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Low heart rate variability is a risk factor for sudden cardiac death in type 2 diabetes

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Abstract

The purpose of this study is to examine the association between sudden cardiac death (SCD) and heart rate variability (HRV) in subjects with and without type 2 diabetes and to determine whether low HRV can predict SCD in type 2 diabetes. Subjects were 8917 consecutively examined persons (3089 diabetic, and 5828 nondiabetic subjects) aged 35–69 years who underwent a 75 g oral glucose tolerance test (OGTT) together with electrocardiography (ECG). HRV was calculated from the 12-lead ECG as the coefficient of variance for 100 R–R intervals (CV_{R-R}). During a median observation period of 5.2 years, SCD occurred in 56 subjects (33 diabetic, and 23 nondiabetic). Among diabetic subjects, mortality from SCD tended to be higher in subjects with a low CV_{R-R} ($P = 0.004$). After adjustment for age, gender, systolic blood pressure, total cholesterol (TC), triglycerides (TG), BMI, ischemic ECG change, and smoking history, relative risk (RR) of SCD was 2.07 (95% CI 1.02–4.17) in diabetic subjects with a CV_{R-R} <2.2% compared with those with a CV_{R-R} ≥2.2%. Diabetic subjects with a CV_{R-R} <2.2% had significantly higher cumulative mortality from SCD than those with a CV_{R-R} ≥2.2% ($P = 0.007$). In type 2 diabetes, a low CV_{R-R} carried an increased risk of SCD.
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Keywords: Type 2 diabetes mellitus; Heart rate variability; Cardiac sudden death

1. Introduction

Sudden death has been reported to occur frequently among patients with type 2 diabetes [1–3]. Severe coronary atherosclerosis [4], coronary artery thrombosis [5], long Q–T syndrome [6,7], and a family history of sudden death [8] have been implicated in sudden death; yet factors leading to sudden death remain controversial.

Heart rate variability (HRV), a recognized indicator of autonomic nerve function is impaired in type 2 diabetes [9,10]. Many reports have identified low HRV as a risk factor for sudden death in patients after myocardial infarction [11–18], but no reports have clearly and specifically identified an association between HRV and sudden death in type 2 diabetes. Ventricular

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tachycardia induced by reduction of parasympathetic nerve activity has been suggested as a cause of sudden death in patients with low HRV [19–22]. Since autonomic nerve dysfunction is a known complication of type 2 diabetes, we hypothesized that sudden cardiac death (SCD) in patients with type 2 diabetes might be precipitated by autonomic nerve dysfunction. We tested the hypothesis with the present prospective observations.

2. Materials and methods

Study subjects included 8917 consecutively examined patients, 35–69 years old, who underwent a 75 g oral glucose tolerance test (OGTT) together with 12-lead electrocardiography (ECG) to assess HRV at the Hiroshima Atomic Bomb Casualty Council Health Management and Promotion Center between January 1983 and May 2001. Subjects with a history of gastrectomy, liver dysfunction, treatment for diabetes mellitus, or any type of arrhythmia were excluded. Written informed consent was obtained from all participants.

Blood samples were obtained in the morning after at least 12 h of fasting for measurement of plasma glucose (PG), serum total cholesterol (TC), and triglyceride (TG). PG was measured by the glucose oxidase method, while TC and TG were analyzed by enzymatic methods.

OGTT was performed in subjects whose PG was ≥100 mg/dl at fasting, ≥130 mg/dl within 1.5 h after eating, ≥120 mg/dl between 1.5 and 2.5 h after eating, or ≥110 mg/dl beyond 2.5 h after eating, as well as those who showed glycosuria, in the course of a screening health examination at our center. By OGTT diagnostic criteria based on the 1999 recommendations of the Japan Diabetes Society [23], we diagnosed 3089 subjects with diabetes (fasting plasma glucose (FPG) ≥126 mg/dl and/or 2 h PG ≥200 mg/dl); 3547 with normal type (FPG <110 mg/dl and 2 h PG <140 mg/dl); and 2281 with borderline type. For this study, we defined subjects with normal or borderline type as nondiabetic subjects. Subjects participating in this study comprised about 10% of all persons undergoing health screening examinations at our center during the study period.

All subjects had 100 successive R–R intervals measured in a 12-lead ECG. The coefficient of variation of 100 successive R–R intervals (CV_{R-R}) was calculated using the following equations:

standard deviation of the R–R interval (SDNN)

$$= \sum_{i=1}^{100} \left(\frac{(\text{R–R}_i) - \text{mean R–R})^2}{\text{mean R–R}} \right) \quad (1)$$

$$CV_{R-R} = \left(\frac{\text{SDNN}}{\text{mean R–R}} \right) \times 100 \quad (2)$$

Blood pressure was measured by a trained staff in the right arm in a sitting position using a mercury sphygmomanometer. Systolic blood pressure (SBP) was determined at the first Korotkof sound. Smoking history was determined from a questionnaire administered by a staff at registration. The ECG was evaluated using the Minnesota code [24], with subjects assigned codes of 1.1, 1.2, 1.3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3, or 7.1 being defined as having ischemic ECG change. BMI was calculated as body weight (kg)/height (m^2).

2.1. Follow-up

Follow-up to determine cause of death based on death certificates was carried out from January 1983 until May 2001. SCD was defined as a death caused by an unexpected cardiac event within 24 h of onset of acute symptoms. Causes of death were classified according to the ninth revision of the International Classification of Disease (ICD-9), with codes 410–414 and 428 representing cardiac events. Follow-up time was calculated from registration date to date of death for decedents or to May 2001 for those still alive. No subjects were lost to follow-up. Causes could be determined for all deaths.

2.2. Statistical analysis

Data were summarized as the mean with standard deviation. Continuous variables in diabetic and nondiabetic subjects were compared using Student's *t*-test. Frequencies of SCD were compared using the chi-squared test. Relative risk was calculated using Cox's proportional hazards model. Cumulative mortality from SCD was estimated using the Kaplan–Meier method. Cumulative mortality in

diabetic and nondiabetic subjects was compared using the log-rank test. Statistical analysis was performed using the SAS statistical analysis system (Version 6.12) [25]. Results were considered statistically significant when a two-tailed *P*-value was less than 0.05.

3. Results

3.1. Baseline characteristics

Baseline characteristics of diabetic and nondiabetic subjects are shown in Table 1. SBP, TC, TG, and BMI were significantly higher in diabetic subjects, while age, and CV_{R-R} were significantly lower. Smokers were also more numerous among diabetic subjects.

3.2. Mortality

During 6.5 ± 4.8 years (mean ± S.D.) of follow-up; range 1 month to 19.3 years, 706 subjects died. Among the deaths; 56 were ascribed to SCD (33 in diabetic; 23 in nondiabetic subjects). The crude SCD rate was 9.59/10,000 person–years.

Subjects were classified by age quartiles to analyze mortality from SCD. Mortality from SCD increased significantly with age ($P = 0.006$) when all subjects were considered together. When subjects were divided into diabetic and nondiabetic subjects, mortality from SCD increased significantly with age in nondiabetic subjects ($P = 0.016$); in diabetic subjects, mortality increased with age up to 67 years ($P = 0.004$), declining thereafter (Fig. 1).

3.3. Association between CV_{R-R} and SCD

Subjects were classified by quartile of CV_{R-R}. Considering all subjects together, mortality from SCD was highest in the lowest CV_{R-R} group ($P = 0.040$). When diabetic and nondiabetic subjects were considered separately, diabetic subjects showed more mortality from SCD in the lowest quartile for CV_{R-R} than in the other three ($P < 0.016$). No association between CV_{R-R} and SCD was seen in nondiabetic subjects (Fig. 2). Among nondiabetic subjects, mortality from SCD by CV_{R-R} quartile were 4.6, 1.9, 6.9, 4.9/10,000 person–years in normal type, and 13.6, 10.0, 5.6, 11.4/10,000 person–years in borderline type, respectively, in which there were no statistical significance both in inter- and intra-group differences.

3.4. Analysis of SCD risk factors in subjects overall

3.4.1. Univariate analysis by Cox's proportional hazards model

Considering all subjects together, age, ischemic ECG changes, diabetes, CV_{R-R}, SBP, and smoking history were significant risk factors for SCD. RR for SCD was 2.04 (95% confidence interval (CI) 1.20–3.49) for diabetic compared with nondiabetic subjects. When CV_{R-R} was divided into two groups including CV_{R-R} <2.2% (first quartile) and CV_{R-R} ≥2.2% (second to fourth quartiles), RR of SCD was 2.01 (95% CI 1.17–3.44) for those with a CV_{R-R} <2.2% compared with risk in those with a CV_{R-R} ≥2.2%. Accordingly, CV_{R-R} <2.2% and

Table 1
Characteristics of subjects at registration

Variables	Nondiabetic subjects ($n = 5828$)	Diabetic subjects ($n = 3089$)	*P*
Males/females	3159/2669	1785/1304	0.003
Age (years)	60.1 ± 7.2	59.6 ± 7.1	<0.001
Fasting plasma glucose (mg/dl)	98.5 ± 10.2	148.1 ± 45.0	<0.001
CV_{R-R} (%)	3.1 ± 1.4	3.0 ± 1.4	<0.001
Systolic blood pressure (mm Hg)	132.7 ±19.1	139.8 ± 19.7	<0.001
Total cholesterol (mg/dl)	217.5 ± 37.3	225.8 ± 43.1	<0.001
Triglycerides (mg/dl)	126.5 ± 84.8	169.3 ± 118.7	<0.001
BMI (kg/m^2)	23.0 ± 3.1	24.2 ± 3.3	<0.001
Smoking (%)	35.0	37.6	<0.001

Continuous variables are expressed as the mean ± S.D.

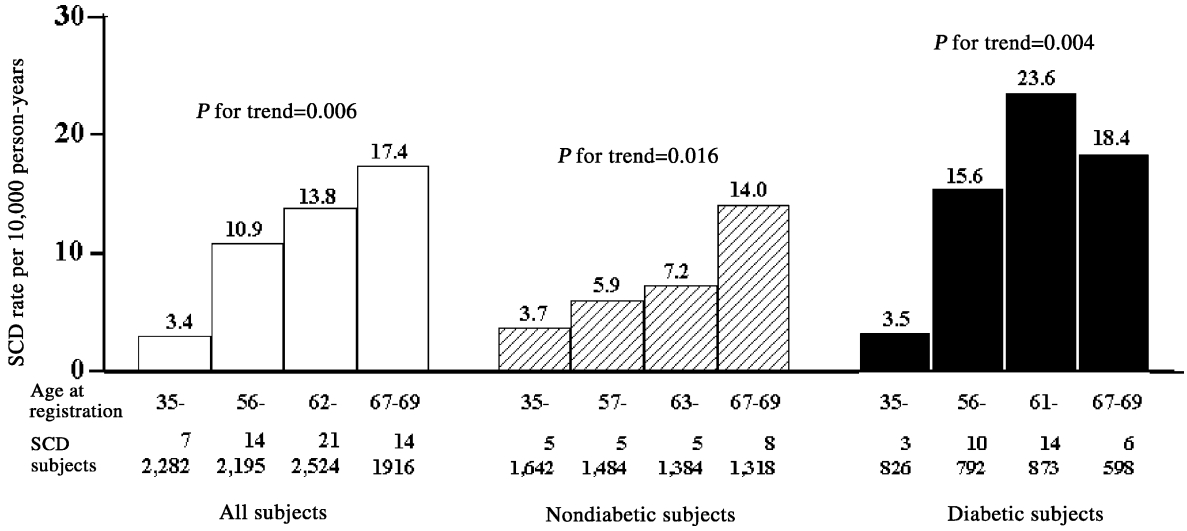

Fig. 1. Mortality rate from sudden cardiac death (SCD) by age quartiles. Open bars, all subjects; hatched columns, nondiabetic subjects; filled bars, diabetic subjects.

CV_{R-R} ≥2.2% were chosen to define lower and higher CV_{R-R} groups, respectively. Gender, TC, TG, and BMI did not significantly influence risk of SCD (Table 2).

3.4.2. Multivariate analysis by Cox's proportional hazards model

Multivariate analysis showed that age, diabetes, SBP and smoking history all remained as statistically

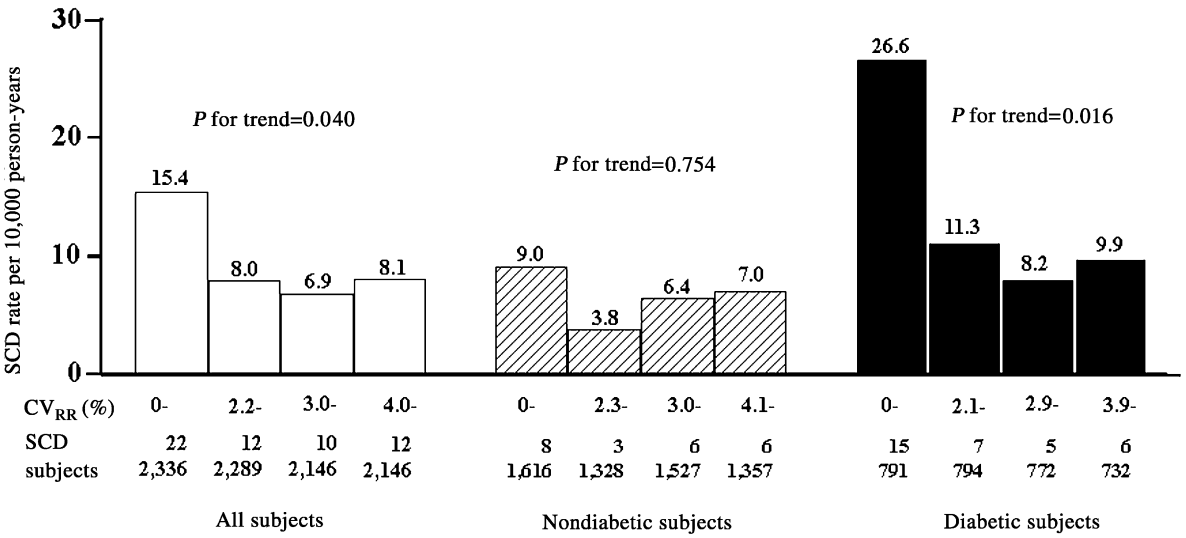

Fig. 2. Mortality rate from sudden cardiac death (SCD) by quartiles of heart rate variability. Open bars, all subjects; hatched bars, nondiabetic subjects; filled bars, diabetic subjects.

Table 2
Crude and multivariate-adjusted relative risk for sudden cardiac death

Variables	Relative risk (95% CI) crude	Relative risk (95% CI) multivariate-adjusted
All subjects		
Age (per 10 years)	1.07 (1.02–1.12)	1.06 (1.02–1.11)
Gender (male/female)	1.37 (0.80–2.36)	1.06 (0.55–2.05)
Ischemic ECG change (yes/no)	2.65 (1.20–5.87)	2.06 (0.92–4.60)
Diabetes/nondiabetes	2.04 (1.20–3.49)	1.86 (1.06–3.23)
CV_{R-R} (<2.2%/≥2.2%)	2.01 (1.17–3.44)	1.64 (0.95–2.82)
Systolic blood pressure (per 10 mmHg)	1.23 (1.08–1.39)	1.15 (1.01–1.31)
Total cholesterol (per 10 mg/dl)	0.85 (0.50–1.44)	0.86 (0.50–1.50)
Triglycerides (per 10 mg/dl)	0.99 (0.94–1.05)	0.98 (0.92–1.04)
BMI (per 1 kg/m^2)	1.01 (0.93–1.09)	0.98 (0.90–1.07)
Smoking (yes/no)	1.90 (1.12–3.21)	1.90 (1.02–3.54)
Nondiabetic subjects		
Age (per 10 years)	1.03 (0.97–1.10)	1.04 (0.97–1.10)
Gender (male/female)	2.30 (0.90–5.86)	2.11 (0.70–6.34)
Ischemic ECG change (yes/no)	3.15 (0.93–10.65)	2.94 (0.85–10.14)
Fasting plasma glucose (per 10 mg/dl)	1.23 (0.79–1.92)	1.12 (0.70–1.79)
CV_{R-R} (<2.2%/≥2.2%)	1.48 (0.60–3.61)	1.34 (0.54–3.29)
Systolic blood pressure (per 10 mmHg)	1.18 (0.97–1.44)	1.08 (0.87–1.33)
Total cholesterol (per 10 mg/dl)	1.08 (0.47–2.45)	1.11 (0.47–2.62)
Triglycerides (per 10 mg/dl)	1.05 (0.97–1.15)	1.04 (0.95–1.13)
BMI (per 1 kg/m^2)	1.45 (0.92–1.18)	1.12 (0.89–1.16)
Smoking (yes/no)	1.85 (0.81–4.21)	1.31 (0.50–3.40)
Diabetic subjects		
Age (per 10 years)	1.10 (1.03–1.18)	1.09 (1.02–1.16)
Gender (male/female)	1.06 (0.53–2.11)	0.79 (0.34–1.82)
Ischemic ECG change (yes/no)	2.10 (0.73–5.98)	1.73 (0.60–5.00)
Fasting plasma glucose (per 10 mg/dl)	0.96 (0.83–1.13)	1.01 (0.87–1.19)
CV_{R-R} (<2.2%/≥2.2%)	2.73 (1.37–5.44)	2.07 (1.02–4.17)
Systolic blood pressure (per 10 mmHg)	1.21 (1.03–1.43)	1.18 (0.99–1.40)
Total cholesterol (per 10 mg/dl)	0.69 (0.34–1.41)	0.76 (0.37–1.58)
Triglycerides (per 10 mg/dl)	0.94 (0.86–1.02)	0.94 (0.86–1.03)
BMI (per 1 kg/m^2)	0.95 (0.85–1.06)	0.96 (0.85–1.07)
Smoking (yes/no)	2.07 (1.04–4.12)	2.23 (1.00–4.96)

Data indicate relative risk (95% CI) estimated with the Cox's proportional hazards model. Multivariate-adjusted relative risk was calculated using age, gender, ischemic ECG change, fasting plasma glucose, CV_{R-R}, systolic blood pressure, total cholesterol, triglycerides, BMI, and smoking as covariance.

significant factors for SCD. RR was 1.86 (95% CI 1.06–3.23) for diabetes compared with nondiabetes. RR was 1.64 (95% CI 0.95–2.82) for those with a CV_{R-R} <2.2% compared with those with a CV_{R-R} ≥2.2% (Table 2).

3.5. Risk factors for SCD according to diabetes status

3.5.1. Univariate analysis using Cox's proportional hazards model

In nondiabetic subjects, there was no statistically significant risk factors for SCD were identified. RR was 3.15 (95% CI 0.93–10.65) for those with ischemic ECG change compared with those without ischemic ECG change, but this fell short of statistical significance. In diabetic subjects, age, CV_{R-R}, SBP, and smoking history were significant risk factors for SCD. RR was 2.73 (95% CI 1.37–5.44) for those with a CV_{R-R} <2.2% compared with those with a CV_{R-R} ≥2.2%. No risk difference was noted for gender, FPG, TC, TG, or BMI (Table 2).

3.5.2. Multivariate analysis using Cox's proportional hazards model

Multivariate analysis showed no statistically significant risk factor for SCD among nondiabetic subjects.

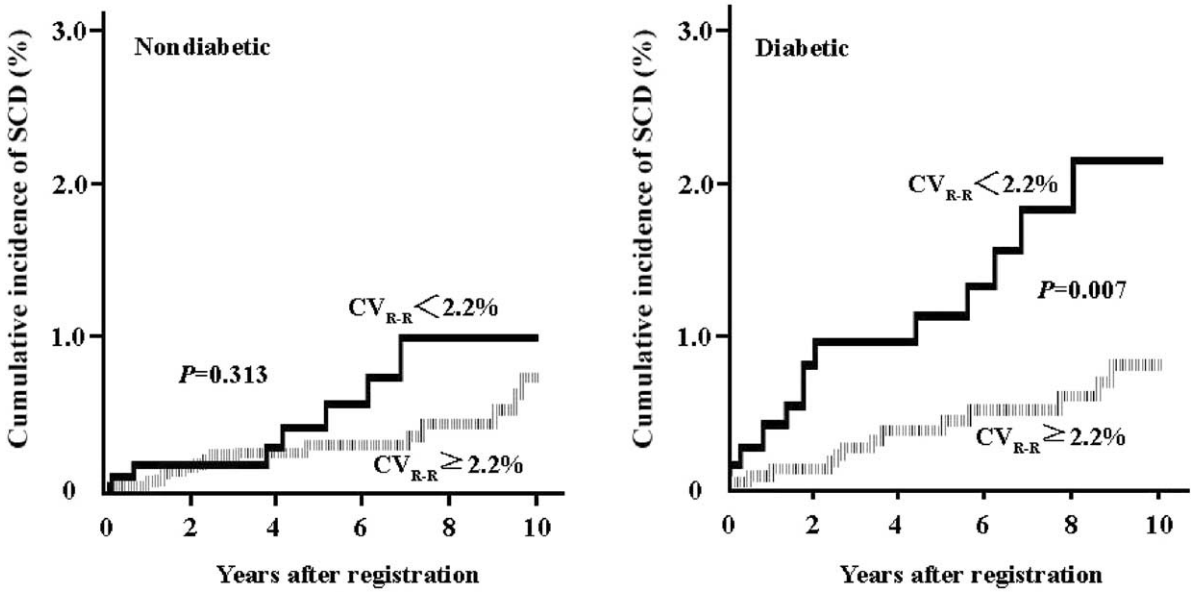

Fig. 3. Cumulative incidence of sudden cardiac death (SCD) with CV_{R-R} less than 2.2% and CV_{R-R} equal to or greater than 2.2%, in nondiabetic and diabetic subjects (left and right, respectively). Cumulative incidence was calculated by the Kaplan–Meier method. A significant difference was detected by the log-rank test between diabetic subjects with a CV_{R-R} less than 2.2% and diabetic subjects with a CV_{R-R} of at least 2.2% ($P = 0.007$).

In diabetic subjects, age, CV_{R-R}, and smoking history remained statistically significant. RR was 2.07 (95% CI 1.02–4.17) for those with a CV_{R-R} <2.2% compared with those with a CV_{R-R} ≥2.2% (Table 2).

3.6. Cumulative mortality from SCD

In diabetic subjects with a CV_{R-R}<2.2%, cumulative mortality from SCD during total observation period was significantly higher than in those with a CV_{R-R}≥2.2% ($P = 0.007$). In nondiabetic subjects, no difference in cumulative mortality from SCD was noted between those with a CV_{R-R} <2.2% and those with a CV_{R-R} ≥2.2% (Fig. 3).

4. Discussion

This is the first report identifying low HRV as a risk factor for SCD among individuals with type 2 diabetes. We demonstrated that type 2 diabetic subjects with low HRV had twice the mortality from SCD of those with higher HRV. RR was 2.07 (95% CI 1.02–4.17) for diabetic subjects with a CV_{R-R}<2.2% compared with those with a CV_{R-R} ≥2.2% after adjustment for age, gender, SBP, TC, TG, BMI, ischemic ECG change, and smoking history. Identification of such a high-risk group for SCD among diabetic patients should aid in SCD prevention.

Diabetes is known as a risk factor for sudden death. In the Honolulu Heart Program [3], in which Japanese–American men are study subjects, RR of sudden death (2.59) was significantly higher in diabetic than nondiabetic subjects after adjusting for risk factors of ischemic heart disease. Recently, the Paris prospective study [8] demonstrated similar results, in which 55.2% of sudden deaths were caused by cardiovascular disease. Kuller et al. also reported similar findings [26]. Cardiovascular disease then is acknowledged as a major cause of sudden death.

An association between autonomic nerve dysfunction and sudden death has been demonstrated in patients after myocardial infarction. Hinkle et al. were the first investigators to report a relationship between heart rate and ischemic heart disease [12]. In a study from a multicenter post-infarction research group, Kleiger et al. reported that patients with low HRV had higher cardiovascular mortality [13]. Subsequent

studies also showed similar results [14,15]. At present, low HRV is recognized as a useful predictor of SCD after myocardial infarction [16–18].

As sudden death is frequently found in subjects with low HRV, it has been suggested that a reduction in parasympathetic nerve function induces fatal arrhythmias [19,20]. Since autonomic nerve dysfunction is one of the major complications of type 2 diabetes, a similar mechanism is likely to underlie fatal arrhythmias after myocardial infarction.

Novella et al. reported that sensory nerve system was impaired in case of impaired glucose tolerance and type 2 diabetes [27]. In current study, however, there was no relationship between HRV and SCD in borderline type.

Controversy persists about the clinical usefulness of HRV. One study suggested that HRV analyzed in short-term ECG is less predictive of SCD than analysis of long-term ECG [28]; other investigators considered these time frames equally predictive [29]. HRV analyzed by short-term ECG would be easier to implement for large-scale screening. Our data showed that HRV analyzed in successive 100 R–R intervals in a 12-lead ECG, a relatively simple method, could predict SCD in type 2 diabetes.

It has been reported that occurrence of SCD can be reduced by administration of β-blockers [30], selective denervation of cardiac nerves [31], and implantable defibrillators [32]. In a high-risk group, an appropriately selected prophylactic treatment might reduce risk of SCD. We conclude that diabetic patients with low HRV are at high risk for SCD, and might benefit from prophylaxis.

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