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Influence of glycemic control on pulmonary function and heart rate in response to exercise in subjects with type 2 diabetes mellitus

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Abstract

Conflicting results exist regarding the impact of glycemic control on peak oxygen uptake ($\dot{V}O_2$peak) in subjects with type 2 diabetes mellitus. The influence of glycemic control on submaximal oxygen uptake ($\dot{V}O_2$) in these subjects is unknown. The aim of this study was to evaluate the impact of fasting blood glucose (FBG) (short-term glycemic control) and glycated hemoglobin (HbA_{1c}) (long-term glycemic control) on submaximal $\dot{V}O_2$ and $\dot{V}O_2$peak during exercise in subjects with type 2 diabetes mellitus without cardiovascular disease. FBG and HbA_{1c} levels and exercise tolerance in 30 sedentary men with type 2 diabetes mellitus treated with oral hypoglycemic agents and/or diet were evaluated. $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), heart rate, pulmonary ventilation ($\dot{V}E$), and the respiratory exchange ratio (RER) were measured throughout the exercise protocol. Subjects were separated into 2 groups of the same age, weight, and body mass index according to median FBG and HbA_{1c} levels (6.5 mmol/L and 6.1%, respectively). Per protocol design, there was a significant difference in FBG and HbA_{1c} levels ($P < .001$), but not for age, weight, or body mass index. There was no significant difference in peak exercise parameters between the 2 groups according to median FBG or median HbA_{1c} levels. However, the subjects with elevated HbA_{1c} level had lower submaximal $\dot{V}E$ throughout the exercise protocol ($P < .03$), and the subjects with elevated FBG concentration had a blunted heart rate pattern during submaximal exercise ($P < .03$). Although relatively small abnormalities in the control of glycemia do not affect $\dot{V}O_2$peak in subjects with type 2 diabetes mellitus without cardiovascular disease, they may influence pulmonary function and the chronotropic response during submaximal exercise in these subjects.

1. Introduction

It is well known that peak exercise capacity in subjects with type 2 diabetes mellitus without cardiovascular disease is reduced compared with that in nondiabetic subjects [1,2]. There is evidence that the capacity to perform submaximal exercise is also abnormal. Attenuated oxygen uptake ($\dot{V}O_2$) in response to incremental exercise and slower $\dot{V}O_2$ kinetics compared with control subjects have been observed [1-3]. Abnormalities related to cardiac output, arteriovenous oxygen difference, and skeletal muscle metabolism have been associated with these altered exercise responses in patients with diabetes [4,5]. However, the underlying pathophysiologic process responsible for these limitations is unknown. Because reduced exercise capacity during submaximal exercise may limit daily life activities in diabetic subjects without cardiovascular disease, understanding of the underlying mechanism would be therapeutically relevant.

Adequate control of blood glucose is an important feature in the management of type 2 diabetes mellitus. Indeed, hyperglycemia is deleterious on several levels: it is associated with (1) endothelial dysfunction [6], (2) increased formation of advanced glycation end products altering the structure and function of molecules in several biologic systems [6-10], (3) altered cardiomyocyte bioenergetics [8], (4) abnormalities in pulmonary function [11], and (4) cardiovascular autonomic neuropathy [12]. However, results of studies evaluating whether glycemic control affects exercise tolerance in patients with type 2 diabetes mellitus are conflicting [2,13-16]. Hyperglycemia appears to have a negative impact on important parameters associated with the regulation of oxygen transport and utilization [11,17-21]. The influence of less than optimal glycemic control on the systemic oxygen transport during exercise responses and on

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the modulation of the submaximal oxygen uptake ($\dot{V}O_2$), pulmonary ventilation ($\dot{V}E$), and heart rate (HR) during exercise have not been investigated.

The aims of the present study were to evaluate the impact of fasting blood glucose (FBG), which reflects short-term glycemic control, and HbA_{1c}, reflecting long-term glycemic control, on submaximal $\dot{V}O_2$ and peak $\dot{V}O_2$ ($\dot{V}O_2$peak) during exercise in subjects with type 2 diabetes mellitus without known cardiovascular disease. We hypothesized that less than optimal glycemic control would be associated with reduced submaximal and maximal exercise capacity in this population.

2. Materials and methods

2.1. Study population

Thirty sedentary men with type 2 diabetes mellitus were consecutively recruited for this study. All subjects were treated with oral hypoglycemic agents and/or diet. No subjects were on insulin. Exclusion criteria were the presence of cardiovascular disease documented from a symptom-limited exercise protocol before enrolment in the present study, a documented office blood pressure greater than 140/90 mm Hg, and the presence of clinically significant comorbidities related to diabetes, ie, renal failure (creatinine level greater than normal upper limit), macroalbuminuria, proliferative retinopathy, and clinically significant sensitive, motor, or autonomic neuropathies. The study was approved by the local hospital ethics committee in accordance with the Helsinki declaration; all subjects gave signed informed consent.

2.2. Blood sampling

On subjects' arrival at the laboratory, an 18-gauge polyethylene catheter was inserted into a forearm vein for blood sampling. For the measurement of FBG and HbA_{1c} levels, blood samples were drawn with the subjects at rest after fasting for at least 8 hours and 30 minutes before the exercise protocol. FBG was assayed by using the hexokinase method (Roche Diagnosis, Indianapolis, IN). HbA_{1c} was assayed by ion-exchange high-performance liquid chromatography method (Bio-Rad, Hercules, CA).

Table 1
Baseline characteristics of the groups according to median HbA_{1c} level

	<6.1%	>6.1%	*P*
n	15	15	–
Age (y)	54 ± 11	54 ± 7	.53
Height (cm)	175 ± 6	171 ± 7	.14
Weight (kg)	93 ± 10	92 ± 18	.65
BMI (kg/m^2)	30 ± 4	31 ± 5	.68
Resting HR (beats/min)	75 ± 16	76 ± 10	.84
Resting SBP (mm Hg)	136 ± 14	130 ± 14	.30
Resting DPB (mm Hg)	85 ± 5	84 ± 9	.77

BMI indicates body mass index; SBP, systolic blood pressure; DPB, diastolic blood pressure.

Table 2
Peak exercise capacity parameters of the groups according to median HbA_{1c} level

	<6.1%	>6.1%	*P*
Total work (W)	188 ± 35	179 ± 34	.50
Exercise duration (s)	771 ± 131	763 ± 123	.60
HR (beats/min)	163 ± 19	162 ± 17	.69
SBP (mm Hg)	223 ± 30	206 ± 24	.11
DPB (mm Hg)	92 ± 15	98 ± 13	.32
$\dot{V}O_2$peak (mL kg^{-1} min^{-1})	29.6 ± 4.3	27.7 ± 5.4	.27
$\dot{V}O_2$peak (L/min)	2.75 ± 0.52	2.49 ± 0.44	.16
$\dot{V}E$max (L/min)	118 ± 22	103 ± 30	.12
RER	1.17 ± 0.08	1.18 ± 0.09	.62
RPP (mm Hg beats min^{-1})	36976 ± 7439	33418 ± 5515	.17
$\dot{V}E/\dot{V}O_2$	40.8 ± 4.0	40.2 ± 9.2	.56
$\dot{V}E/\dot{V}CO_2$	35.5 ± 3.6	34.5 ± 6.3	.55
Oxygen pulse (mL/beat)	16.8 ± 2.5	15.2 ± 2.5	.10

$\dot{V}E$max indicates maximal minute ventilation; RPP, rate pressure product; $\dot{V}E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

2.3. Exercise protocol

Exercise tolerance was evaluated for each subject by using an incremental protocol of 15 W/min after a warm-up period of 1 minute at 15 W, and 2 minutes at 30 W, performed on an electromagnetically braked cycle ergometer (Corival, Lode, Netherlands) at a pedaling rate of 50 to 70 rpm. Expired air was continuously recorded on a breath-by-breath basis for the determination of $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), $\dot{V}E$, and the respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$). The HR was obtained from electrocardiographic monitoring. Blood pressure was measured every 2 minutes by using an automated

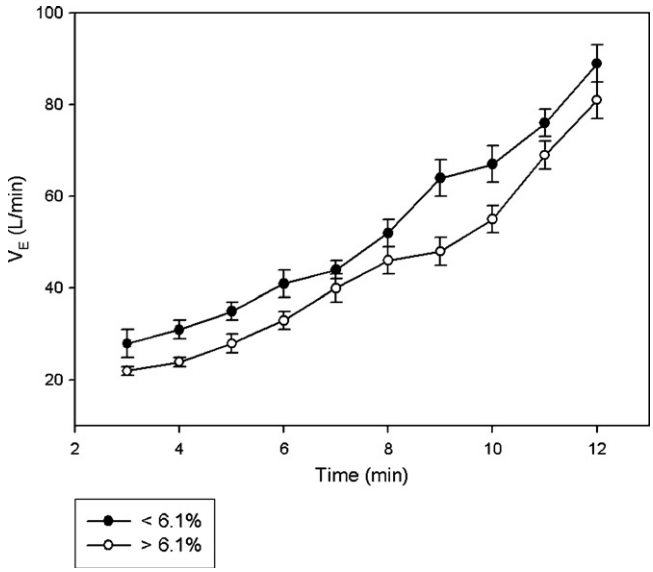

Fig. 1. Influence of HbA_{1c} level on submaximal pulmonary ventilation in response to exercise in subjects with and without optimal long-term glycemic control. $\dot{V}E$ indicates pulmonary ventilation. All $P < .0001$ between subjects with optimal long-term glycemic control vs subjects without optimal control.

sphygmomanometer with a headphone circuit option (Model 412, Quinton Instrument, Bothell, WA). The specific submaximal exercise variables analyzed were the $\dot{V}O_2$, HR, and $\dot{V}E$. Submaximal data were analyzed between the 3rd and 12th minute of the incremental exercise protocol. The 3rd minute was chosen because before 3 minutes, the protocol was considered as a warm-up period, and the 12th minute was chosen because most subjects were able to achieve the workload associated with this time. $\dot{V}O_2$peak was defined as the mean $\dot{V}O_2$ recorded in the last 15 seconds of the incremental exercise protocol concurrent with an RER of 1.15 or greater. The exercise protocol was always performed in the fasting state at the same time of the day and at 20°C room temperature. The subjects were then divided into 2 groups according to the median FBG and HbA_{1c} levels.

2.4. Statistical analysis

A crossed-nested design and a Student unpaired *t* test were used to evaluate submaximal and peak exercise parameter differences, respectively, between the subjects. The Mann-Whitney test was used for data not normally distributed. The Tukey test was used for post hoc analysis. When appropriate, Pearson correlation was used for the analysis of associations between variables. All data are presented as mean ± SD unless otherwise specified. A *P* value less than .05 was considered statistically significant. Data were analyzed by using the statistical software packages SigmaStat (SPSS, Chicago, IL) and SAS (SAS Institute, Cary, NC).

3. Results

Table 1 presents baseline characteristics according to HbA_{1c} level. As per study design, HbA_{1c} level was significantly different between the groups (5.7% ± 0.3% vs 6.9% ± 0.2%; $P < .001$). There was no other statistical difference in the anthropometric data between groups. FBG concentration was higher in the group with elevated HbA_{1c} level (7.5 ± 1.3 vs 5.9 ± 1.0 mmol/L; $P < .001$).

Results from the evaluation of peak exercise tolerance are presented in Table 2. There was no significant difference in $\dot{V}O_2$peak between the groups, nor was there a statistical difference in the other exercise tolerance parameters between the groups. There was no significant relation between HbA_{1c} level and peak exercise tolerance parameters. Specific submaximal exercise variables, ie, $\dot{V}O_2$, HR, and $\dot{V}E$, were also compared. There was no significant difference between groups in submaximal $\dot{V}O_2$ and HR responses. However, subjects with elevated HbA_{1c} levels had lower submaximal $\dot{V}E$ throughout the exercise protocol ($P < .03$) (Fig. 1).

Table 3
Baseline characteristics of the groups according to median FBG level

	<6.5 mmol/L	>6.5 mmol/L	*P*
n	15	15	–
Age (y)	54 ± 11	54 ± 7	.76
Height (cm)	175 ± 6	172 ± 7	.24
Weight (kg)	94 ± 13	90 ± 16	.50
BMI (kg/m^2)	31 ± 4	31 ± 4	.86
Resting HR (beats/min)	73 ± 14	78 ± 11	.31
Resting SBP (mm Hg)	132 ± 12	134 ± 16	.74
Resting DPB (mm Hg)	86 ± 6	82 ± 11	.21

Table 4
Peak exercise parameters observed in the groups according to median FBG level

	<6.5 mmol/L	>6.5 mmol/L	*P*
Total work (W)	189 ± 33	183 ± 33	.53
Exercise duration (s)	781 ± 122	753 ± 130	.59
HR (beats/min)	163 ± 18	159 ± 21	.56
SBP (mm Hg)	211 ± 26	217 ± 30	.57
DPB (mm Hg)	92 ± 15	98 ± 13	.31
$\dot{V}O_2$peak (mL kg^{-1} min^{-1})	29.3 ± 3.9	28.1 ± 5.8	.52
$\dot{V}O_2$peak (L/min)	2.71 ± 0.57	2.49 ± 0.44	.24
$\dot{V}E$max (L/min)	118 ± 25	103 ± 27	.13
RER	1.18 ± 0.09	1.17 ± 0.08	.80
RPP (mm Hg beats min^{-1})	34793 ± 5513	35445 ± 7732	.80
$\dot{V}E/\dot{V}O_2$	41.0 ± 5.3	40.1 ± 8.4	.74
$\dot{V}E/\dot{V}CO_2$	35.6 ± 4.0	34.6 ± 6.0	.62
Oxygen pulse (mL/beat)	16.6 ± 3.0	15.9 ± 3.4	.52

Table 3 presents baseline characteristics according to FBG level. As per study design, FBG concentration was significantly different between the groups (5.6 ± 0.8 vs 7.7 ± 1.0 mmol/L; $P < .001$). There was no other statistical difference in the anthropometric data between groups. As expected, HbA_{1c} level was higher in the group with elevated FBG level (6.7% ± 1.0% vs 5.9% ± 0.5%; $P < .01$).

Results from the evaluation of peak exercise tolerance are shown in Table 4. There was no difference in $\dot{V}O_2$peak between the groups, nor were there any statistical differences in the other peak exercise parameters. As for the groups compared according to HbA_{1c} level, we analyzed specific submaximal data between the 3rd and the 12th minute of the

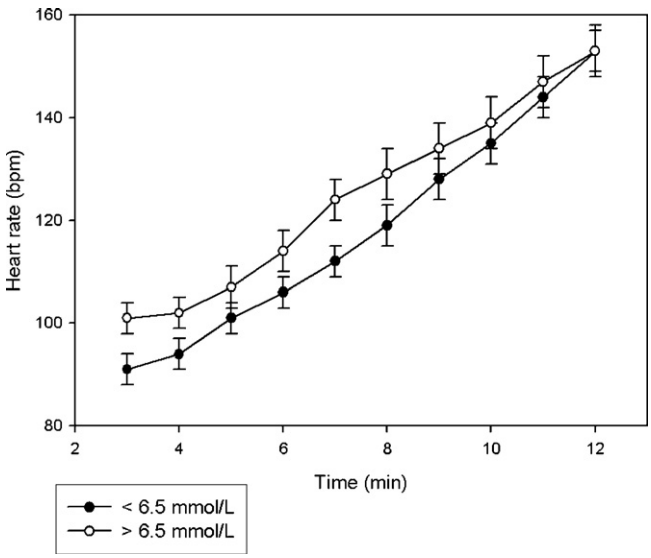

Fig. 2. Influence of FBG concentration on submaximal HR in response to exercise in subjects with and without optimal short-term glycemic control.

peak exercise protocol. There was no significant difference between groups in submaximal $\dot{V}O_2$, HR, and $\dot{V}E$. However, the group with higher FBG levels had an attenuated HR response to exercise compared with the group with lower FBG levels ($P < .03$) (Fig. 2).

4. Discussion

The principal findings of this study in subjects with type 2 diabetes mellitus without cardiovascular disease are the following: (1) relatively small abnormalities in short- and long-term glycemic control do not affect $\dot{V}O_2$peak; (2) higher HbA_{1c} level is associated with altered pulmonary function, characterized by a reduced $\dot{V}E$ response during submaximal exercise; and (3) higher FBG concentration is associated with a negative impact on the HR increase in response to incremental exercise.

4.1. Peak exercise tolerance

The literature examining the association between hyperglycemia and exercise tolerance in subjects with type 2 diabetes mellitus have conflicting results. To our knowledge, 5 studies did not observe any significant relationship between blood glucose control and exercise capacity [2,13,22-24], whereas 2 studies did [14,15]. In our study, we did not observe a significant correlation between HbA_{1c} level and $\dot{V}O_2$peak, or FBG level and $\dot{V}O_2$peak. Specific patient characteristics might account for these discordant findings. First, our subjects had a lower mean FBG level compared with subjects studied by Vanninen et al [15] (6.9 ± 1.7 vs 8.6 ± 0.7 mmol/L). Thus, the blood glucose control of our subjects was better than that of the subjects in the latter study [15]. Important differences in baseline and clinical characteristics such as hypertension, gender distribution, and smoking status also exist between our subjects and those studied by Demir et al [14]. Furthermore, when we specifically compared our groups of subjects according to median HbA_{1c} and median FBG levels, there was no difference in $\dot{V}O_2$peak. These results might be explained by the fact that although HbA_{1c} and FBG were statistically different between our groups, these differences were not abnormal enough to significantly affect $\dot{V}O_2$peak. However, even if inadequate control of blood glucose does not alter $\dot{V}O_2$peak, it does not rule out the possibility that less than optimal glycemic control might alter parameters related to exercise capacity during submaximal exercise.

4.2. Chronic hyperglycemia

The subjects with higher HbA_{1c} levels had reduced $\dot{V}E$ during submaximal exercise compared with subjects with better-controlled long-term glycemia. The link between hyperglycemia and $\dot{V}E$ is unclear. However, long-term hyperglycemia might have repercussions on lung structures and pulmonary function. Indeed, in their cohort of patients with type 2 diabetes mellitus, Davis et al [11] observed that blood glucose exposure was related to reduced pulmonary function. This observation might be explained by several changes in the lungs in response to chronic higher blood glucose exposure. Patients with diabetes have been found to have glycated proteins such as collagen in their chest wall and/or their pulmonary tree [25,26], a thickening of the basal lamina [27], and fibrosis [28]. Hence, the reduced $\dot{V}E$ during submaximal exercise in our subjects with higher HbA_{1c} levels may be related in part to a direct negative impact of long-term hyperglycemia on lung structures. In addition, subjects with type 2 diabetes mellitus have altered control of breathing that might have a negative impact on exercise hyperpnea. Indeed, a blunted $\dot{V}E$ response to a hypoxic stimulus, suggesting an altered peripheral chemoreflex, has been observed in these subjects, probably related to an altered breathing pattern [29]. Diabetes is also known to have a deleterious impact on groups III and IV nerve fibers [30]. This could lead to an altered feedback from muscle afferences, namely, ergoreceptors (mechanoreceptors and/or metaboreceptors), which are usually sending important reflex signals to the cardiovascular and the respiratory control centers to support chronotropic, ventilatory, and appropriate vasoconstrictive responses during exercise.

4.3. Acute hyperglycemia

The impact of FBG concentration on exercise tolerance parameters and, specifically, the submaximal HR response in subjects with type 2 diabetes mellitus is not well defined. Correction of acute hyperglycemia after a 3-month diet is associated with improved exercise tolerance in obese patients with type 2 diabetes mellitus [31]. Other studies have observed an inverse correlation [15] or the absence of correlation [2] between FBG concentration and maximal exercise performance in these patients. Nevertheless, a lower submaximal HR response during exercise was actually noted in patients with diabetes compared with healthy controls [32]. In the present study, we have observed a significant (group by step increment) interaction difference when the groups were separated according to median FBG level. The HR response to exercise is regulated by several factors [33]. Indeed, the autonomic nervous system, through sympathetic and vagal activity conducted to innervated fibers of the heart and the sinoatrial node, the activity of afferent receptors (ie, baroreflex, chemoreflex, and Bainbridge reflex), the catecholamines, and the intrinsic HR are important contributors to the regulation of HR [33]. The alteration of one or more of these parameters is thus likely to contribute to a reduced submaximal HR response during exercise. Subjects with type 2 diabetes mellitus are known to have reduced baroreflex sensitivity [34] that may be related to an abnormal chronotropic response. Fukuma et al [35] studied 2 groups of patients with heart disease separated according to baroreflex sensitivity and observed a significant reduction in HR increment in the group with a lower baroreflex sensitivity. Hence, the slower HR increment in subjects with elevated FBG level could be the result of

reduced baroreceptor sensitivity related to glucose exposure or to the presence of hyperinsulinemia [36].

Impaired exercise capacity is associated with cardiac autonomic dysfunction in subjects with type 2 diabetes mellitus. Subclinical autonomic dysfunction has been shown to be present early after the diagnosis of type 2 diabetes mellitus [37,38]. The development of an autonomic neuropathy can lead to alterations of autonomic fibers innervating the blood vessels and heart, inducing abnormal HR control and vascular dynamics [39,40]. One of the clinical manifestations of cardiac autonomic neuropathy is exercise intolerance, probably through a reduced response in HR and blood pressure during exercise [41]. Hence, an alteration of autonomic nervous pathways might be implicated in the blunted HR response during submaximal exercise in our group of subjects with less than optimal short-term glycemic control.

The principal limitation of the present study is the absence of a control group without diabetes. However, an important goal of this study was to investigate submaximal and maximal exercise tolerance in the presence of small changes in short- and long-term glycemic control. Consequently, the groups with FBG levels less than 6.5 mmol/L and HbA_{1c} level less than 6.1% could be considered control subjects because it was our aim to evaluate the impact of less than optimal glycemic control on exercise tolerance parameters in these subjects with diabetes. In addition, even if all subjects were carefully screened in light of our inclusion and exclusion criteria, we cannot rule out the possibility that the differences we observed were related to the presence of a more important insulin-resistant state, left ventricular diastolic dysfunction, and/or subclinical symptoms of cardiac autonomic neuropathy [38,42].

5. Conclusion

The results of this study suggest that relatively small abnormalities in glycemic control might not impact $\dot{V}O_2$peak in subjects with type 2 diabetes mellitus without cardiovascular disease. However, less than optimal glycemic control seems to influence pulmonary function and the chronotropic response during submaximal exercise in these subjects.

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