# Reduced Heart Rate Variability Among Youth With Type 1 Diabetes

## The SEARCH CVD study

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**OBJECTIVE**—This study compared heart rate variability (HRV) parameters in youth with and without type 1 diabetes and explored potential contributors of altered HRV.

**RESEARCH DESIGN AND METHODS**—HRV parameters were measured among 354 youth with type 1 diabetes (mean age 18.8 years, diabetes duration 9.8 years, and mean A1C 8.9%) and 176 youth without diabetes (mean age 19.2 years) participating in the SEARCH CVD study. Multiple linear regression was used to assess the relationship between diabetes status and HRV parameters, adjusting for covariates.

**RESULTS**—Compared with control subjects, youth with type 1 diabetes had reduced overall HRV (10.09 ms lower SD of NN intervals [SDNN]) and markers of parasympathetic loss (13.5 ms reduced root mean square successive difference of NN intervals [RMSSD] and 5.2 normalized units (n.u.) reduced high frequency [HF] power) with sympathetic override (5.2 n.u. increased low frequency [LF] power), independent of demographic, anthropometric, and traditional cardiovascular risk factors. Older age, female sex, higher LDL cholesterol and triglyceride levels, and presence of microalbuminuria were independently associated with lower HRV but did not account for the observed differences between youth with and without diabetes. Youth with type 1 diabetes and A1C levels ≥7.5% had significantly worse HRV parameters than control subjects; however, in youth with optimal glycemic control (A1C <7.5%), HRV parameters did not differ significantly from control subjects.

**CONCLUSIONS**—Youth with type 1 diabetes have signs of early cardiac autonomic neuropathy: reduced overall HRV and parasympathetic loss with sympathetic override. The main driver of these subclinical abnormalities appears to be hyperglycemia.

*Diabetes Care* **36:157–162, 2013**

Cardiac autonomic neuropathy (CAN) is one of the most overlooked chronic complications of diabetes, progressing silently over time before it becomes clinically apparent (1). Since individuals with diabetes and CAN have a 3.4 times higher risk of mortality than those without CAN, early identification may mitigate the increased risk (2). Reduced heart rate variability (HRV) is the earliest subclinical marker of CAN and has been shown to increase the risk of arrhythmia, sudden death, and silent myocardial ischemia in adults (1). Subclinical CAN has been detected within a year of diagnosis in individuals with type 2 diabetes and within 2 years in individuals with type 1 diabetes (3). Several epidemiological studies have documented the prevalence and correlates of CAN in adults with diabetes (1,4–6). The European Epidemiology and Prevention of Diabetes (EURODIAB) study reported 36% CAN prevalence among nearly 3,000 adults with type 1 diabetes (4). However, data regarding the presence and correlates of subclinical CAN among contemporary youth and young adults with type 1 diabetes are sparse (7–10). On one hand, these individuals with type 1 diabetes have a younger age at onset and thus a longer duration of hyperglycemia (11); on the other hand, they are benefiting from more sophisticated insulin regimens and improved glucose monitoring than persons with type 1 diabetes diagnosed in earlier years (12). To address this gap, we explored the presence of subclinical markers of CAN among youth with and without type 1 diabetes and assessed the demographic, anthropometric, and metabolic risk factors associated with these markers in the SEARCH Cardiovascular Disease Study (SEARCH CVD).

## RESEARCH DESIGN AND METHODS

—SEARCH CVD is an ancillary study to the SEARCH for Diabetes in Youth study, conducted in Colorado and Ohio. SEARCH is a multicenter study that conducts population-based ascertainment of nongestational cases of physician-diagnosed diabetes in youth aged <20 years at diagnosis (13). A total of 406 youth who had a physician diagnosis of type 1 diabetes were registered with SEARCH, were residents of Colorado or Ohio, were aged 11–26 years during 2009–2011, and had duration of diabetes of at least 5 years were enrolled in the SEARCH CVD study. During the same time period, a total of 204 frequency-matched (by age, sex, and race/ethnicity) youth without diabetes (control subjects) were also recruited in the study. Because all SEARCH cases arose from health care provider offices, we recruited control youth from primary care offices in the same geographic areas. Within clinical sites, control recruitment sampled youth based on the distribution of age, sex, and

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Received 8 March 2012 and accepted 8 July 2012.
DOI: 10.2337/dc12-0463

racial/ethnic background of case subjects. For defined periods of time, participating primary care offices provided an initial study brochure, and patients and their parent or guardian were asked to complete a one-page information form and an indication of permission for study staff to contact them regarding participation in the study. The study staff contacted those interested in learning more about the study and recruited participants accordingly. Control participants were confirmed to be nondiabetic based on fasting glucose levels <126 mg/dL (14). The study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study population, and all participants provided signed informed consent or assent.

### Anthropometric and metabolic measurements

Participants were invited for an outpatient research visit after an 8-h overnight fast. Youth with diabetes were asked to withhold their diabetes medications, including short-acting insulin, on the morning of the visit until after the blood draw was complete. All participants were asked to refrain from any strenuous exercise, smoking, or caffeinated drinks 12 h prior to the visit. Race/ethnicity was self-reported using 2000 U.S. Census–based questions. For these analyses, race/ethnicity was categorized as non-Hispanic white (NHW) and race/ethnicity other than NHW, including Hispanic, African American, and Asian/Pacific Islander racial/ethnic groups. Participants completed standardized questionnaires including medical history, medication inventory, smoking status, physical activity, daily insulin dose, family history of diabetes, and CVD. Cigarette smoking was defined as having smoked cigarettes on ≥1 of the 30 days preceding the survey. Youth who had never smoked a whole cigarette were considered nonsmokers. Participants were asked the average number of days in a typical week that they participated in physical activity for at least 20 min that made them sweat or breathe hard and were then categorized as physically inactive (0–2 days/week) or physically active (3–7 days/week) (15). Height was measured in centimeters using a stadiometer and weight in kilograms using a standardized weighing machine. BMI was calculated as weight in kilograms divided by the square of height in meters, and age- and sex-specific BMI *z* scores were derived based on the Centers for Disease Control and Prevention national standards (16). Waist circumference was measured to the nearest 0.1 cm with the National Health and Nutrition Examination Survey (NHANES) protocol (17). Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times, using aneroid sphygmomanometer, while the subjects were seated for at least 5 min, and the average of the three measurements was taken. Laboratory samples were obtained under conditions of metabolic stability, defined, for subjects with type 1 diabetes, as no episodes of diabetic ketoacidosis during the previous month. A fasting blood draw was conducted for the assessment of the metabolic parameters (A1C, LDL cholesterol, HDL, and triglyceride levels). Blood specimens were processed locally and shipped to a central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). Urinary albumin was measured from overnight timed urine samples by radioimmunoassay and was expressed as albumin excretion rate (AER). AER between 20 and 200 μg/min was defined as microalbuminuria, while ≥200 μg/min was defined as macroalbuminuria. High-performance liquid chromatography (TOSOH Bioscience, San Francisco, CA) was used to measure A1C. Measurements of triglyceride and HDL cholesterol were performed enzymatically on a Hitachi 917 autoanalyzer (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN). LDL cholesterol was calculated by the Friedewald equation for individuals with triglyceride concentration <400 mg/dL and the Beta Quantification procedure for those with triglycerides of ≥400 mg/dL.

### Assessment of HRV

All measurements of HRV were conducted in the morning between 7 and 11 A.M. in a room with a stable room temperature while the participant was lying in the resting supine position for 10 min and breathing at a normal pace, using the SphygmoCor device (AtCor Medical). The device takes into account the normal heart beats, ignoring the ectopic beats, to derive the statistical parameters of the normal *R-R* intervals (NN intervals) of the ECG and computes several time and frequency domain HRV indices. The time domain indices of HRV used in these analyses were the SD of the NN intervals (SDNN) and the root mean square differences of successive NN intervals (RMSSD). The frequency domain indices of HRV that were measured were the normalized HF (high frequency) power, LF (low frequency) power, and the LF-to-HF ratio. The SphgmoCor device derives the normalized LF and HF power by expressing them as a fraction of the total power [LF n.u. = LF/(total power [TP] − very low frequency [VLF]) × 100 and HF n.u. = HF/(TP − VLF) × 100], where n.u. is normalized units. SDNN is a measure of overall HRV, so lower SDNN levels indicate reduced overall HRV (18). RMSSD and HF power represent the parasympathetic component of the HRV (19), and thus parasympathetic loss is quantified by the reduction in the RMSSD and HF power. The LF power is indicative of the sympathetic control of the cardiac function, and an increased LF-to-HF ratio denotes the increased sympathovagal balance (20). Combined parasympathetic and sympathetic loss is indicated by a reduction in all the above HRV parameters including the LF-to-HF ratio.

### Statistical analyses

Statistical analyses were performed using SAS for Windows (version 9.2; SAS Institute, Cary, NC). SDNN, RMSSD, triglyceride, and AER were log transformed to better meet model assumptions (e.g., homogeneity of variance). *t* tests and $\chi^2$ tests were used to test for differences in continuous and categorical variables between youth with and without type 1 diabetes, respectively. ANCOVA was used to assess the relationship between diabetes status (type 1 diabetic vs. control subjects) and several HRV parameters, independent of demographic, anthropometric, and traditional CVD risk factors. For a better understanding of the influence of hyperglycemia on HRV abnormalities, youth with type 1 diabetes were categorized according to their glycemic control as optimal (A1C <7.5%) and suboptimal (A1C ≥7.5%), based on American Diabetes Association (ADA) recommendations (21), and each category was compared with the referent control group.

**RESULTS**—A total of 530 youth, 354 with and 176 without type 1 diabetes, with complete HRV measurements were included in these analyses. Table 1 shows the characteristics of the study population by diabetes status. There were no significant differences in mean age or sex distribution among youth with and without diabetes, although youth with diabetes were more likely to be NHW than control

**Table 1—*Characteristics of youth with and without type 1 diabetes participating in SEARCH CVD***

| Variable | Type 1 diabetic subjects | Control subjects | *P* |
|---|---|---|---|
| *N* | 354 | 176 | |
| Race (% NHW) | 308 (87%) | 132 (75%) | 0.0005 |
| Sex (% female) | 170 (48%) | 95 (54%) | 0.1 |
| Age (years) | 18.8 (3.3) | 19.2 (3.3) | 0.1 |
| Diabetes duration (years) | 9.8 (3.8) | N/A | — |
| BMI (kg/m$^2$) | 24.5 (4.7) | 25.2 (6.5) | 0.1 |
| BMI *z* score | 0.6 (0.9) | 0.6 (1.1) | 0.9 |
| Smoking status, *n* (%) | | | 0.6 |
| Smoker | 149 (42) | 77 (44) | |
| Nonsmoker | 205 (58) | 99 (56) | |
| Waist circumferences (cm) | 85.4 (12.8) | 87.3 (16.4) | 0.1 |
| Physical activity status, *n* (%) | | | 0.7 |
| Inactive (0–2 days/week) | 149 (42) | 72 (41) | |
| Active (3–7 days/week) | 205 (58) | 104 (59) | |
| SBP (mmHg) | 110.9 (9.8) | 110.4 (10.7) | 0.6 |
| DBP (mmHg) | 70.3 (8.9) | 68.8 (8.6) | 0.04 |
| HR (bpm) | 68.2 (11.8) | 62.2 (9.5) | <0.0001 |
| $HbA_{1c}$ (%) | 8.9 (1.8) | 5.0 (0.3) | <0.0001 |
| % microalbuminuria (≥20 μg/min) | 31 (9.0) | 5 (2.7) | 0.006 |
| HDL cholesterol (mg/dL) | 53.4 (13.5) | 49.6 (13.6) | 0.001 |
| Triglyceride (mg/dL) | 95.0 (58.1) | 102.0 (58.1) | 0.06* |
| LDL cholesterol (mg/dL) | 98.0 (28.6) | 92.8 (25.8) | 0.03* |
| SDNN (ms) | 70.2 (35.4) | 79.4 (31.7) | 0.003 |
| RMSSD (ms) | 63.7 (41.5) | 77.7 (40.3) | 0.0003 |
| HF power (n.u.) | 51.8 (18.5) | 58.4 (18.5) | 0.0001 |
| LF power (n.u.) | 48.1 (18.5) | 41.5 (18.5) | 0.0001 |
| LF-to-HF ratio | 1.31 (1.32) | 1.0 (1.1) | 0.007 |

Data are means (SD) unless otherwise indicated. *P value based on log-transformed variables.

subjects (87 vs. 75%, $P = 0.0005$). BMI, waist circumference, and SBP were similar among youth with and without type 1 diabetes. However, youth with type 1 diabetes had a worse metabolic profile with higher A1C ($P < 0.0001$) and LDL cholesterol ($P = 0.03$) levels and a higher prevalence of microalbuminuria (9 vs. 2.7%, $P = 0.006$). DBP and heart rate were also significantly higher among youth with type 1 diabetes compared with their healthy counterparts ($P = 0.04$ and <0.0001, respectively). The prevalence of smoking and physical activity was similar in the two groups. Youth with type 1 diabetes had significantly worse HRV parameters with lower SDNN, RMSSD, and HF and higher LF and LF-to-HF ratio (all $P < 0.05$) compared with youth without diabetes.

Table 2 displays the results of the multiple linear regression analyses exploring the association between diabetes status and HRV parameters, independent of other demographic, anthropometric, and traditional CVD risk factors. All HRV variables were altered among youth with type 1 diabetes compared with control subjects, independent of age, sex, race/ethnicity, and traditional CVD risk factors, suggesting a role for diabetes-related hyperglycemia in mediating these abnormalities.

### Reduced overall HRV

SDNN, a marker of overall HRV, was 10 ms lower among youth with type 1 diabetes compared with control subjects ($P = 0.003$). Other variables independently associated with lower SDNN were older age ($P = 0.05$), female sex ($P = 0.0007$), elevated LDL cholesterol ($P = 0.05$), triglyceride levels ($P = 0.03$), and presence of microalbuminuria ($P = 0.02$).

### Markers of parasympathetic loss

RMSSD and HF power are markers of parasympathetic function. RMSSD was 13.5 ms lower in youth with type 1 diabetes versus control subjects ($P = 0.001$). Other variables associated with lower RMSSD, independent of diabetes status, were older age ($P = 0.02$) and higher LDL cholesterol ($P = 0.01$). HF power was lower among youth with type 1 diabetes by 5.2 n.u. ($P = 0.004$). Increasing age, female sex, and race/ethnicity other than NHW were also significantly associated with lower HF power.

### Markers of sympathetic override

LF power, a surrogate for sympathetic dysfunction, was higher among youth with type 1 diabetes compared with healthy control subjects by 5.2 n.u. ($P = 0.004$), suggesting sympathetic overdrive. As a consequence, the LF-to-HF ratio was higher by 0.2 units among youth with type 1 diabetes compared with control subjects ($P = 0.005$).

Table 3 further explores the role of hyperglycemia by comparing adjusted mean levels of various HRV parameters in youth with type 1 diabetes with optimal (A1C <7.5%) and suboptimal (A1C ≥7.5%) glycemic control versus those observed among healthy youth after adjustment for demographic, anthropometric, and traditional CVD risk factors. Youth with type 1 diabetes and suboptimal glycemic control had significantly lower SDNN, RMSSD, and HF power and higher LF power compared with the youth without diabetes. Differences in HRV parameters between youth with type 1 diabetes and optimal glycemic control and youth without diabetes were substantially reduced and were not statistically significant.

**CONCLUSIONS**—We found evidence of reduced overall HRV, including a pattern of parasympathetic loss with sympathetic overdrive, among youth and young adults with type 1 diabetes, independent of traditional CVD risk factors. Our findings suggest an important role for hyperglycemia in mediating these abnormalities in a contemporary cohort of diverse youth with an average duration of diabetes of ~10 years. Older age, female sex, elevated LDL cholesterol and triglyceride levels, and microalbuminuria were also associated with reduced HRV, independent of diabetes status.

Although reduced HRV has been associated with an increased risk of arrhythmia, sudden death, and silent myocardial infarction in adults (1), it is difficult to directly quantify the clinical importance of the observed reduction in overall HRV among youth with type 1

**Table 2—*Associations between HRV parameters and type 1 diabetes status from multiple linear regression analysis***

| | Overall HRV: SDNN (ms) | | Parasympathetic function | | | | Sympathetic function | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | RMSSD (ms) | | HF (n.u.) | | LF (n.u.) | | LF-to-HF ratio | |
| | β (95% CI) | *P* | β (95% CI) | *P* | β (95% CI) | *P* | β (95% CI) | *P* | β (95% CI) | *P* |
| Diabetes versus no diabetes | **−10.09 (−16.8 to −3.2)** | **0.003** | **−13.5 (−21.7 to −5.3)** | **0.001** | **−5.2 (−8.8 to −1.6)** | **0.004** | **5.2 (1.6–8.4)** | **0.004** | **0.2 (0.07–0.4)** | **0.005** |
| Age (/1 year) | **−0.7 (−1.6 to 0.1)** | **0.05** | **−1.3 (−2.4 to −0.1)** | **0.02** | **−0.6 (−1.1 to −0.1)** | **0.01** | **0.6 (0.1–1.1)** | **0.01** | **0.02 (0.002–0.05)** | **0.02** |
| Female versus male sex | **−12.0 (−18.8 to −5.2)** | **0.0007** | −4.9 (−13.1 to 3.2) | 0.2 | **−7.1 (−10.7 to −3.5)** | **0.0001** | **7.1 (3.1–10.7)** | **0.0001** | **−0.3 (−0.1 to −0.4)** | **0.0002** |
| NHW versus other | 4.1 (−4.3 to 12.6) | 0.3 | 0.1 (−10.3 to 10.1) | 0.9 | **4.3 (8.8 to −0.1)** | **0.05** | **4.3 (−0.1 to 8.8)** | **0.05** | **0.2 (0.001–0.4)** | **0.04** |
| BMI (/1 unit) | −0.09 (−0.7 to 0.5) | 0.7 | −0.04 (−0.8 to 0.7) | 0.9 | −0.2 (−0.5 to 0.06) | 0.1 | 0.2 (−0.06 to 0.5) | 0.1 | 0.01 (−0.003 to 0.02) | 0.1 |
| DBP (/1 mmHg) | −0.15 (−0.5 to 0.2) | 0.3 | −0.3 (−0.7 to 0.008) | 0.1 | −0.12 (−0.3 to 0.06) | 0.1 | 0.12 (−0.06 to 0.32) | 0.1 | 0.006 (−0.002 to 0.01) | 0.1 |
| LDL (/1 mg/dL) | **−0.1 (−0.2 to −0.001)** | **0.05** | **−0.17 (−0.3 to −0.03)** | **0.01** | −0.02 (−0.08 to 0.03) | 0.4 | 0.02 (−0.03 to 0.08) | 0.4 | 0.001 (−0.001 to 0.004) | 0.3 |
| HDL (/1 mg/dL) | −0.01 (−0.2 to 0.001) | 0.9 | −0.01 (−0.3 to 0.2) | 0.9 | −0.03 (−0.1 to 0.05) | 0.5 | 0.03 (−0.09 to 0.1) | 0.5 | 0.002 (−0.004 to 0.008) | 0.4 |
| TG (/1 mg/dL) | **−0.06 (−0.1 to −0.017)** | **0.03** | −0.05 (−0.1 to 0.01) | 0.1 | 0.0004 (−0.03 to 0.03) | 0.9 | −0.0004 (−0.03 to 0.03) | 0.9 | −0.00006 (−0.001 to 0.001) | 0.9 |
| Microalbuminuria (yes versus no) | **−11.3 (−23.6 to 0.9)** | **0.02** | −9.0 (−23.9 to 5.8) | 0.2 | −1.8 (−8.3 to 4.6) | 0.5 | 1.8 (−4.6 to 8.3) | 0.5 | 0.09 (−0.21 to 0.39) | 0.5 |

Data in boldface are significant parameter estimates and *P* values. TG, triglycerides.

diabetes seen in our study. In a recent metanalysis of 21 studies of nearly 3,489 post–myocardial infarction patients, individuals with SDNN <70 ms had four times greater risk of death compared with those with SDNN >70 ms (22). The youth with suboptimal glycemic control in our study also had an adjusted mean value of SDNN <70 ms, suggesting that their HRV impairment is likely to be clinically important.

Our finding of a specific pattern of early CAN in youth with type 1 diabetes is consistent with previous studies in other young-adult populations (23,24). However, our study is larger and more diverse than previous ones. We also found that altered HRV parameters among youth with type 1 diabetes compared with control subjects were independent of traditional CVD risk factors, suggesting an important role for hyperglycemia in the pathogenesis of CAN. Hyperglycemia induces abnormal signaling of the autonomic neurons via accumulation of advanced glycation end products, activation of polyol pathway, and ischemic atrophy of the autonomic nerve fibers innervating cardiac and vascular tissue (25).

Both the parasympathetic and sympathetic divisions of the autonomic nervous system are typically affected in CAN, with parasympathetic impairment preceding the sympathetic dysfunction (1). Our data suggest that contemporary youth with type 1 diabetes with an average disease duration of 10 years already display early signs of CAN characterized by overall reduced HRV and vagal impairment with sympathetic override. However, it has been shown that the shift in cardiac sympathovagal balance from parasympathetic to sympathetic control over heart rhythm may lead to increased cardiovascular morbidity and mortality in people with diabetes (4). Therefore, the ADA recommends that persons with type 1 diabetes be screened for CAN starting 5 years after diagnosis with the goal of detecting early abnormalities that may be reversible (26). The role of improved glycemic control in attenuating the risk of microvascular and macrovascular complications of diabetes has been documented by landmark studies such as the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) (27,28). A beneficial effect of tight glycemic control on early CAN has been shown in young adults with type 1 diabetes (27,28). Burger et al. (29)

**Table 3—*Differences (95% CI) in adjusted mean HRV parameters between youth with type 1 diabetes with optimal (A1C <7.5%) and suboptimal (A1C ≥7.5%) glycemic control compared with control youth***

| HRV variables | Diabetes, A1C <7.5% | *P** | Control subjects | *P*† | Diabetes, A1C ≥7.5% |
|---|---|---|---|---|---|
| *N* | 82 | | 176 | | 272 |
| Overall HRV | | | | | |
| SDNN (ms) | 72.1 (63.3–80.8) | 0.2 | 78.2 (72.4–84.0) | 0.002 | 67.2 (61.7–72.6) |
| Parasympathetic function | | | | | |
| RMSSD (ms) | 71.7 (61.1–82.3) | 0.2 | 77.9 (70.9–84.9) | 0.0002 | 61.5 (55.0–68.1) |
| HF power (n.u.) | 56.6 (51.9–61.2) | 0.2 | 59.4 (56.4–62.5) | 0.0003 | 53.3 (50.4–56.2) |
| Sympathetic function | | | | | |
| LF power (n.u.) | 43.3 (38.7–48.0) | 0.2 | 40.5 (37.4–43.5) | 0.001 | 46.6 (43.7–49.5) |
| LF-to-HF ratio | 1.0 (0.7–1.3) | 0.2 | 0.92 (0.7–1.1) | 0.001 | 1.2 (1.0–1.3) |

**P* value for differences in adjusted means between type 1 diabetic, A1C <7.5%, and healthy control subjects. †*P* value for differences in adjusted means between type 1 diabetic, A1C ≥7.5%, and healthy control subjects. Model adjusted for age, sex, race, BMI, DBP, LDL and HDL cholesterol, triglyceride, and AER.

demonstrated an improvement in HRV parameters 1 year after an intensive therapy among 10 patients with early CAN but not among the 13 patients with advanced CAN, thus suggesting that early CAN is amenable to improved glycemic control. Long-term poor glycemic control has been identified as a major factor in the development and progression of diabetic CAN (30). In our study, nearly 78% of youth with diabetes had A1C levels >7.5%, indicating an urgent need for efforts focused at improving glycemic control even among contemporary cohorts of youth with type 1 diabetes in developed countries such as the U.S., which may, in turn, result in reduction in subclinical cardiovascular abnormalities.

Cardiovagal function is known to be age and sex dependent (31–33). We found that SDNN was 7 ms lower for each 10-year increase in age, while females had on average 12 ms lower SDNN compared with males. The reduced HRV among female participants in our study is in agreement with that shown by the Pittsburgh Epidemiology of Diabetes Complications Study (31). Similar sex and age influences on the HRV have also been demonstrated in healthy adults (34), although the factors responsible for these differences are not clear. Similar to our findings, higher triglyceride and lower HDL cholesterol have been associated with CAN among adults with type 1 diabetes in the EURODIAB study (4). Previous studies have demonstrated a significant relationship between CAN and decline in renal function in individuals with diabetes (35). We found that SDDN was 11.3 ms lower in youth with microalbuminuria compared with those with normal urinary albumin excretion levels.

Our study has several limitations. First, the cross-sectional nature of the study limits our ability to evaluate the temporal trend in the development and progression of CAN among youth with type 1 diabetes. We therefore intend to longitudinally follow this cohort to better understand the progression of CAN over time. Second, and related, while our results strongly suggest a role for diabetes-related hyperglycemia in mediating the HRV abnormalities, the design of the study did not permit us to directly quantify this effect. Finally, the HRV measures used in our study are derived from a 10-min recording of the baseline ECG. While this is a relatively short length of recording, it is considered standard practice for clinical and research purposes and it is advocated by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (36), as opposed to the HRV measures derived from the 24-h Holter recordings. The major strengths of our study are the relatively large and diverse sample of contemporary youth with type 1 diabetes and the simple noninvasive, bedside assessment of multiple measures of HRV that have been validated as surrogate markers of the autonomic function in several human studies (37,38).

In summary, we found evidence of reduced HRV among youth with type 1 diabetes with a relatively short duration of diabetes compared with healthy control subjects. The specific pattern identified suggests an early and potentially reversible CAN stage, characterized by parasympathetic loss with sympathetic overdrive. These abnormalities were independent of traditional CVD risk factors, suggesting a major role for diabetes-related hyperglycemia. Improved glycemic control may be beneficial in slowing the progression or reversing the signs of early CAN among youth with type 1 diabetes.

**Acknowledgments**—This study was funded by National Institutes of Health grant R01-DK-078542 (to D.D.).

No potential conflicts of interest relevant to this article were reported.

M.J. analyzed the data and wrote the manuscript. E.M.U. helped with the research and writing of the manuscript. J.W.T. helped with the research of data. R.F.H. contributed to the discussion and reviewed and edited the manuscript. T.E.F. helped with the analyses of data, contributed to the discussion, and reviewed and edited the manuscript. S.D., L.M.D., R.B.D., R.P.W., and S.M.M. contributed to the discussion and reviewed and edited the manuscript. D.D. helped with the research and writing of the manuscript. D.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011, and at the 47th Annual Meeting of the European Association for the Study of Diabetes, Lisbon, Portugal, 12–16 September 2011.

The SEARCH for Diabetes in Youth Study is indebted to the many youth, and their families and their health care providers, whose participation made this study possible.

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