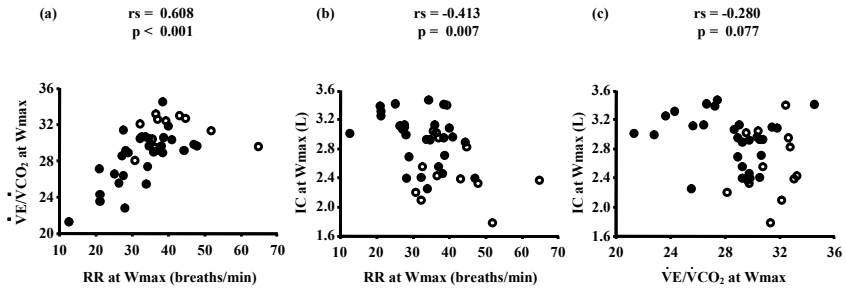

Fig. 4. The relationship between respiratory variables at maximal workload (Wmax). Closed circles (●) and open circles (○) represent non-current smokers and current smokers, respectively. There was a positive correlation between minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) and respiratory rate (RR) (panel a; rs = 0.608, $p < 0.001$), and an inverse correlation between RR and inspiratory capacity (IC) (panel b; rs = -0.413, p = 0.007). IC tended to decrease with an increase in $\dot{V}E/\dot{V}CO_2$ (panel c; rs = -0.280, p = 0.077).

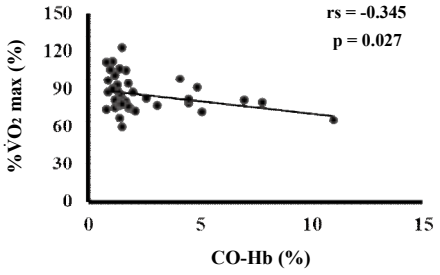

Fig. 5. The relationship between venous carboxyhemoglobin (CO-Hb) levels and the percentage of predicted oxygen uptake at maximal workload (%$\dot{V}O_2$max).
There was an inverse correlation between the two variables (rs = -0.345, p = 0.027)

decrease with increasing CO-Hb levels, although these changes were not statistically significant. Venous CO-Hb levels correlated inversely with %$\dot{V}O_2$max (rs = -0.345, p = 0.027) (Fig. 5).

DISCUSSION

As far as we are aware, this is the first report that has focused on the direct influence of cigarette smoking on both exercise capacity and dynamic changes in lung volume in patients with type 2 diabetes.

The mean venous CO-Hb levels in current smokers in our study was 4.9%, which is almost the same level reported by previous studies[10,17]. In addition,%$\dot{V}O_2$max was found to be correlated inversely with CO-Hb levels in diabetic patients, which is consistent with reports in healthy subjects[1,7-9,12,17,19,26]. The ATS guidelines define a $\dot{V}O_2$max > 84% of predicted values as normal[1]. Based on this criterion, the mean %$\dot{V}O_2$max in current smokers was lower than the normal range, whereas in non-current smokers it was within the normal range. These results suggest the importance of paying attention to smoking habits when interpreting CPET results in diabetic patients[1,7-9,12,17,19,26].

We found some differences between our findings and the results of a previous study which concluded that HbA_{1C} levels, but not cigarette smoking, affected exercise capacity in diabetic patients[5]. This discrepancy may be explained by the selection criteria of patients in our study, in which subjects with a high HbA_{1C} level were excluded.

Another new finding in the current study was that the changing patterns in RR, respiratory equivalent and IC during incremental exercise were significantly different between non-current smokers and current smokers with type 2 diabetes. Interestingly, current smokers had rapid breathing, decreased respiratory efficiency and a limited increase in IC, while lung function was similar between the two groups. Venous CO-Hb levels were associated closely with RR, $\dot{V}E/\dot{V}CO_2$ and IC at Wmax, suggesting that cigarette smoking has a marked influence on respiratory responses and dynamic changes in lung volume during exercise. Moreover, based on our finding of significant correlations between these respiratory variables at Wmax, we speculate that current smokers have physiological increases in RR during exercise in order to compensate for reduced respiratory efficiency[13,19,20]. This rapid breathing must lead to a reduction in expiratory time and a limited increase in IC during exercise.

Previous studies have shown that COPD is a risk factor for development of diabetes[24], and that diabetes is an established common co-morbidity in COPD patients[16]. Conversely, the Framingham Heart Study showed that a diagnosis of diabetes or of higher levels of fasting glucose was associated with lower levels of lung function[30]. Considering these close associations between diabetes and COPD, diabetic patients with the complication of COPD are not a rare population. Since dynamic hyperinflation and a decrease in IC are known to occur during exercise even in patients with stage I COPD, ($FEV_1/FVC < 70\%$ and $\%FEV_1 \geq 80\%$)[23], cigarette smoking must play an additional role in the dynamic hyperinflation and deterioration of exercise capacity in diabetic patients with the complication of COPD.

We recognize a number of limitations in our study. Firstly, the number of patients in the study group, especially the current smoking group, was too small to show a statistically significant difference in %$\dot{V}O_2$max between the two groups. Secondly, the study population was limited to male patients with type 2 diabetes and therefore it remains to be established whether the results are applicable to non-diabetic and female subjects. Thirdly, we could not evaluate the diffusing capacity of the lung for carbon monoxide (DLco), which is well known to be reduced in diabetic patients[15]. A reduction in DLco would lead to a ventilation-perfusion mismatch and an increase in RR during exercise[18]. Finally, as this study was a cross sectional investigation, the effect of smoking cessation on exercise capacity and respiratory responses could not be analyzed. Further studies are therefore required to clarify these points.

In conclusion, we found that cigarette smoking not only impairs exercise capacity but also diminishes increases in IC during incremental exercise in patients with type 2 diabetes. Since this effect of smoking on dynamic change in lung volume must exacerbate dynamic hyperinflation and lead to further impairment of exercise in cases complicated by COPD, physicians should consider smoking habits and lung function when evaluating exercise capacity in patients with type 2 diabetes.

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

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