



Differential Patterns of Impaired Cardiorespiratory Fitness and Cardiac Autonomic Dysfunction in Recently Diagnosed Type 1 and Type 2 Diabetes

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OBJECTIVE

Both impaired cardiorespiratory fitness (CRF) and heart rate variability (HRV) are predictors of mortality, but their relative roles in recent-onset diabetes are unknown. We determined to which extent CRF and HRV are reduced and interrelated in recent-onset diabetes.

RESEARCH DESIGN AND METHODS

Participants from the German Diabetes Study with type 1 ($n = 163$) or type 2 ($n = 188$) diabetes with known diabetes duration <1 year and two age-matched glucose-tolerant control groups ($n = 40$ each) underwent spiroergometry and HRV assessment during a hyperinsulinemic-euglycemic clamp.

RESULTS

Compared with control subjects, patients with type 2 diabetes showed reduced VO_{2max} (median [1st–3rd quartiles] 19.3 [16.5–22.9] vs. 25.6 [20.7–29.9] mL/kg body weight/min; $P < 0.05$), diminished VCO_{2max} (23.0 [19.1–26.8] vs. 30.9 [24.5–34.4] mL/kg body weight/min; $P < 0.05$), blunted heart rate recovery after 2 min (-29.0 [-35.0 to -23.0] vs. -36.0 [-42.8 to -28.0] beats/min; $P < 0.05$), and reduced HRV in four of nine indices, whereas patients with type 1 diabetes had unaltered CRF but reduced HRV in three of nine indices ($P < 0.05$), indicating diminished vagal and sympathetic HRV modulation. HRV measures correlated with VO_{2max} in patients with type 1 diabetes ($r > 0.34$; $P < 0.05$) but not in those with type 2 diabetes.

CONCLUSIONS

CRF is reduced in recently diagnosed type 2 diabetes but preserved in type 1 diabetes, whereas cardiac autonomic function is reduced in both diabetes types but is strongly associated with CRF only in type 1 diabetes. These results support the therapeutic concept of promoting physical fitness in the early course of diabetes.

Both impaired cardiorespiratory fitness (CRF) and cardiac autonomic dysfunction are associated with an increased risk of mortality in individuals with long-term type 1 and type 2 diabetes (1–3). Cardiac autonomic neuropathy (CAN), assessed by reduced heart rate variability (HRV), is encountered in ~20% of patients with known diabetes (4,5) and predicts an increased risk of major cardiac events (2,6,7). On the other hand, prospective studies have suggested that reduced HRV predicts

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*A complete list of the members of the German Diabetes Study Group can be found in the APPENDIX.

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the development of type 2 diabetes in healthy adults (8,9), and lifestyle modification has been associated with improvement in HRV and, hence, an associated risk reduction for type 2 diabetes independent of weight change (10).

The prevalence of CAN increases with age and duration of diabetes in patients with type 1 or type 2 diabetes. Risk factors for CAN, particularly in type 2 diabetes, are poor glycemic control, dyslipidemia, abdominal obesity, and hypertension (11,12). CAN is characterized by damage of the autonomic nerve fibers that innervate the heart and blood vessels. The impairment of the autonomic nervous system leads to abnormalities in heart rate control and vascular dynamics, resulting in exercise intolerance, a decrease in peripheral blood flow to skeletal muscle, and reduced heart rate response and cardiac output (4,5).

Early studies in small groups of patients with long-standing diabetes demonstrated blunted circulatory, metabolic, and hormonal responses to exercise (13,14), which were more pronounced in patients with CAN than in those without

CAN (15). Furthermore, patients with long-standing diabetes and CAN have shown evidence of reduced CRF as assessed by VO_{2max} compared with those without CAN (16), suggesting a mechanistic link between CAN and impaired CRF. Disturbances in vagal and sympathetic modulation may contribute to a malfunction of the cardiorespiratory system, leading to reduced CRF (5). Furthermore, patients with diabetes and CAN show a reduced ventilatory response to hypercapnia, which has been attributed to an altered central control of respiration (17). On the other hand, reduced VO_2 and VCO_2 have also been observed in patients without CAN (15,18,19), suggesting that factors other than CAN may contribute to reduced CRF in diabetes. However, the relationship between CRF and cardiac autonomic dysfunction has not been previously investigated in the early phase of both type 1 and type 2 diabetes. We hypothesize that 1) patients with recently diagnosed type 1 or type 2 diabetes show early impairment in CRF and HRV compared with age-matched glucose-tolerant control subjects, and 2) parameters of CRF are associated with HRV indices.

RESEARCH DESIGN AND METHODS

Participants

Participants aged 18–69 years were recruited consecutively from the baseline cohort of the ongoing German Diabetes Study (GDS), a prospective observational study investigating the natural course of metabolic abnormalities in individuals given a recent diagnosis of type 1 or type 2 diabetes (known diabetes duration <1 year) compared with glucose-tolerant control subjects as well as the development of diabetes-associated chronic complications. Informed written consent was obtained from all participants before inclusion in the trial, which was approved by the ethics board of Heinrich Heine University. All GDS participants enrolled before December 2015 with complete data sets for spirometry and HRV were included in this analysis. The study design and cohort profile of GDS are described in detail elsewhere (20). In the current study, CRF and HRV were determined in 163 patients with type 1 diabetes and compared with 40 age-matched glucose-tolerant control subjects (control 1), and 188 patients with type 2 diabetes were compared with another 40 control subjects (control 2) (Table 1). Participants

Table 1—Demographic and clinical characteristics of the study participants

	Control 1	Type 1 diabetes	Control 2	Type 2 diabetes
<i>n</i>	40	163	40	188
Male sex	78.0	62.6	80.0	68.1
Age (years)	35 (25–46)	33 (26–45)	53 (45–61)	52 (45–59) ³
Height (cm)	179 (170–187)	177 (169–183)	177 (169–186)	175 (166–180)
BMI (kg/m ²)	25.7 (24.3–28.6)	24.5 (22.1–27.4) ¹	26.8 (25.7–30.8)	30.2 (26.3–33.4) ^{2,3}
Lean mass (kg)§	67.6 (56.5–72.2)	59.2 (49.6–66.0) ¹	61.6 (53.0–71.3)	59.7 (52.1–68.2)
Fat mass (kg)§	19.2 (13.7–28.7)	17.9 (13.4–24.0)	24.3 (20.6–33.2)	30.1 (23.1–38.0) ^{2,3}
Diabetes duration (years)	—	0.47 (0.33–0.74)	—	0.50 (0.33–0.74)
Regular smokers	30.0	22.7	22.5	22.3
Heart rate (bpm)	71 (66–78)	75 (67–84)	72 (65–78)	75 (67–85)
Systolic BP (mmHg)	112 (103–122)	113 (104–125)	117 (110–130)	121 (109–136)
Diastolic BP (mmHg)	76 (69–84)	78 (70–84)	82 (76–91)	82 (76–89)
Triglycerides (mg/dL)§	86 (54–112)	79 (58–109)	98 (78–155)	134 (95–203)
Creatinine (mg/dL)	0.90 (0.85–1.06)	0.90 (0.76–1.00)	0.92 (0.84–1.03)	0.84 (0.74–1.04)
HDL cholesterol (mg/dL)§	60 (47–74)	59 (49–71)	59 (42–68)	45 (37–52) ^{2,3}
LDL cholesterol (mg/dL)§	108 (88–133)	108 (90–128)	136 (113–153)	131 (110–158)
HbA _{1c} (%)	5.1 (5.0–5.3)	6.3 (5.8–7.0) ¹	5.3 (5.1–5.5)	6.2 (5.8–6.7) ²
HbA _{1c} (mmol/mol)	32.2 (31.1–33.9)	45.4 (39.9–53.0) ¹	34.4 (32.2–36.3)	44.3 (39.9–49.7) ²
Insulin	0.0	92.0	0.0	10.7 ³
Antidiabetic drugs	0.0	14.8	0.0	67.4 ³
Antihypertensive drugs	10.0	9.9	20.0	48.1 ^{2,3}
Micro/macroalbuminuria	5.9	6.9	2.9	15.6 ^{2,3}
Diabetic retinopathy	0.0	2.1	0.0	0.7

Data are % or median (1st–3rd quartile) unless otherwise indicated. BP, blood pressure; bpm, beats/min. ¹*P* < 0.05 vs. control 1; ²*P* < 0.05 vs. control 2; ³*P* < 0.05 vs. type 1 diabetes; §After adjustment for sex, age, BMI, HbA_{1c}, and smoking status.

who did not achieve the exhaustion criteria during spiroergometry, as defined below, were excluded (control $n = 6$, type 1 diabetes $n = 28$, type 2 diabetes $n = 103$).

Study Protocol and Assessment of CRF Parameters

On the first day of the study, each participant underwent an incremental exhaustive exercise test on an electronically braked cycle ergometer (Ergometrics 900; Ergoline, Bitz, Germany) at 60 revolutions/min. Respiratory gas exchange measurements were determined by open-air spirometry (MasterScreen CPX; Jaeger/VIASYS, Hoechberg, Germany). Work rate was increased by 10 W/min, and exhaustion was reached on average after 12–15 min. Heart rate and a 12-lead electrocardiogram (ECG) were recorded continuously, and arm blood pressure was recorded every 2 min during the test. Lactate was measured during the resting phase at the beginning and end of the incremental exhaustive exercise test, and the maximal change of lactate was determined. Parameters of CRF included VO_{2max} , oxidative capacity at anaerobic threshold (VO_{2AT}) and at the respiratory compensation point (VO_{2RCP}), and VCO_{2max} . Heart rate recovery (HRR_{ec}) was determined at 2 min after exercise termination during the cool-down phase. Heart rate reserve (HRR_{es}) was calculated as the difference between resting and maximal heart rate (HR_{max}). Mitochondrial plasticity was measured by the difference between the initial respiratory exchange ratio (RER) and maximal RER during the incremental exhaustive exercise test by determining ΔRER (21). Maximal minute ventilation (VE_{max}) was measured at the maximum load of the exercise test. Respiratory efficiency (VE/VCO_2 slope) was calculated by the response of VE to VCO_2 from continuous recordings at 5-s intervals until exhaustion (22). Exhaustion was defined in accordance with the statement of the American Thoracic Society/American College of Chest Physicians on cardiopulmonary exercise testing by the presence of one or more of the following criteria: 1) RER >1.15 or whether 2) predicted HR_{max} , 3) predicted VO_{2max} and/or a plateau, or 4) predicted maximal work rate were achieved (23).

HRV

R-R intervals were measured in the supine position on the second day of the study during a hyperinsulinemic-euglycemic clamp over 3 h by using a digital Spiderview Holter recorder with seven electrodes to record three-channel ECGs (Sorin Group, Munich, Germany). HRV was analyzed from the Holter monitor recordings with the SynScope version 3.00 analysis system (Sorin Group). The sampling rate or the ECG signal was 200 Hz (5-ms resolution). The system automatically filters all artifacts and ectopic beats and generates a regular signal by linear interpolation of the heart rate tachogram. Time domain and frequency domain measures were computed according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (24). Time domain measures included normal-to-normal (NN) mean R-R intervals, the SD of NN averages over 5 min (SDANN), SD of differences between adjacent NN intervals, SD of all NN intervals (SDNN), the number of pairs of adjacent NN intervals differing by >50 ms in the entire recording divided by the total number of NN intervals (pNN50), and the root mean square of successive differences (RMSSD). Frequency domain indices were the very-low-frequency (VLF) band (0.003–0.04 Hz), low-frequency (LF) band (0.04–0.15 Hz), high-frequency (HF) band (0.15–0.40 Hz), and LF/HF ratio as previously described (25).

Insulin Sensitivity

All participants underwent the modified Botnia clamp test with [6,6-2H]glucose to measure whole-body insulin sensitivity as previously described and validated (20). Whole-body insulin sensitivity (M-value: mg glucose \cdot body weight in $kg^{-1} \cdot min^{-1}$) was calculated from the difference between mean glucose infusion rates during steady state in the last 30 min of the clamp and glucose space correction.

Laboratory Analyses

HbA_{1c} , HDL, LDL, triglycerides, and creatinine were measured as previously described (20).

Bioelectrical Impedance

Fat-free mass and fat mass were measured using Nutriguard-S (Data Input, Darmstadt, Germany) by determining

resistance and reactance. Participants were examined in the morning after an overnight fast in the supine position with arms and legs abducted from their body. BIANOSTIC-AT double-size electrodes (Data Input, Pöcking, Germany) were fixed on the dorsum of the hand and foot of the dominant side of the body (26). Resistance and reactance were integrated into an equation to calculate fat-free mass and fat mass (27).

Statistical Analysis

Data are presented as median (1st–3rd quartiles) or percentages (95% CI). Variables with skewed distribution (CRF and HRV variables) were log-transformed before analyses. To determine differences between groups or correlations between variables, Mann-Whitney U test and Spearman rank correlation and Student t test and Pearson correlation analyses were applied for nonparametric and parametric data, respectively. Multiple linear regression analyses were performed using adjustments for sex, age, BMI, HbA_{1c} , and smoking status or sex, age, height, weight, HbA_{1c} , and smoking status, as indicated. To determine the factors associated with VO_{2max} , bivariate correlation analyses with demographic, clinical, and metabolic parameters were computed followed by multiple linear regression analyses that included VO_{2max} as a dependent variable and sex, age, BMI, smoking, systolic blood pressure, M-value, LDL cholesterol, triglycerides, and HRV parameters as independent variables. All statistical tests were two-sided, and the level of significance was set at $\alpha = 0.05$. P values were adjusted for multiple comparisons using the Bonferroni correction. All analyses were performed using SPSS version 22.0 software (IBM Corporation, Chicago, IL).

RESULTS

The demographic and clinical characteristics of the groups studied are listed in Table 1. Participants with type 2 diabetes had higher BMI, fat mass, HbA_{1c} , and rate of micro- and macroalbuminuria than control 2 and were older and had higher BMI and fat mass than the participants with type 1 diabetes (all $P < 0.05$). After adjusting for age, sex, BMI, HbA_{1c} , and smoking status, participants with type 2 diabetes had lower HDL cholesterol levels than control 2 and participants with type 1 diabetes ($P < 0.05$).

Participants with type 1 diabetes did not differ from control 1, except for lower BMI, lean mass, and higher HbA_{1c} (all $P < 0.05$). Participants with type 2 diabetes were more frequently treated with antihypertensive agents and showed a higher rate of micro- and macroalbuminuria than those with type 1 diabetes and control 2 (both $P < 0.05$). The individual antidiabetic and antihypertensive drugs and drug classes are listed in Supplementary Table 1.

The CRF parameters during the incremental exhaustive exercise test and HRV data in the four groups studied are listed in Table 2. Compared with control 2, participants with type 2 diabetes had reduced CRF as indicated by lower levels of VO_{2max} and VO_{2AT} and at VO_{2RCP} , VCO_{2max} , and VE_{max} , whereas initial RER was increased (all $P < 0.05$ vs. control 2). Participants with type 1 diabetes who showed preserved CRF, except for a reduced VCO_{2max} and VE_{max} and higher initial RER (all $P < 0.05$), also showed decreased levels of maximal lactate production and change of lactate after exercise termination compared with control 1 (both $P < 0.05$) (Supplementary Table 2). Participants with type 2 diabetes exhibited reduced HRV in four of nine indices and blunted heart rate

modulation to exercise as indicated by HR_{max} , HRR_{rec} , and HRR_{res} (all $P < 0.05$ vs. control 2). Participants with type 1 diabetes showed reductions in three of nine HRV indices (all $P < 0.05$ vs. control 1).

Table 3 lists the correlations of cardiorespiratory parameters with HRV, HRR_{rec} , and HRR_{res} . In participants with type 2 diabetes, HRR_{res} and four of eight indices of HRV correlated positively (all $P < 0.01$), whereas HRR_{rec} correlated inversely ($P < 0.001$) with VO_{2max} , even after adjustment for sex, age, height, weight, and smoking status. However, after Bonferroni correction (132 comparisons [three groups with 10 HRV and heart rate variables and 4 CRF variables], $P = 0.0000416$), only HRR_{res} and HRR_{rec} remained statistically significant (both $P < 0.0001$). The adjusted analyses of VO_{2RCP} exhibited positive associations with HRR_{res} and seven of eight indices of HRV (all $P < 0.05$) and an inverse correlation with HRR_{rec} ($P = 0.004$), but only the correlation with HRR_{res} remained statistically significant after Bonferroni correction ($P < 0.0001$). After adjustment for sex, age, height, weight, and smoking status, VO_{2AT} showed a positive association with HRR_{res} , even after Bonferroni

correction ($P < 0.0001$). VCO_{2max} correlated positively with HRR_{res} and LF power (all $P < 0.05$) and inversely with HRR_{rec} ($P < 0.0001$) after adjustment for sex, age, height, weight, and smoking status, but significance was lost after Bonferroni correction, except for HRR_{res} and HRR_{rec} (both $P < 0.0001$).

In participants with type 1 diabetes, all HRV parameters and HRR_{res} (all $P < 0.0001$) correlated positively, whereas HRR_{rec} ($P = 0.004$) was inversely associated with VO_{2max} after adjustment for sex, age, height, weight, and smoking status. Except for HRR_{rec} , all aforementioned associations remained statistically significant after Bonferroni correction (all $P < 0.0001$). In the adjusted analyses, VO_{2RCP} , VO_{2AT} , and VCO_{2max} showed positive correlations with HRR_{res} and seven of eight indices of HRV (all $P < 0.001$) that remained significant after Bonferroni correction (all $P < 0.0001$), except for SDANN and VO_{2AT} . In addition, HRR_{rec} correlated inversely with VCO_{2max} ($P = 0.005$), but this significance was lost after Bonferroni correction. Figure 1 illustrates the stronger positive association of VO_{2max} with SDNN in participants with type 1 diabetes compared with those with type 2 diabetes.

Multiple linear regression analysis showed that in participants with type 1

Table 2—Cardiorespiratory parameters and HRV in the four study groups

	Control 1	Type 1 diabetes	Control 2	Type 2 diabetes
VO_{2max} (mL/kg BW/min)	28.1 (25.0–36.1)	25.7 (22.5–31.6)	25.6 (20.7–29.9)	19.3 (16.5–22.9) ^{2,3}
VO_{2AT} (mL/kg BW/min)	17.6 (15.0–21.6)	15.2 (12.4–18.8)	16.6 (13.5–18.6)	11.7 (10.2–13.9) ^{2,3}
VO_{2RCP} (mL/kg BW/min)	26.1 (21.0–30.3)	23.2 (19.6–28.2)	22.2 (19.3–27.2)	17.3 (15.3–20.4) ^{2,3}
VCO_{2max} (mL/kg BW/min)	34.4 (29.6–43.5)	31.6 (26.2–38.6)	30.9 (24.5–34.4)	23.0 (19.1–26.8) ^{2,3}
VE_{max} (L/min)	102 (74–123)	73 (57–89) ¹	85 (72–111)	63 (51–78) ^{2,3}
VE/VCO_2 slope	33.1 (30.6–38.1)	36.0 (32.5–38.9)	33.0 (30.6–36.1)	33.9 (30.4–38.5)
HR_{max} (bpm)	175 (165–184)	175 (163–184)	161 (153–171)	156 (139–169) ^{2,3}
HRR_{rec} (bpm)	−37.0 (−41.8 to −30.5)	−34.0 (−40.0 to −27.8)	−36.0 (−42.8 to −28.0)	−29.0 (−35.0 to −23.0) ²
HRR_{res} (bpm)	99 (89–116)	98 (83–109)	87 (80–97)	77 (64–89) ^{2,3}
pNN50 (%)	19.3 (5.6–37.0)	15.0 (3.9–29.5)	5.6 (2.0–17.6)	4.7 (1.3–11.6)
RMSSD (ms)	43.6 (28.1–67.4)	40.3 (25.1–59.0)	28.2 (21.7–43.4)	26.9 (19.6–36.6)
SDNN (ms)	80.5 (51.8–105.5)	71.0 (52.1–90.6)	60.0 (48.8–76.4)	50.7 (41.1–63.9) ²
SDANN (ms)	56.7 (31.9–71.7)	38.2 (27.7–49.2) ¹	41.6 (31.7–58.5)	30.4 (22.4–40.6) ²
SD of differences between adjacent NN intervals (ms)	98 (69–134)	85 (63–107) ¹	78 (66–92)	64 (51–80) ²
VLF power (ms ²)	3,636 (1,819–6,814)	2,772 (1,463–4,495) ¹	1,991 (1,576–3,090)	1,498 (976–2,434) ²
LF power (ms ²)	1,386 (601–2,025)	1,269 (691–1,987)	678 (467–1,412)	577 (342–1,005)
HF power (ms ²)	459 (187–1,016)	464 (164–896)	187 (104–458)	154 (79–312)
LF/HF ratio	3.14 (1.84–4.21)	2.94 (2.03–4.97)	3.76 (2.66–5.68)	3.73 (2.50–5.76)

Data are median (1st–3rd quartiles). All analyses were adjusted for sex, age, BMI, HbA_{1c}, and smoking status, except for HRV measures compared between the diabetes and control groups. bpm, beats/min; BW, body weight.¹ $P < 0.05$ vs. control 1; ² $P < 0.05$ vs. control 2; ³ $P < 0.05$ vs. type 1 diabetes.

Table 3—Correlations of respiratory parameters with HRV, HRRec, and HRRes

	VO _{2max}		VO _{2RCP}		VO _{2AT}		VCO _{2max}	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
HRRec								
Type 1 diabetes	-0.256	<u>0.004</u>	-0.178	0.056	-0.129	0.157	-0.252	<u>0.005</u>
Type 2 diabetes	-0.309	<u>9 × 10⁻⁵</u>	-0.234	<u>0.004</u>	-0.232	<u>0.004</u>	-0.319	<u>5 × 10⁻⁵</u>
HRRes								
Type 1 diabetes	0.547	<u>5 × 10⁻¹⁴</u>	0.531	<u>2 × 10⁻¹²</u>	0.432	<u>1 × 10⁻¹⁰</u>	0.589	<u>2 × 10⁻¹⁶</u>
Type 2 diabetes	0.563	<u>5 × 10⁻¹⁷</u>	0.489	<u>3 × 10⁻¹²</u>	0.446	<u>2 × 10⁻¹⁰</u>	0.563	<u>5 × 10⁻¹⁷</u>
pNN50								
Type 1 diabetes	0.405	<u>9 × 10⁻⁸</u>	0.397	<u>4 × 10⁻⁷</u>	0.312	<u>5 × 10⁻⁵</u>	0.360	<u>3 × 10⁻⁶</u>
Type 2 diabetes	0.116	0.113	0.169	<u>0.022</u>	0.061	0.407	0.095	0.193
RMSSD								
Type 1 diabetes	0.401	<u>1 × 10⁻⁷</u>	0.385	<u>8 × 10⁻⁷</u>	0.342	<u>8 × 10⁻⁶</u>	0.350	<u>5 × 10⁻⁶</u>
Type 2 diabetes	0.123	0.092	0.165	<u>0.026</u>	0.088	0.230	0.097	0.185
SDNN								
Type 1 diabetes	0.461	<u>6 × 10⁻¹⁰</u>	0.443	<u>9 × 10⁻⁹</u>	0.397	<u>2 × 10⁻⁷</u>	0.404	<u>9 × 10⁻⁸</u>
Type 2 diabetes	0.228	<u>0.002</u>	0.260	<u>4 × 10⁻⁴</u>	0.142	<u>0.052</u>	0.210	<u>0.004</u>
SDANN								
Type 1 diabetes	0.297	<u>1 × 10⁻⁴</u>	0.302	<u>1 × 10⁻⁴</u>	0.303	<u>8 × 10⁻⁵</u>	0.299	<u>1 × 10⁻⁴</u>
Type 2 diabetes	0.039	0.597	0.128	0.085	0.078	0.289	0.037	0.611
SD of differences between adjacent NN intervals								
Type 1 diabetes	0.460	<u>6 × 10⁻¹⁰</u>	0.446	<u>7 × 10⁻⁹</u>	0.407	<u>7 × 10⁻⁸</u>	0.417	<u>3 × 10⁻⁸</u>
Type 2 diabetes	0.190	<u>0.009</u>	0.250	<u>0.001</u>	0.146	<u>0.046</u>	0.178	<u>0.015</u>
VLF power								
Type 1 diabetes	0.475	<u>1 × 10⁻¹⁰</u>	0.445	<u>7 × 10⁻⁹</u>	0.394	<u>2 × 10⁻⁷</u>	0.420	<u>2 × 10⁻⁸</u>
Type 2 diabetes	0.232	<u>0.001</u>	0.253	<u>0.001</u>	0.138	<u>0.059</u>	0.219	<u>0.003</u>
LF power								
Type 1 diabetes	0.442	<u>3 × 10⁻⁹</u>	0.429	<u>3 × 10⁻⁸</u>	0.393	<u>2 × 10⁻⁷</u>	0.379	<u>6 × 10⁻⁷</u>
Type 2 diabetes	0.230	<u>0.002</u>	0.247	<u>0.001</u>	0.133	0.068	0.214	<u>0.003</u>
HF power								
Type 1 diabetes	0.344	<u>7 × 10⁻⁶</u>	0.360	<u>4 × 10⁻⁶</u>	0.298	<u>1 × 10⁻⁴</u>	0.290	<u>2 × 10⁻⁴</u>
Type 2 diabetes	0.113	0.121	0.149	<u>0.045</u>	0.054	0.465	0.098	0.179

Bonferroni adjusted ($P < 0.0000416$): boldface indicates that the value remains significant after Bonferroni correction; underlined indicates that the value remains significant after adjustment for sex, age, height, weight, and smoking status. All data were log-transformed before analysis, except for HRRec.

diabetes, lower VO_{2max} was independently associated with lower HRV (e.g., SDNN: $\beta = 0.227$; $P = 0.005$), female sex ($\beta = -0.209$; $P = 0.006$), and lower M-value ($\beta = 0.408$; $P < 0.0001$). In the group with type 2 diabetes, lower VO_{2max} was independently associated with female sex ($\beta = -0.368$; $P < 0.0001$), lower M-value ($\beta = 0.200$;

$P = 0.008$), and higher BMI ($\beta = -0.296$; $P < 0.0001$).

CONCLUSIONS

The results of this study demonstrate reduced CRF in patients with recently diagnosed type 2 diabetes compared with age-matched glucose-tolerant control

subjects. In contrast, patients with type 1 diabetes showed no clear differences in CRF compared with healthy control subjects. Moreover, the current study not only points to reduced HRV in both recent-onset type 1 and type 2 diabetes but also suggests an association between CRF and HRV in type 1 diabetes rather than in type 2 diabetes.

Previous studies have demonstrated reduced CRF in patients with long-standing type 2 diabetes (15) but no impairment of CRF in small samples of individuals with long-term type 1 diabetes without CAN (28). In studies that reported diminished CRF in long-term type 1 diabetes, the latter was attributed to the presence of CAN (5). Thus, we extend this differential pattern of CRF involvement in type 2 as opposed to type 1 diabetes to the early phase of diabetes. One possible explanation for the differences between both diabetes

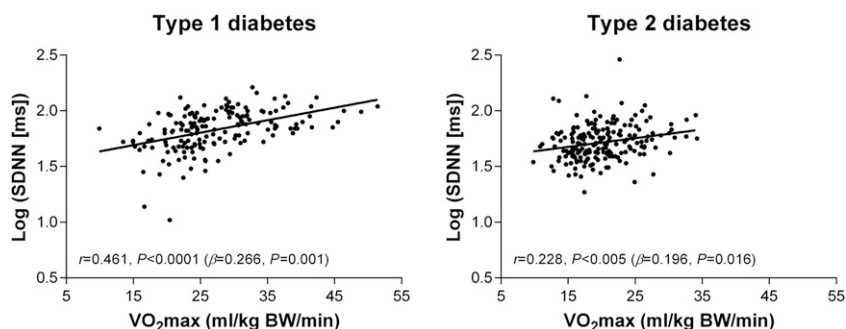


Figure 1—Correlation between VO_{2max} and SDNN in patients with type 1 and type 2 diabetes. Analyses were adjusted for sex, age, height, weight, and smoking status. BW, body weight.

types in this study could be the influence of insulin resistance, body composition (e.g., BMI), and mitochondrial impairment, which are more pronounced in long-term type 2 diabetes (29). Oxidative metabolism, which is primarily controlled by mitochondria, appears to play a critical role in glucose uptake. Therefore, defects in mitochondria biogenesis can decrease the ability of the muscle to oxidize substrates (21). In patients with insulin resistant type 2 diabetes, molecular impairments as well as morphological alterations lead to a decrease of mitochondrial activity and oxidative phosphorylation capacity (21). A recent study indirectly supports this notion by showing a positive correlation between insulin sensitivity and VO_{2max} in patients with recently diagnosed type 2 diabetes (30). On the other hand, disturbed vascular dynamics caused by autonomic dysfunction might lead to an impaired peripheral blood flow to skeletal muscles as well as to diminished cardiac output and, subsequently, to reduced CRF (4).

Furthermore, we demonstrate reduced HRR_{rec} and HRR_{es} in the type 2 diabetes group compared with age-matched glucose-tolerant control subjects, which persisted after adjustment for sex, age, BMI, HbA_{1c}, and smoking status. This has also been shown in people with impaired glucose tolerance (31) as well as in healthy adults with an increased risk for diabetes (9,32). This reduction could be due to a defective parasympathetic and sympathetic control of heart rate, which is a typical sign of cardiac autonomic dysfunction (4). Similar to the CRF parameters, participants with recently diagnosed type 1 diabetes did not show altered HRR_{rec} and HRR_{es} compared with age-matched control subjects. In contrast, patients with long-term type 1 diabetes (33) have shown reduced HRR_{rec} and HRR_{es}. Factors such as increasing age, diabetes duration, and poor glycemic control (4) conceivably contribute to altered heart rate modulation to exercise during the further course of type 1 diabetes. Furthermore, HRR_{es} was more strongly associated with CRF parameters in type 2 than in type 1 diabetes. Reduced CRF leads to impaired parasympathetic modulation, resulting in a lower HR_{max} during exercise and, as a consequence, to reduced HRR_{es} (4).

We also found that participants recently diagnosed with type 1 and type 2 diabetes already showed signs of cardiac

autonomic dysfunction. In line with our observations, a recent study in patients with newly diagnosed type 2 diabetes reported a prevalence of 1.8% for confirmed CAN and 15.3% for early CAN based on cardiovascular autonomic reflex tests (34). We previously found a similar rate in newly diagnosed type 1 diabetes (35). The current study extends these findings by measuring HRV over a prolonged period during resting euglycemic conditions. An explanation for the presence of CAN in recent-onset diabetes could be that HRV is impaired by early subtle glucometabolic disturbances. A recent study reported associations between glycemic variability and reduced cardiac autonomic modulation in patients with newly diagnosed and long-term type 2 diabetes (36). In line with this, nondiabetic hyperinsulinemia was associated with decreased HRV in the Atherosclerosis Risk in Communities (ARIC) study (37).

These results agree with findings of exercise intervention studies in a small sample of patients with long-term type 2 diabetes (38) and in people at increased risk for diabetes, showing that increased physical activity, which may reflect an increase in oxidative capacity, is associated with an improvement in HRV (10,38). However, a predominant association of CRF with cardiac autonomic function in type 1 diabetes was found. Multiple regression analysis revealed that lower VO_{2max} was associated with higher BMI in type 2 but not in type 1 diabetes, whereas lower VO_{2max} was positively associated with lower insulin sensitivity in both diabetes types. Thus, the predominant association of VO_{2max} with HRV in type 1 diabetes may be explained by the attenuation of this relationship by higher BMI in type 2 diabetes rather than by differences in insulin sensitivity.

Of note, the current study identified reduced VE_{max} in both diabetes types as well as reduced VCO_{2max} during exercise in recent-onset type 2 diabetes. In contrast, studies in small samples of patients with long-term type 2 diabetes with diabetic autonomic neuropathy (DAN) found no difference in VE_{max} compared with healthy control subjects (18,19). An explanation for these apparently contradictory results could be that DAN in long-term diabetes contributes to both vagal damage and overactivity in the sympathetic nervous system, the latter leading to an increased VE_{max} comparable to

levels observed in control subjects (5,18,19). On the other hand, individuals with type 1 and type 2 diabetes have shown reduced lung function independent of DAN (19,39). A reduction in the ventilatory response could be interpreted as an early sign of DAN, influencing the central chemoreceptors of the medullary neurons (17,22).

The strengths of this study are the relatively large number of patients per group who had well-controlled diabetes and underwent detailed phenotypic characterization assessed by a state-of-the-art methodology. Furthermore, HRV was determined during a 3-h hyperinsulinemic-euglycemic clamp, avoiding the impact of confounding factors such as glycemic imbalances (40), although we admit that this approach may not take into account possible sympathetic activation by insulin (40). However, if sympathetic activation would have been relevant, a higher LF/HF ratio as an indicator of sympathovagal balance would be expected due to higher insulin levels in the participants with type 2 diabetes than in control subjects. In fact, the LF/HF ratio was similar in the two groups, suggesting that sympathetic activation due to increased insulin levels did not appear to bias the HRV data to a relevant extent. A study limitation is the cross-sectional design, which does not provide insight into the temporal sequence of the observed abnormalities.

In conclusion, this study demonstrates that CRF is reduced in patients recently diagnosed with type 2 diabetes but preserved in those with recent-onset type 1 diabetes. Cardiac autonomic function was decreased in both diabetes types compared with age-matched glucose-tolerant control subjects, but a strong association of CRF with cardiac autonomic function was found primarily in type 1 diabetes. The temporal sequence of these findings remains to be established in a prospective study. Overall, the results support the therapeutic concept to promote physical activity and to achieve physical fitness, especially in the early course of diabetes. Indeed, exercise intervention programs show improvement in HRV in people with prediabetes and patients with early CAN independent of weight change (10,38). Improvement in CRF during exercise programs conceivably is mediated by favorably modulating the autonomic nervous system, which should be considered in future studies.

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Appendix

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References

- Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med* 2000;132:605–611
- Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 2006;29:334–339
- Ziegler D, Voss A, Rathmann W, et al.; KORA Study Group. Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: the KORA S4 survey. *Diabetologia* 2015;58:1118–1128
- Vinik AJ, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;115:387–397
- Hilsted J. Pathophysiology in diabetic autonomic neuropathy: cardiovascular, hormonal, and metabolic studies. *Diabetes* 1982;31:730–737
- Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes* 2002;51:3524–3531
- Young LH, Wackers FJ, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;301:1547–1555
- Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study, 1987–1998. *Circulation* 2003;107:2190–2195
- Carnethon MR, Jacobs DR Jr, Sidney S, Liu K; CARDIA Study. Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study. *Diabetes Care* 2003;26:3035–3041
- Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME; Diabetes Prevention Program Research Group. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care* 2006;29:914–919
- Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011;27:639–653
- Voulgari C, Psallas M, Kokkinos A, Argiana V, Katsilambros N, Tentolouris N. The association between cardiac autonomic neuropathy with metabolic and other factors in subjects with type 1 and type 2 diabetes. *J Diabetes Complications* 2011;25:159–167
- Storstein L, Jervell J. Response to bicycle exercise testing in long-standing juvenile diabetes. *Acta Med Scand* 1979;205:227–230
- Hilsted J, Galbo H, Christensen NJ, Parving HH, Bønn J. Haemodynamic changes during graded exercise in patients with diabetic autonomic neuropathy. *Diabetologia* 1982;22:318–323
- Bottini P, Tantucci C, Scionti L, et al. Cardiovascular response to exercise in diabetic patients: influence of autonomic neuropathy of different severity. *Diabetologia* 1995;38:244–250
- Kremser CB, Levitt NS, Borow KM, et al. Oxygen uptake kinetics during exercise in diabetic neuropathy. *J Appl Physiol* (1985) 1988;65:2665–2671
- Wanke T, Abrahamian H, Lahrmann H, et al. No effect of naloxone on ventilatory response to progressive hypercapnia in IDDM patients. *Diabetes* 1993;42:282–287
- Tantucci C, Bottini P, Dottorini ML, et al. Ventilatory response to exercise in diabetic subjects with autonomic neuropathy. *J Appl Physiol* (1985) 1996;81:1978–1986
- Tantucci C, Scionti L, Bottini P, et al. Influence of autonomic neuropathy of different severities on the hypercapnic drive to breathing in diabetic patients. *Chest* 1997;112:145–153
- Szendroedi J, Saxena A, Weber KS, et al.; GDS Group. Cohort profile: the German Diabetes Study (GDS). *Cardiovasc Diabetol* 2016;15:59
- Szendroedi J, Phielix E, Roden M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. *Nat Rev Endocrinol* 2011;8:92–103
- Bernardi L, Bianchi L. Integrated cardiorespiratory control: insight in diabetes. *Curr Diab Rep* 2016;16:107
- American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–1065
- Herder C, Schamarek I, Nowotny B, et al.; German Diabetes Study Group. Inflammatory markers are associated with cardiac autonomic dysfunction in recent-onset type 2 diabetes. *Heart*. 1 August 2016 [Epub ahead of print]. DOI: 10.1136/heartjnl-2015-309181
- Norman K, Smoliner C, Valentini L, Lochs H, Pirllich M. Is bioelectrical impedance vector analysis of value in the elderly with malnutrition and impaired functionality? *Nutrition* 2007;23:564–569
- Segal KR, Van Loan M, Fitzgerald PI, Hodgdon JA, Van Itallie TB. Lean body mass estimation by bioelectrical impedance analysis: a four-site cross-validation study. *Am J Clin Nutr* 1988;47:7–14
- Veves A, Saouaf R, Donaghue VM, et al. Aerobic exercise capacity remains normal despite impaired endothelial function in the micro- and macrocirculation of physically active IDDM patients. *Diabetes* 1997;46:1846–1852
- Kaul K, Apostolopoulou M, Roden M. Insulin resistance in type 1 diabetes mellitus. *Metabolism* 2015;64:1629–1639
- Apostolopoulou M, Strassburger K, Herder C, et al.; GDS Group. Metabolic flexibility and oxidative capacity independently associate with insulin sensitivity in individuals with newly diagnosed type 2 diabetes. *Diabetologia* 2016;59:2203–2207
- Panzer C, Lauer MS, Brieke A, Blackstone E, Hoogwerf B. Association of fasting plasma glucose with heart rate recovery in healthy adults: a population-based study. *Diabetes* 2002;51:803–807
- Jae SY, Kurl S, Laukkanen JA, et al. Exercise heart rate reserve and recovery as predictors of incident type 2 diabetes. *Am J Med* 2016;129:536.e7–536.e12
- Turker Y, Aslantas Y, Aydin Y, et al. Heart rate variability and heart rate recovery in patients with type 1 diabetes mellitus. *Acta Cardiol* 2013;68:145–150
- Zoppini G, Cacciatori V, Raimondo D, et al. Prevalence of cardiovascular autonomic neuropathy in a cohort of patients with newly diagnosed type 2 diabetes: the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS). *Diabetes Care* 2015;38:1487–1493
- Ziegler D, Dannehl K, Volksw D, Mühlen H, Spüler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis and standard tests of heart-rate variation in newly diagnosed IDDM patients. *Diabetes Care* 1992;15:908–911
- Fleischer J, Lebeck Cichosz S, Hoeyem P, et al. Glycemic variability is associated with reduced cardiac autonomic modulation in women with type 2 diabetes. *Diabetes Care* 2015;38:682–688
- Schroeder EB, Chambless LE, Liao D, et al.; Atherosclerosis Risk in Communities (ARIC) Study. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2005;28:668–674
- Voulgari C, Pagoni S, Vinik A, Poirier P. Exercise improves cardiac autonomic function in obesity and diabetes. *Metabolism* 2013;62:609–621
- Innocenti F, Fabbri A, Anichini R, et al. Indications of reduced pulmonary function in type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res Clin Pract* 1994;25:161–168
- Weissman A, Lowenstein L, Peleg A, Thaler I, Zimmer EZ. Power spectral analysis of heart rate variability during the 100-g oral glucose tolerance test in pregnant women. *Diabetes Care* 2006;29:571–574