Does the coefficient of variation of the R-R intervals in diabetic patients and healthy subjects reflect the cardiovascular response during exercise?

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Key words : 1. diabetes mellitus 2. diabetic neuropathy 3. cardiovascular response

OBJECTIVE: We investigated the relation of the coefficient of variation of the R-R intervals in diabetic patients and healthy subjects, and the cardiovascular responses during exercise. **RESEARCH DESIGN AND METHOD:** The subjects were 8 males with type 2 diabetes mellitus, and 8 age-matched healthy non-diabetic males (healthy controls). All subjects performed an incremental test on a bicycle ergometer at a work rate of 15 Watt•min^{-1} to determine the maximum oxygen uptake and to calculate ventilatory threshold. Subsequently, on another day, they all performed a constant-load exercise at a work rate chosen to elicit an oxygen uptake equivalent to 80% of their individual the ventilatory threshold. The coefficient of variation of the R-R intervals (CV_{R-R}) was calculated from the electrocardiogram at rest and used as an index of autonomic nerve function. The time constant (tau) and steady state level of the kinetic response for oxygen uptake ($\dot{V}O_2$) and heart rate (HR) were calculated using a mono-exponential model under constant-load exercise. **RESULTS:** 1) CV_{R-R} and $\dot{V}O_2max$ were significantly lower in the diabetic patients than in the healthy controls. Tau HR and tau $\dot{V}O_2$ were significantly longer in the diabetic patients than in the healthy controls. 2) Tau $\dot{V}O_2$ and tau HR were significantly positively correlated in both groups, whereas CV_{R-R} and tau HR, and tau $\dot{V}O_2$ were significantly negatively correlated in both groups. 3) $\dot{V}O_2max$ and tau HR, and tau $\dot{V}O_2$ were significantly negatively correlated only in the healthy controls. **CONCLUSIONS:** These results suggest that CV_{R-R} may reflect the characteristics of cardiovascular responses to exercise. However, though some previous studies have postulated that these characteristics of cardiovascular responses to exercise reflect cardiorespiratory endurance in healthy controls, our study confirmed no such correlation in diabetic patients.

Introduction

It has been reported that diabetic patients exhibit abnormalities in reaction to exercise, such as heart rate (HR) kinetics [9)], oxygen uptake ($\dot{V}O_2$) kinetics [3)], and increase in stroke volume and blood pressure [13)] as compared to healthy individuals. Furthermore, lowered cardiorespiratory endurance capacity compared to healthy individuals is also observed[5, 18)]. As well, complications of autonomic neuropathy occur in diabetic patients[6, 15)]. Autonomic neuropathy or other complications may be considered to be participating in the abnormal cardiovascular response during exercise by diabetic patients, however; this has not been definitively demonstrated. Although several previous studies have investigated the correlation between cardiorespiratory endurance capacity and the characteristics of oxygen uptake kinetic responses to exercise in healthy subjects and patients with heart or respiratory failure [4, 11)], there are still virtually no studies involving patients with diabetes mellitus. Meanwhile, an

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attempt to evaluate the parasympathetic nerve activity using CVR-R as an evaluation of the autonomic nerve in diabetic patients has been proposed by Wheeler and Watkins[22]. On the other hand, there is also a report that it is difficult to use information from CVR-R alone to estimate parasympathetic nerve activity[17]. However, there are some reports that CVR-R is useful for making an indirect and overall assessment of the reflex function of the parasympathetic nerve activity[8, 21]. Therefore, CVR-R is often used clinically as a simple method of examining autonomic nervous function, such as in diabetic neuropathy[7, 14, 15]. Hence, this study postulated the hypothesis that autonomic nerve activity of the living matter, which is observed indirectly, is reflected in the response of the heart rate and oxygen uptake response at the beginning of exercise, and is aimed to observe the characteristics of the cardiovascular response at the beginning of exercise in diabetic patients and healthy controls.

Method

Subjects

Subjects were eight patients from Yoshijima Hospital with type 2 diabetes. A control group of eight healthy subjects, who had no obvious history of diabetes mellitus, were age-matched to the diabetic patients (Table 1).

Table 1. Subject characteristics

		Diabetic subjects (n=8)	Healthy controls (n=8)	
Age	(years)	59.8 ± 8.3	54.0 ± 4.6	N.S.
Height	(cm)	168.4 ± 6.8	169.1 ± 9.0	N.S.
Weight	(kg)	67.8 ± 10.8	67.1 ± 8.2	N.S.
Body mass index	(kg/m^2)	23.8 ± 3.3	23.4 ± 2.5	N.S.
Blood sugar	(mg/dl)	181.1 ± 40.6	———	
HbA1c	(%)	7.8 ± 1.9	———	
Duration of diabetes	(years)	6.6 ± 9.3	———	

Values are mean ± S.E. N.S. : no significant difference

A. Subject demographics

Age, height, weight and body mass index (BMI) of the subjects in the two groups were recorded. The duration of diabetes, fasting blood sugar level, and glycosylated hemoglobin (HbA1c) level of subjects with diabetes mellitus were extracted from their medical records. The duration of diabetes was determined to be from the initiation of medical treatment for diabetes mellitus to the time of enrollment in the exercise program at Yoshijima Hospital, and was expressed in years.

B. Experimental measurements and analysis

The purpose of the measurements and the study was fully explained to the subjects before starting, and measurements were only conducted after informed consent was obtained. None of the subjects were taking beta-blockers.

1. Exercise tolerance test

All subjects performed incremental exercise tests at a work rate of 15-watt・min^{-1} on an electromagnetically braked bicycle ergometer (aerobike 232c-XL, Combi Inc., Tokyo, Japan). The number of pedal rotations was 50 revs・min^{-1}. When HR reached the target number of beats [(210-age)×85%], the loading was stopped. $\dot{V}O_2$ was measured with the subject at rest, seated on the ergometer, and throughout the exercise period, using an Aeromonitor AE-280S (Minato Medical Science Inc., Osaka, Japan)[19]. This system consists of a microcomputer, a hot-wire flow meter, and oxygen and carbon dioxide gas analyzers (zirconium element-based oxygen analyzer and infra-red carbon dioxide analyzer). Gas was sampled at the rate of 220 mL・min^{-1} through a filter by a suction pump through the analyzers. The Aeromonitor AE-280S calculated the breath-by-breath $\dot{V}O_2$ based on the mathematical analysis described by Beaver[1]. The system was calibrated before each study. Electrocardiogram and HR were monitored with an electrocardiograph (DS-3140, Fukuda Denshi Co., LTD, Tokyo, Japan). A linear regression formula was calculated from the relationship between the oxygen intake ($\dot{V}O_2$) and HR using the least squares method. Predicted maximum HR [(210-age)×85%] was substituted into this formula, and the estimated maximum oxygen uptake ($\dot{V}O_2max$) was computed. Ventilatory threshold (VT) was computed by the V-slope method[2] using the values for the oxygen intake and carbon dioxide output obtained during the incremental exercise test.

2. Six minutes constant-load test

Aside from the exercise tolerance test, a constant-load exercise for 6 minutes was conducted at an exercise intensity of 80 % of VT with subjects who had shown no abnormalities in their electrocardiogram.

C. Method of Analysis

1. Calculation of coefficient of variation of R-R intervals (CVR-R).

Electrocardiogram data recorded during supine resting was converted from 12-bit Analog to digital (AD12-8PM, CONTEC Ltd., Tokyo, Japan) with sampling frequency 250 Hz, and stored in a personal computer (Think Pad 390, IBM, Tokyo, Japan). The positions of the R wave peaks in the stored data were identified by waveform recognition, and then 100 consecutive R-R intervals were analyzed by the MemCalc method[16]. The average value (M) of an R-R interval and standard deviation (SD) were determined from this analysis, and the coefficient of variation was computed using the following formula:

$CV_{R\text{-}R}$ (%) = SD/M×100.

2. Calculation of time constants (tau $\dot{V}O_2$, tau HR)

For smoothing the values from breath-by-breath recording for an analysis of the $\dot{V}O_2$ kinetics, we determined a moving average for every 9 breaths, and found the exponential function, which most approximated the curve, showing the $\dot{V}O_2$ kinetics at the time of the 6 minutes constant-load exercise began. By using this, the time constant (τ) and steady-state level of the kinetic response for $\dot{V}O_2$ were calculated using a mono-exponential model under constant-load exercise[12, 20] (Fig. 1A).

$$Y(t) = \Delta \dot{V}O_2(0) \times \{1-e(-(t-TD)/\tau)\} + \dot{V}O_2(1)$$

Tau HR at the beginning of exercise onset was computed using the following formula: (Fig. 1B).

$$Z(t) = \Delta HR(0) \times \{1-e(-(t-TD)/\tau)\} + HR(1)$$

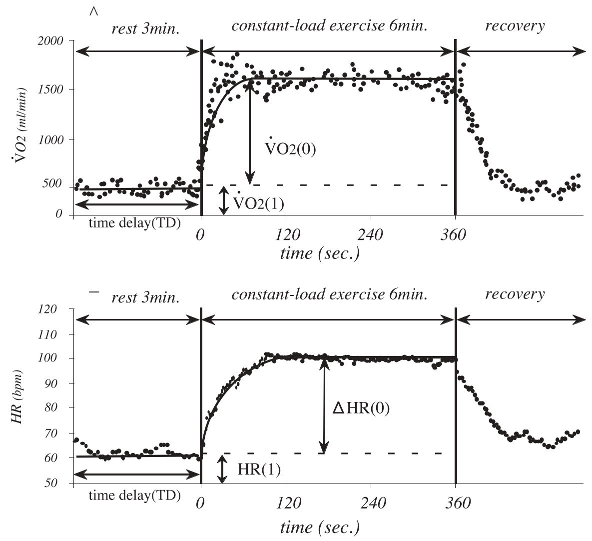

Fig. 1. Schematic illustration of the calculation of the tau $\dot{V}O_2$ (A), and tau HR (B).

3. Statistical processing

Data were expressed as mean ± standard error. Unpaired t-test was used for comparison of $CV_{R\text{-}R}$, tau $\dot{V}O_2$, tau HR, and $\dot{V}O_2$ max between the diabetes mellitus patients and healthy controls. Further correlations between $CV_{R\text{-}R}$, tau $\dot{V}O_2$, tau HR and $\dot{V}O_2$max of the groups were analyzed using Pearson's single correlation coefficient test. Statistics software Stat View 5.0J (SAS Institute Inc., Berkeley, CA, USA) was used for the statistical processing. All statistical significance levels were set at less than 5%.

Results

1) $CV_{R\text{-}R}$ and $\dot{V}O_2$max were significantly lower in the diabetic patients than in the healthy controls (Table 2). Tau $\dot{V}O_2$ and tau HR were significantly longer in the diabetic patients than in the healthy controls (Table 3). 2) Tau $\dot{V}O_2$ and tau HR were significantly positively correlated in both groups, whereas $CV_{R\text{-}R}$ and tau $\dot{V}O_2$, and tau HR were significantly negatively correlated in both groups (Table 4). 3) $\dot{V}O_2$max and tau HR, and tau $\dot{V}O_2$ were significantly negatively correlated only in the healthy controls (Table 4).

Table 2. Coefficient of variation of the R-R intervals and maximum oxygen uptake

	Diabetic subjects (n=8)	Healthy controls (n=8)
$CV_{R\text{-}R}$ (%)	2.3 ± 1.3	4.1 ± 1.8*
$\dot{V}O_2$max (ml/min・kg^{-1})	23.7 ± 3.4	26.6 ± 1.7*

Values are mean ± S.E. *p < 0.05 for difference between the group with diabetic subjects and the healthy controls.

Table 3. Oxygen uptake and heart rate kinetics during constant-load test

	Diabetic subjects (n=8)	Healthy controls (n=8)
τHR (sec.)	69.5 ± 2.2	60.1 ± 3.5*
τ$\dot{V}O_2$ (sec.)	80.9 ± 5.3	67.9 ± 2.5*

Values are mean ± S.E. *p < 0.05 for difference between the group with diabetic subjects and the healthy controls.

Table 4. Relation of each parameter in the diabetic subjects and healthy controls

	Diabetic subjects (n=8)	Healthy controls (n=8)
$CV_{R\text{-}R}$ (%) V.S. τ$\dot{V}O_2$ (sec.)	r = -0.802 (p <0 .05)	r = -0.714 (p < 0.05)
$CV_{R\text{-}R}$ (%) V.S. τHR (sec.)	r = -0.896 (p < 0.05)	r = -0.922 (p <0 .05)
τ$\dot{V}O_2$ (sec.) V.S. τHR (sec.)	r = 0.829 (p < 0.05)	r = 0.791 (p < 0.05)
τHR (sec.) V.S. $\dot{V}O_2$max (ml/min・kg^{-1})	N.S.	r = -0.896 (p <0 .05)
τ$\dot{V}O_2$ (sec.) V.S. $\dot{V}O_2$max (ml/min・kg^{-1})	N.S.	r = -0.859 (p < 0.05)

N.S. : not significant

Discussion

This study proposed the hypothesis that parasympathetic nervous activity of the living matter, which is observed indirectly at rest, correlates with cardiovascular responses to exercise and cardiorespiratory endurance, and examined the issue in healthy controls who did not regularly exercise, as well as in diabetic patients.

In our results, $CV_{R\text{-}R}$ was significantly lowered in the diabetic patients compared to the healthy subjects. From this, it was suspected that autonomic neuropathy was progressing in the diabetic subjects compared to the healthy controls. Moreover, $\dot{V}O_2$max was significantly lower in the diabetic subjects compared to the healthy controls. It was suggested that cardiorespiratory endurance capacity was lowered in the diabetic patients, as has been previously reported [3, 5]. And tau $\dot{V}O_2$ and tau HR were significantly extended in the diabetic subjects, and were significantly positively correlated to each other within each of the two groups. This suggests that the heart rate response at the beginning of exercise onset related to the ability to transport oxygen, and then, to the ability to utilize oxygen in working muscle. Generally it is said that the ability of working muscle to utilize oxygen affects tau $\dot{V}O_2$ [10, 24]. The ability of working muscle to utilize oxygen is described by cardiac output; the ability of muscle to utilize oxygen is described by the arteriovenous oxygen difference [22]. Although we have not inspected, we supposed that disturbances in cardiovascular responses to exercise with diabetic patients might stem from various causes such as decreased ability to transport oxygen including reduced cardiac output, or a lowered ability of working muscles to use oxygen.

Moreover, CVR-R and tau HR showed significant negative correlation and CVR-R and tau $\dot{V}O_2$ showed significant negative correlation within both groups. Therefore, it is thought that the decrease in CVR-R caused the delay of HR response at the beginning of exercise, and as a result, produced the delay in oxygen uptake kinetic response. It is thought that tau $\dot{V}O_2$ and tau HR could be estimated to some extent by measuring CVR-R.

In this study, both tau $\dot{V}O_2$ and $\dot{V}O_2$max, and tau HR and $\dot{V}O_2$max showed significant negative correlations in healthy individuals. This result matches the report that oxygen uptake kinetic response at the beginning of exercise reflects cardiorespiratory endurance capacity in healthy controls [4, 11]. It is thought that the HR response at the beginning of exercise affects the oxygen uptake kinetic response, and as a result this has been connected with cardiorespiratory endurance capacity. On the other hand, in the diabetic subjects, there was no relationship observed between tau $\dot{V}O_2$ and $\dot{V}O_2$max, nor between tau HR and $\dot{V}O_2$max. For the target diabetic subjects in this study, it was suggested that neither tau $\dot{V}O_2$ nor tau HR relate to cardiorespiratory endurance capacity. It would be necessary to examine how the CVR-R influences the ability to transport oxygen and the ability to utilize oxygen, which is the factor specifying tau $\dot{V}O_2$, and to examine how tau HR was affected; and then to examine the relationship to cardiorespiratory endurance capacity.
Since CVR-R reflected tau $\dot{V}O_2$ and tau HR in both groups, it was thought that CVR-R not only evaluates autonomic nervous system activity in diabetic patients, but also that CVR-R could be used as an index reflecting the cardiovascular response at the beginning of exercise. Examination of the relationship between diabetic autonomic neuropathy and cardiovascular response during exercise becomes a standard for risk management when prescribing exercise for diabetic patients.

Conclusions

We observed a delay in heart rate and oxygen uptake kinetic responses to exercise in diabetic patients compared to healthy controls. And our results for both the healthy and diabetic patients showed that CVR-R reflects the characteristics of cardiovascular responses to exercise. Meanwhile, although some previous studies have postulated that these characteristics of cardiovascular responses to exercise reflect cardiorespiratory endurance capacity in healthy controls, our study confirmed no such correlation in diabetic patients. However, it did not go so far as to explain the mechanism of why a relation was not found in diabetic patients. In future, it appears that a more detailed study, including the cardiac output increase reaction when exercise beginning and the oxygen uptake kinetic in working muscles, must be carried out.

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糖尿病患者と健常者における R-R 間隔変動係数は運動中の循環応答を反映するか？

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キーワード（Key words）１．糖尿病　２．糖尿病性神経症　３．心循環反応

糖尿病患者と健常者のR-R間隔変動係数（$CV_{R\text{-}R}$）と運動時における循環応答との関連を検討した。対象は２型糖尿病患者８名と，年齢をマッチさせた健常男性８名とした。対象者に自転車エルゴメータを用いた漸増負荷を行い，最大酸素摂取量（$\dot{V}O_2max$）と換気性作業閾値（VT）を算出した。次に日を改めて，80%VTに相当する負荷強度で一定負荷運動を行わせた。その後，安静時における$CV_{R\text{-}R}$と，一定負荷運動における酸素摂取と心拍数の時定数を算出した。その結果，１）$CV_{R\text{-}R}$と$\dot{V}O_2max$はDM群で健常群と比較して低下していた。また，tau HRとtau $\dot{V}O_2$はDM群で延長していた。２）tau $\dot{V}O_2$ とtau HRは二群共に正の相関を，$CV_{R\text{-}R}$とtau $\dot{V}O_2$は二群共に負の相関を認めた。２ $\dot{V}O_2max$とtau HR，$\dot{V}O_2max$とtau $\dot{V}O_2$は健常群のみ負の相関を認めた。以上の結果から，$CV_{R\text{-}R}$は運動に対する循環応答を反映する指標になる可能性が示唆された。また，先行研究において，健常者では運動開始時における循環応答特性は全身持久力を反映するものであることが示唆されているが，本研究では糖尿病患者においては関連を認めないことが明らかとなった。