Original Article

Association between Maximal Oxygen Uptake and the Heart Rate Corrected-QT Interval in Postmenopausal Overweight Women

Ryoma Michishita¹, Naoko Shono^{2,3}, Takaki Kasahara¹, and Toshiyuki Tsuruta¹

¹Clinic of Tsuruta Orthopaedic Surgery, Saga, Japan

²Institute of Lifestyle Medical Science, Saga, Japan

³Department of Rehabilitation Science, Nishikyushu University, Saga, Japan

Background: Increased aerobic capacity can reduce the incidence of cardiovascular disease and the mortality rate. On the other hand, a prolonged heart rate corrected-QT (QTc) interval is associated with an increased risk of arrhythmias, cardiac sudden death and coronary artery disease.

Aims: The association of the aerobic capacity and coronary risk factors with QTc interval was investigated in postmenopausal overweight women.

Subjects and Methods: The subjects included 84 postmenopausal overweight women [age: 58.7 ± 6.4 years, body mass index (BMI): 27.9 ± 3.3] with coronary risk factors. Electrocardiogram (ECG) was recorded with a standard resting 12-lead ECG after more than 5 minutes of rest. The QTc interval was automatically calculated according to Bazett's formula. A multistage graded submaximal exercise test was performed on an electric bicycle ergometer to determine the estimated maximal oxygen uptake ($\dot{V}O_{2\max}$).

Results: Single correlation analysis showed the QTc interval to be positively associated with hemoglobin A_{1c} (HbA_{1c}), fasting glucose, fasting insulin, BMI, waist circumference, serum potassium and the number of coronary risk factors, while negatively correlated with $\dot{V}O_{2\max}$. Stepwise multiple regression analysis demonstrated the strong association of the QTc interval with HbA_{1c} and $\dot{V}O_{2\max}$ ($r^2 = 0.244$, $p < 0.0001$). In both patients with and without metabolic syndrome ($n = 15$, $n = 69$, respectively), the QTc interval was independently associated with the HbA_{1c} ($r^2 = 0.318$, $p < 0.05$, $r^2 = 0.115$, $p < 0.05$, respectively).

Conclusions: These results suggest that decreased aerobic capacity and glucose intolerance may be independent risk factors for a prolonged QTc interval, while demonstrating no relationship with metabolic syndrome.

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Key words; Heart rate-corrected QT interval, Maximal oxygen uptake, Electrolyte imbalance, Metabolic syndrome, Glucose intolerance

Introduction

Physical inactivity and decreased aerobic capacity are associated with a significantly higher incidence of coronary artery disease (CAD)^{1, 2)}. Conversely, habitual exercise training can control the incidence of

CAD^{1, 2)}. In addition, several studies have demonstrated that the risk of CAD increased in line with the accumulation of coronary risk factors such as visceral fat accumulation, diabetes mellitus, hypertension and dyslipidemia^{3, 4)}.

On the other hand, a prolonged heart rate corrected-QT (QTc) interval, as measured with a standard electrocardiogram (ECG), is associated with an increased risk of arrhythmias, cardiac sudden death, CAD, left ventricular hypertrophy (LVH) and cardiac autonomic nervous system dysfunction⁵⁻⁹⁾. Specifically, the QTc interval is longer in women than in

Address for correspondence: Ryoma Michishita, Clinic of Tsuruta Orthopaedic Surgery, 174-8 Kamitogawa Ushizumachi, Saga 849-0305, Japan

E-mail: rheuma.clinic.21@lime.ocn.ne.jp

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men and it is also influenced by age, sex hormones and an electrolyte imbalance dysfunction^{6, 10}. Previous studies have reported that morbid obesity is also correlated with a prolonged QTc interval^{11, 12}. Several studies have observed that weight loss could improve the QTc in obese subjects¹²⁻¹⁴. These results suggest that the resolution of obesity by diet or exercise can therefore help to improve the autonomic nervous system, arrhythmia, LVH, prevention of cardiac sudden death and coronary artery disease. However, the associations between either aerobic capacity or the accumulation of coronary risk factors and the QTc interval are still unknown, despite the observation that lower aerobic capacity and the accumulation of coronary risk factors influences the development of CAD and other ECG abnormalities^{1, 2, 15}.

This study was designed to clarify the associations of aerobic capacity and coronary risk factors with the QTc interval in postmenopausal overweight women. The hypothesis is that reduced aerobic capacity may be a sensitive factor for predicting a prolonged QTc interval and electrolyte imbalance dysfunction. The resting ECG, blood sampling and exercise test as screening tests are therefore considered to be important for preventing the incidence of CAD and cardiac sudden death in overweight subjects. As mentioned above, a prolonged QTc interval is a good predictor of CAD and cardiac sudden death. Therefore, the linkage between aerobic capacity and coronary risk factors with the QTc interval may be useful for detecting early stage CAD and cardiac sudden death in overweight subjects. We focused on subjects to be only postmenopausal overweight women to exclude the influence of sex differences and hormones.

Subjects and Methods

Subjects

This study enrolled 84 postmenopausal obese women (age: 58.7 ± 6.4 years, BMI: 27.9 ± 3.3 kg/m²) with coronary risk factors, including hypertension, impaired glucose tolerance, or dyslipidemia. Those taking cardioactive drugs, such as anti-hypertensive drugs, statins or hypoglycemic agents, or patients with a history of cerebrovascular disease, CAD, LVH, cardiac valve disease, or diabetic complications (diabetic neuropathy, diabetic nephropathy and diabetic retinopathy) or an electrolyte disturbance, bundle branch block, intraventricular conduction disturbance, abnormal Q wave, abnormal ST-T wave and a regular smoking habit, were excluded. The local institutional review board approved the study protocol and written informed consent was obtained from each patient

prior to commencement of the study.

Resting ECG, Blood Sampling and Anthropometric Measurements

ECG was recorded with a standard resting 12-lead ECG (FCP-2155, Fukuda Denshi, Tokyo, Japan) at a paper speed of 25 mm per second after more than 5 minutes of rest. The QTc interval was automatically calculated according to Bazett's formula¹⁶ (QTc interval = QT interval/square root of R-R interval).

Blood samples were collected early in the morning by venipuncture from an antecubital vein, after at least a 12hr fast. The fasting blood samples were used to measure the following parameters: high-density lipoprotein cholesterol (HDL-C) by the direct method, low-density lipoprotein cholesterol (LDL-C), triglyceride and plasma glucose by enzymatic methods, serum insulin by the enzyme immunoassay method, hemoglobin A_{1c} (HbA_{1c}) by high performance liquid chromatography, and serum sodium and potassium by the electrode method. Abdominal obesity (waist circumference: ≥ 90 cm), hyperglycemia (fasting glucose: ≥ 110 mg/dL), dyslipidemia (HDL-C: < 40 mg/dL and/or fasting triglyceride: ≥ 150 mg/dL) and normal high blood pressure (resting systolic blood pressure: ≥ 130 mmHg and/or resting diastolic blood pressure: ≥ 85 mmHg) were defined as coronary risk factors, and the total number of risk factors was also calculated for each subject. Metabolic syndrome was defined according to the metabolic syndrome diagnostic criteria in Japan^{17, 18}.

The height and body weight were measured, while BMI was calculated as the ratio of the body weight (kg) divided by the height squared (m²). Waist circumference was measured at the level of the umbilicus.

Exercise Test

A multistage graded submaximal exercise stress test was performed on each subject using an electric bicycle ergometer. The workload was increased every 4 minutes, depending on their daily activity levels. A CM₅-lead ECG (ML-1800; Fukuda Denshi) was recorded continuously during exercise testing. The following parameters were measured at rest and during the last minute of each stage: the rate of perceived exhaustion, blood pressure (FB-300; Fukuda Denshi) and blood lactate concentration (Lactate Pro; Arkray). Maximal oxygen uptake ($\dot{V}O_{2\max}$) was estimated by the nomogram of Åstrand and Ryhming¹⁹, using the heart rate measured at three different submaximal workloads. The end point of exercise testing was determined on the basis of either achieving a blood lactate

concentration ≥ 4 mmol/L or the criteria described in the guidelines of the American College of Sports Medicine²⁰). The subjects were divided into three categories, which were defined as equally trisected distributions of the $\dot{V}O_2\text{max}$ [low (15.3–24.4 mL/kg/min), moderate (24.6–28.2 mL/kg/min) and high (28.3–38.9 mL/kg/min)].

Statistical Analysis

Data are expressed as the means $\pm$ SD. Statistical analyses were performed using the StatView software package. Inter-group comparisons were performed using the unpaired *t*-test for continuous variables. The inter-multiple group relationships were determined using one-way repeated measure analysis of variance (ANOVA) and the Tukey-Kramer method. Pearson's univariate regression and stepwise multivariate regression analyses were performed in order to determine the association of the QTc interval with the $\dot{V}O_2\text{max}$ and coronary risk factors. A probability value of < 0.05 was considered significant.

Results

Table 1 shows patient characteristics, and **Fig. 1** compares the QTc interval and electrolyte indices among the low, moderate and high $\dot{V}O_2\text{max}$ groups. The QTc interval was significantly longer in the low $\dot{V}O_2\text{max}$ group than in the high $\dot{V}O_2\text{max}$ group (428.9 ± 23.5 vs. 425.0 ± 20.7 vs. 414.7 ± 17.0 msec, $p < 0.05$). Serum sodium was significantly higher (142.1 ± 1.6 vs. 141.1 ± 1.4 vs. 140.4 ± 1.9 mEq/L, $p < 0.01$), while serum potassium was significantly lower in the low $\dot{V}O_2\text{max}$ group than in the high $\dot{V}O_2\text{max}$ group (4.0 ± 0.3 vs. 4.1 ± 0.3 vs. 4.2 ± 0.3 mEq/L, $p < 0.05$). **Table 2** compares patients characteristics between low, moderate and high $\dot{V}O_2\text{max}$ groups. HbA_{1c}, fasting glucose, fasting insulin levels and diastolic blood pressure were significantly higher in the low $\dot{V}O_2\text{max}$ group than in the high $\dot{V}O_2\text{max}$ group ($p < 0.05$, respectively). BMI was significantly higher in the low $\dot{V}O_2\text{max}$ group than in moderate and high $\dot{V}O_2\text{max}$ groups ($p < 0.05$, respectively). Waist circumference was significantly higher (low < moderate < high) and $\dot{V}O_2\text{max}$ was significantly lower in high, moderate and low $\dot{V}O_2\text{max}$ groups [(high < moderate < low), $p < 0.05$, respectively]. The number of coronary risk factors was significantly higher in low and moderate $\dot{V}O_2\text{max}$ groups than in the high $\dot{V}O_2\text{max}$ group. In addition, **Fig. 2** shows comparisons of the QTc interval and electrolyte indices between patients with and without metabolic syndrome. In patients with metabolic syndrome, QTc interval (435.5 ± 19.0 vs. 419.6 ± 20.6 msec, $p < 0.01$)

Table 1. Patient characteristics

Age (years)	58.7 $\pm$ 6.4
HDL-C (mg/dL)	59.8 $\pm$ 12.1
LDL-C (mg/dL)	135.4 $\pm$ 30.0
Triglyceride (mg/dL)	115.8 $\pm$ 62.1
HbA _{1c} (%)	5.3 $\pm$ 0.7
Fasting glucose (mg/dL)	97.8 $\pm$ 18.6
Fasting insulin (μ U/mL)	8.7 $\pm$ 5.3
Serum sodium (mEq/L)	141.2 $\pm$ 1.8
Serum potassium (mEq/L)	4.1 $\pm$ 0.3
BMI (kg/m ²)	27.9 $\pm$ 3.3
Waist circumference (cm)	90.0 $\pm$ 8.8
Resting systolic blood pressure (mmHg)	121.8 $\pm$ 16.2
Resting diastolic blood pressure (mmHg)	80.3 $\pm$ 10.2
Resting heart rate (beats/min)	68.2 $\pm$ 10.0
RR interval (msec)	891.4 $\pm$ 135.7
QT interval (msec)	400.1 $\pm$ 29.7
QTc interval (msec)	422.9 $\pm$ 21.2
$\dot{V}O_2\text{max}$ (mL/min/kg)	26.3 $\pm$ 4.5
Number of coronary risk factors	1.7 $\pm$ 0.8

Data are expressed as the mean $\pm$ SD, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, HbA_{1c}, BMI = body mass index, QTc = heart rate corrected QT interval, $\dot{V}O_2\text{max}$ = maximum oxygen uptake. Abdominal obesity, hyperglycemia, dyslipidemia and normal high blood pressure were defined as coronary risk factors, and the total number of risk factors was also calculated for each subject.

was significantly longer and serum sodium (141.8 ± 1.5 vs. 140.1 ± 1.8 mEq/L, $p < 0.05$) was significantly higher than in patients without metabolic syndrome.

Table 3 shows the association between the QTc interval and coronary risk factors, determined by univariate regression analysis in all patients, with and without metabolic syndrome. In all patients, the QTc interval correlated positively with HbA_{1c} ($r = 0.452$, $p < 0.0001$), fasting glucose ($r = 0.410$, $p < 0.0001$), fasting insulin ($r = 0.255$, $p < 0.05$), BMI ($r = 0.262$, $p < 0.05$), waist circumference ($r = 0.292$, $p < 0.01$), the number of coronary risk factors ($r = 0.331$, $p < 0.01$) and negatively with serum potassium ($r = -0.231$, $p < 0.05$) and $\dot{V}O_2\text{max}$ ($r = -0.294$, $p < 0.01$). In patients with metabolic syndrome ($n = 15$), QTc interval correlated positively with HbA_{1c} ($r = 0.563$, $p < 0.05$), fasting glucose ($r = 0.542$, $p < 0.05$), fasting insulin ($r = 0.521$, $p < 0.05$), serum sodium ($r = 0.516$, $p < 0.05$) and negatively with $\dot{V}O_2\text{max}$ ($r = -0.515$, $p < 0.05$). In patients without metabolic syndrome ($n = 69$), QTc interval correlated positively with HbA_{1c} ($r = 0.339$, $p < 0.01$), fasting glucose ($r = 0.279$, $p < 0.05$), fasting insulin ($r = 0.236$, $p < 0.05$), BMI ($r = 0.267$, $p < 0.05$), waist circumference ($r = 0.257$, $p < 0.05$) and negatively

Fig. 1. Difference in the QTc interval (A) and electrolyte indices [serum sodium (B) and potassium (C)] in the low ($n=28$, 15.3–24.4 mL/kg/min), moderate ($n=28$, 24.6–28.2 mL/kg/min) and high $\dot{V}O_{2\max}$ groups ($n=28$, 28.3–38.9 mL/kg/min).

The results are shown as the means $\pm$ SD.

Table 2. Differences in coronary risk factors in low, moderate and high $\dot{V}O_{2\max}$ groups

	Low ($n=28$) (15.3–24.4 mL/kg/min)	Moderate ($n=28$) (24.6–28.2 mL/kg/min)	High ($n=28$) (28.3–38.9 mL/kg/min)
$\dot{V}O_{2\max}$ (mL/kg/min)	21.8 $\pm$ 2.8 ^{*,†}	25.9 $\pm$ 1.1 [*]	31.2 $\pm$ 2.7
Age (years)	58.4 $\pm$ 5.3	59.4 $\pm$ 6.9	58.2 $\pm$ 7.0
HDL-C (mg/dL)	56.5 $\pm$ 10.4	59.5 $\pm$ 12.1	63.3 $\pm$ 13.2
LDL-C (mg/dL)	137.6 $\pm$ 34.5	132.6 $\pm$ 28.9	135.8 $\pm$ 27.1
Triglyceride (mg/dL)	125.9 $\pm$ 54.0	125.0 $\pm$ 84.6	96.5 $\pm$ 34.6
HbA1c (%)	5.5 $\pm$ 0.8 [*]	5.4 $\pm$ 0.7	5.1 $\pm$ 0.3
Fasting glucose (mg/dL)	103.0 $\pm$ 24.8 [*]	97.8 $\pm$ 15.0	90.6 $\pm$ 9.8
Fasting insulin (μ U/mL)	10.5 $\pm$ 7.3 [*]	9.0 $\pm$ 4.1	6.6 $\pm$ 2.7
BMI (kg/m ²)	30.5 $\pm$ 3.7 ^{*,†}	27.4 $\pm$ 2.3	25.9 $\pm$ 1.4
Waist circumference (cm)	95.8 $\pm$ 8.2 ^{*,†}	89.6 $\pm$ 8.0 [*]	84.7 $\pm$ 6.6
Resting systolic blood pressure (mmHg)	121.9 $\pm$ 16.0	125.8 $\pm$ 17.0	117.7 $\pm$ 15.1
Resting diastolic blood pressure (mmHg)	83.2 $\pm$ 11.7 [*]	80.6 $\pm$ 8.5	77.2 $\pm$ 9.7
The number of coronary risk factors	2.0 $\pm$ 0.9 [*]	1.8 $\pm$ 0.9 [*]	1.2 $\pm$ 0.5

Data are expressed as the mean $\pm$ SD. ^{*}; $p < 0.05$, Compared with high group. [†]; $p < 0.05$, Compared with moderate group. Abbreviations as in Table 1.

with serum potassium ($r = -0.237$, $p < 0.05$).

In stepwise multivariate regression analysis, the QTc interval was used as a continuous variable, and was entered as a dependent variable. The following factors were entered as independent variables: age, HbA1c, fasting insulin, waist circumference, serum sodium, serum potassium, $\dot{V}O_{2\max}$ and the number of coronary risk factors. This analysis showed that the QTc interval was associated independently with the HbA1c and $\dot{V}O_{2\max}$ in all patients ($r^2 = 0.244$, $p < 0.0001$). In both patients with and without metabolic syndrome, the QTc interval was associated indepen-

dently with the HbA1c [$r^2 = 0.318$, $p < 0.05$, $r^2 = 0.115$, $p < 0.05$, respectively (Table 4)].

Discussion

The major finding of this study was that the QTc interval and serum sodium were higher and the serum potassium was lower in the low $\dot{V}O_{2\max}$ group than in the high $\dot{V}O_{2\max}$ group. In addition, our stepwise multiple regression analysis showed the HbA1c and $\dot{V}O_{2\max}$ to be more powerfully associated with the QTc interval than other risk factors. In the

Fig. 2. Difference in the QTc interval (A) and indices of electrolyte [serum sodium (B) and potassium (C)] between patients with ($n=15$) and without ($n=69$) metabolic syndrome.

The results are shown as the means $\pm$ SD. Metabolic syndrome was defined according to the metabolic syndrome diagnostic criteria in Japan^{17, 18}.

Table 3. Association between QTc interval and coronary risk factors calculated by simple regression analysis in all patients, with and without metabolic syndrome

	All patients	Metabolic Syndrome	
		(+)	(-)
Age	0.040	0.062	0.042
HDL-C	-0.004	-0.133	-0.015
LDL-C	0.057	0.397	0.109
Triglyceride	0.060	0.285	0.028
HbA _{1c}	0.452**	0.563 [†]	0.339*
Fasting glucose	0.410**	0.542 [†]	0.279 [†]
Fasting insulin	0.255 [†]	0.521 [†]	0.236 [†]
BMI	0.262 [†]	0.109	0.267 [†]
Waist circumference	0.292*	0.146	0.257 [†]
Resting systolic blood pressure	0.163	0.089	0.069
Resting diastolic blood pressure	0.045	0.013	0.204
Serum sodium	0.123	0.516 [†]	0.002
Serum potassium	-0.231 [†]	-0.404	-0.237 [†]
$\dot{V}O_2$ max	-0.294*	-0.515 [†]	-0.122
Number of coronary risk factors	0.331*	0.119	0.044

Data are expressed as the coefficient of correlation. [†]; $p < 0.05$, *; $p < 0.01$, **; $p < 0.0001$. Abbreviations as in Table 1.

current study, the QTc interval was significantly associated with obesity indices and glucose metabolism indices and those findings were consistent with previous studies^{5, 7, 8, 11, 21}. However, the association between the $\dot{V}O_2$ max and QTc interval remains unknown, despite the observation that a lower aerobic capacity influences the development of diabetes mellitus, CAD and ECG abnormalities^{1-4, 15, 18, 22}.

According to our data, the indices of glucose

metabolism, obesity, blood pressure and the number of coronary risk factors were significantly higher in the low $\dot{V}O_2$ max group than in the high $\dot{V}O_2$ max group. Furthermore, our stepwise multiple regression analysis showed HbA_{1c} to be strongly associated with the QTc interval, while it showed no relation to metabolic syndrome. It has been reported²² that reduced aerobic capacity and physical inactivity influences the development of diabetes mellitus, metabolic syndrome and

Table 4. Association between QTc interval and coronary risk factors calculated by stepwise multip regression analysis in all patients, with and without metabolic syndrome

	All patients		Metabolic Syndrome			
			(+)		(-)	
	β	<i>p</i> vallue	β	<i>p</i> vallue	β	<i>p</i> vallue
Age	0.025	NS	0.051	NS	0.031	NS
HbA _{1c}	0.423	<i>p</i> <0.0001	0.563	<i>p</i> <0.05	0.339	<i>p</i> <0.05
Fasting insulin	0.118	NS	0.219	NS	0.136	NS
Waist circumference	0.079	NS	0.214	NS	0.174	NS
Serum sodium	0.031	NS	0.337	NS	0.051	NS
Serum potassium	-0.201	NS	-0.332	NS	-0.184	NS
$\dot{V}O_{2\max}$	-0.210	<i>p</i> <0.0001	-0.351	NS	-0.100	NS
Number of coronary risk factors	0.111	NS	0.144	NS	-0.183	NS
<i>r</i> ²	0.244		0.318		0.115	

β ; standard regression coefficient. In stepwise multiple regression analysis the QTc interval was entered as dependent variable. The following factors were entered as independent variables: age, HbA_{1c}, fasting insulin, waist circumference, serum sodium, serum potassium, $\dot{V}O_{2\max}$ and the number of coronary risk factors.

CAD. Several studies have demonstrated^{4, 18)} that metabolic syndrome was also associated with an increased risk of future diabetes mellitus and CAD. Recently, the association between a prolonged QTc interval and ischemic heart disease has been clearly demonstrated⁵⁻⁷⁾. Although none of the patients underwent coronary angiography, some might possibly have had occult atherosclerotic coronary artery disease. Abnormal glucose metabolism is considered to be associated with micro-vessel coronary artery disease²³⁾, which might cause a prolonged QTc interval in some patients. Namely, continuing hyperglycemia involved lower aerobic capacity and increased coronary risk factors may be a good predictor of a prolonged QTc interval through myocardial ischemia.

In addition, sympathetic nervous system dysfunction is also known to influence a prolonged QTc interval^{6, 9)}. Previous studies have reported that morbid obesity also correlates with sympathetic nervous system dysfunction²⁴⁾. Moreover, the plasma catecholamine concentration is improved by endurance aerobic exercise training²⁵⁾.

Furthermore, the QTc interval is influenced by an electrolyte imbalance, such as a reduction in outward potassium channel currents or an increased in inward sodium or calcium channel currents²⁶⁾. According to our data, fasting insulin was correlated positively with serum sodium ($r=0.258$, $p<0.05$, data not shown). In addition, the serum sodium level was higher and the serum potassium was lower in the low $\dot{V}O_{2\max}$ group than in the high $\dot{V}O_{2\max}$ group, and the serum sodium level was higher in patients with metabolic

syndrome than in patients without metabolic syndrome. Previous studies have observed that insulin resistance or hyperinsulinemia promoted sodium reabsorption in the kidney^{27, 28)}. Moreover, the sodium/potassium ratio in skeletal muscle in obese subjects with glucose intolerance and the potassium concentration in skeletal muscle is increased by aerobic endurance training²⁹⁾.

Therefore, the association of reduced aerobic capacity, physical inactivity and glucose intolerance with a prolonged QTc interval might be caused by overactivity of the sympathetic nervous system, micro-vessel coronary artery disease and electrolyte imbalance dysfunction. The current findings suggest that decreases in aerobic capacity and glucose intolerance may be a predictive factor for indirectly detecting the development of a prolonged QTc interval in postmenopausal overweight women.

Study Limitations and Clinical Implications

There are several limitations related to this study. First, the limited study population resulted in small number of subjects, in patients without complications or on medications and with a predominance of middle-aged women. Therefore, it remains unclear whether our findings are consistent with premenopausal women or men, CAD patients and those with other complications. Second, since the study had a cross-sectional design, it was not possible to clarify the causative role of the QTc interval on the $\dot{V}O_{2\max}$ and other coronary risk factors. Finally, the $\dot{V}O_{2\max}$ in this study was estimated using the nomogram of

Åstrand and Ryhming. However, the $\dot{V}O_2\text{max}$ estimated by this method has been used in many large epidemiologic studies. Moreover, a prolonged QTc interval has been observed to be associated with future cardiac sudden death and coronary artery disease⁴⁻⁶. Therefore, the results of the linkage between the QTc interval and $\dot{V}O_2\text{max}$ combined with general coronary risk factors, such as glucose intolerance, may suggest the hypothesis that reduced aerobic capacity leads to future cardiac sudden death and CAD. Furthermore, additional research in a large number of subjects is required to more precisely clarify the mechanisms, clinical implications and associations between aerobic capacity and the QTc interval following exercise therapy.

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