Prospective Investigation of Autonomic Nervous System Function and the Development of Type 2 Diabetes

The Atherosclerosis Risk In Communities Study, 1987–1998

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Background—Autonomic nervous system (ANS) dysfunction has been correlated with fasting insulin and glucose, independent of clinically diagnosed diabetes. We tested whether men and women (aged 45 to 64 years) from the Atherosclerosis Risk In Communities study (n=8185) with ANS dysfunction, estimated by high heart rate (HR) and low HR variability (HRV), were at increased risk for developing type 2 diabetes.

Methods and Results—Supine HR and HRV indices were measured for 2 minutes at baseline; indices were divided into quartiles for analyses. From 1987 to 1998 (mean follow-up 8.3 years), there were 1063 cases of incident diabetes. The relative risk (RR) of developing diabetes for participants with low-frequency (LF) power (0.04 to 0.15 Hz) HRV in the lowest quartile (<7.7 ms^2) compared with the highest quartile (≥ 38.9 ms^2) was 1.2 (95% CI 1.0–1.4) after adjustment for age, race, sex, study center, education, alcohol drinking, current smoking, prevalent coronary heart disease, physical activity, and body mass index. Participants in the uppermost (>72.7 bpm) versus the lowest (≤ 60.1 bpm) quartile of HR had a 60% increased risk (95% CI 33%–92%) of developing diabetes. Results were similar when the sample was restricted to participants with normal fasting glucose (glucose <6.1 mmol/L) at baseline (n=7192) or when adjusted for baseline glucose (HR quartile 4 versus quartile 1, RR=1.4, 95% CI 1.2–1.7).

Conclusions—These findings suggest that ANS dysfunction may be associated with the development of diabetes in healthy adults. **(*Circulation*. 2003;107:2190-2195.)**

Key Words: nervous system, autonomic ■ heart rate ■ diabetes mellitus ■ epidemiology

There is ample clinical and cross-sectional epidemiological evidence connecting diabetes to subsequent autonomic nervous system dysfunction.[1–3] It is generally accepted that hyperglycemia among persons with diabetes causes degradation of the microvasculature that results in central and peripheral autonomic neuropathy. Yet, there are numerous pathways whereby autonomic dysfunction could in turn affect insulin function and glucose regulation. Major organs, including the pancreas, liver, and skeletal muscle, which are responsible for insulin secretion, glucose production, and glucose metabolism, respectively, are innervated by autonomic fibers.[4–6]

Impaired autonomic function has previously been associated with elevated concentrations of serum insulin and decreased insulin sensitivity (markers of insulin resistance), independent of glucose levels.[2,3,7,8] This suggests that autonomic dysfunction may not only be the consequence of but also a precursor to hyperglycemia. At a minimum, autonomic dysfunction is a correlate of insulin resistance that could influence glucose dysregulation as seen in new-onset type 2 diabetes mellitus. Alternatively, it is possible that both insulin resistance and autonomic dysfunction have a shared precursor, such as physical inactivity or obesity, both of which are established risk factors for developing diabetes[9] and are correlates of autonomic function.[10,11]

We tested the hypothesis that persons with autonomic dysfunction, estimated by low heart rate variability (HRV) and high resting heart rate, were at increased risk for developing diabetes over follow-up in the Atherosclerosis Risk In Communities (ARIC) study. We also evaluated whether any observed relationship between autonomic dysfunction and incident diabetes persisted after accounting for established diabetes risk factors. Despite challenges inherent to studying causal pathways by epidemiological approaches, we also investigated the role of obesity and physical inactivity in the relation between autonomic dysfunction and incident diabetes.

Received December 23, 2002; revision received February 13, 2003; accepted February 18, 2003.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000066324.74807.95**

Methods

Study Population

The ARIC study is a prospective cohort study designed to evaluate subclinical and clinical atherosclerotic disease and clinical outcomes. Men and women aged 45 to 64 years were identified via probability sampling in 4 US communities: the northwest Minneapolis, Minn, suburbs; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Miss. Study participants represent the ethnic makeup of their community, with the exception of Jackson, Miss, which sampled black adults exclusively. From 1986 to 1989 (baseline), 15 792 black and white adults participated in a comprehensive home interview and clinic examination; participants were reexamined 3 times at approximately 3-year intervals through 1998 and are interviewed annually by telephone to update their health status. A detailed description of the study design, response rates, and methods has been published.[12,13]

For the present analysis, we excluded participants for the following reasons: absent or invalid HRV data at baseline (n=3156); self-reported ethnicity other than black or white, and those who reported black race and lived in the Minnesota or Maryland centers (small numbers; n=78); fasting <8 hours before any examination (n=451); prevalent diabetes at baseline (n=1316); did not return for follow-up (n=1444); and missing glucose values or ambiguous diabetes reports during follow-up (n=1162). After these exclusions, 8185 participants were included in these analyses.

Data Collection

All measurements were collected according to standardized protocols common to all ARIC sites.[14] Measurements took place in the morning in examination rooms that were maintained at a comfortable temperature (70°F) with dim light. After a 20-minute rest, ECG R waves were recorded from participants in a supine position at a sampling frequency of 1000 Hz for 2 minutes, then converted into beat-to-beat heart rate, including a record of the real time of each beat. Variance-preserving imputation software (PREDICT II HRVECG, Arrhythmia Research Technology, Inc) was used to impute data in segments with artifacts.[15] Records were excluded if artifacts affected >20% of intervals, the total record was <60 seconds, or there were fewer than 30 acceptable intervals. After imputation, heart rate data were converted back into RR intervals for data processing and spectrum analysis.

A fast Fourier transformation was used to calculate the power spectral density curve.[16] Area under the curve in the high-frequency (HF) range (0.15 to 0.40 Hz) was used to estimate parasympathetic modulation of variability, whereas low-frequency (LF) power (0.04 to 0.15 Hz) was used to estimate the joint contribution of parasympathetic and sympathetic variability, although it reflects primarily parasympathetic modulation at rest.[17] The standard deviation of all normal RR intervals (SDNN) was used to estimate the overall modulation of autonomic nervous system function. Heart rate (beats per minute), a general marker of autonomic function and fitness, was derived from the RR-interval record (heart rate=1/RR interval length, in milliseconds).

Fasting (≥8 hours) blood samples were drawn from an antecubital vein and assayed at a central laboratory. Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device. Impaired fasting glucose was defined as serum glucose ≥6.1 and <7 mmol/L (110–126 mg/dL). Type 2 diabetes was defined as any of the following: fasting serum glucose ≥7 mmol/L (126 mg/dL), nonfasting glucose ≥11.1 mmol/L (200 mg/dL), self-reported use of medications for diabetes, or a self-reported previous physician diagnosis.[18] Participants diagnosed with diabetes at examinations 2, 3, or 4 were considered to have incident diabetes. Diabetes diagnosis date was calculated at the midpoint of the examination interval before a diagnosis of diabetes. Follow-up time was calculated as the difference between the baseline examination and diagnosis date for persons with diabetes and the difference between baseline and the last examination for persons without diabetes.

Serum insulin was measured by radioimmunoassay (Cambridge Medical Diagnosis, Inc). Blood pressure was measured from seated participants 3 times with a random-zero sphygmomanometer. The average of the last 2 measurements is reported. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medications to lower blood pressure in the 2 weeks before the clinic examination. Weight was measured to the nearest pound, and height was measured to the nearest centimeter. Body mass index (BMI) was calculated as the ratio of weight (kilograms) to standing height (meters) squared (kg/m^2). Waist girth (centimeters) was measured at the umbilicus.

Demographic and lifestyle characteristics were assessed from home interviews with standardized questionnaires.[14] Education was categorized according to the highest level completed: less than high school (year 12), at least high school, and more than high school. Smoking and alcohol drinking were reported. Participation in sports-related physical activity (eg, jogging) was measured on a 5-point scale (1=low, 5=high) with the Baecke questionnaire.[19] Medication use was identified and defined by coding all reported medications, vitamins, and supplements used in the 2 weeks before the clinic examination. Participants who reported using medications thought to be associated with both autonomic function and diabetes at any visit (β-blockers, ACE inhibitors, calcium channel blockers, diuretics, or other antihypertensive medications) were identified. Prevalent coronary heart disease (CHD) was defined as a history of coronary artery bypass surgery, angioplasty, or myocardial infarction based on self-report.

Statistical Methods

We computed the baseline distribution of demographic and clinic characteristics for the total sample and by HRV. Median values of HRV indices and heart rate were calculated for the total sample and stratified by incident diabetes status; statistical comparisons were made with a Wilcoxon test. For purposes of prediction, we categorized HRV and heart rate into quartiles of the distribution: HF power 3.9/8.9/19.4 ms^2; LF power 7.7/17.8/38.9 ms^2; SDNN 25.5/34.3/46.1 ms; heart rate 60.1/66/72.7 bpm. Kaplan-Meier estimation and log-rank χ^2 tests were used to plot and statistically compare the crude survival function for diabetes by quartiles of HRV and heart rate. Before modeling, we evaluated the validity of the proportional hazards assumption using log (−log) survival plots; it was not violated. Using multivariable Cox proportional hazards modeling, we tested the association between quartiles of HRV and heart rate and incident diabetes. Additionally, we tested the association between heart rate and incident diabetes per SD increase (9.7 bpm). Statistical interaction was evaluated by including a multiplicative interaction term between each covariate and the primary exposure in a multivariate model. Effects were found to be homogenous across demographic characteristics studied, obesity, physical activity, smoking, and alcohol use, so all results were pooled for presentation. Statistical significance was denoted at $P<0.05$. All analyses were conducted with Statistical Analysis Software, version 8.1 (the SAS Institute).

Results

The mean age of the sample was 54 years (SD=6); 57% were women, and 19% were black. The majority of participants had at least a high school education (43% at least high school, 40% more than high school). Sixty percent of participants reported current alcohol intake, and 21% were current smokers. On average, participants were overweight (BMI=27.1 kg/m^2, SD=4.9), with an average waist circumference of 95.4 (SD=13.1) cm. The prevalence of obesity (BMI ≥30 kg/m^2) and hypertension were 22% and 29%, respectively. Over the course of the study, 46% used antihypertensive medications (19% β-blockers, 24% diuretics, 14% ACE inhibitors, 15% calcium channel blockers, and 11.4% other antihypertensive medications). In this nondiabetic sample, mean fasting glu-

TABLE 1. Median (Interquartile Range) of HRV at Baseline in the ARIC Sample at Risk for Diabetes and by Incident Diabetes Status

		Incident Diabetes		
	Total Sample (n=8185)	No (n=7122)	Yes (n=1063)	P*
HR power, ms^2	8.9 (15.5)	8.9 (15.4)	9.1 (16.4)	0.56
LF power, ms^2	17.8 (31.2)	18.2 (31.9)	15.8 (28.1)	0.002
SDNN, ms	34.3 (20.6)	34.5 (20.4)	32.8 (21.3)	0.03
Heart rate, bpm	66.0 (12.6)	65.8 (12.5)	67.8 (13.6)	<0.0001

*P value from Wilcoxon test for differences by diabetes status.

cose at baseline was 5.5 mmol/L (SD=0.5), and fasting insulin was 10.5 μU/mL (SD=7.8). Over an average of 8.3 years of follow-up (SD=1.9), 1063 participants (13%) developed diabetes. Characteristics of participants who developed diabetes during follow-up were consistent with previous reports from the ARIC cohort.[20]

At baseline, median LF power and SDNN were significantly lower among participants who developed diabetes than among those who did not (Table 1). There was no difference in HF power. Among participants who developed diabetes, median heart rate was 2 bpm higher at baseline than among persons who did not develop diabetes (68 versus 66 bpm, $P<0.0001$).

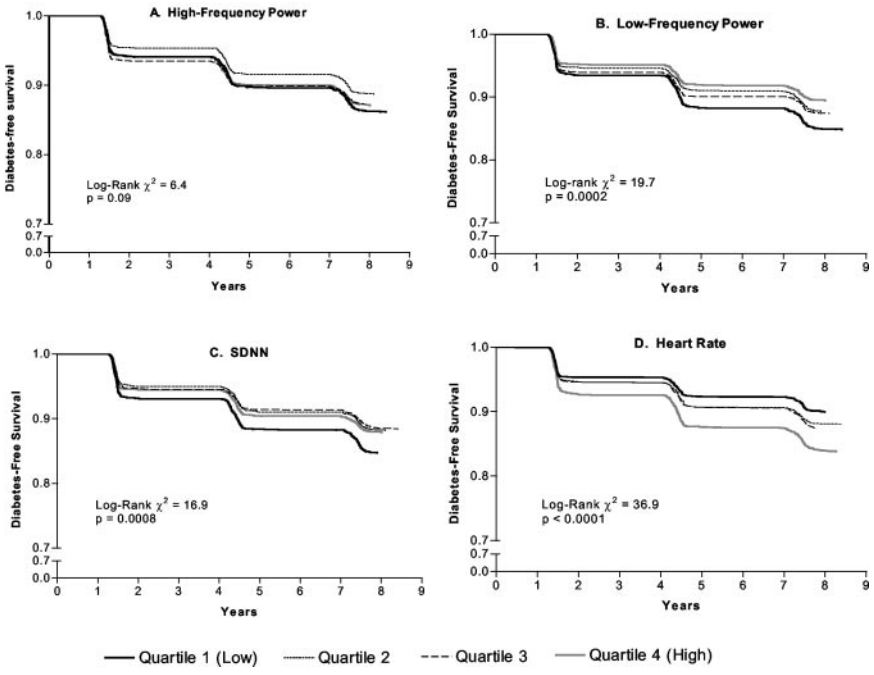
Unadjusted Kaplan-Meier survival estimates of diabetes incidence were calculated by quartiles of each HRV index and heart rate (Figure). Although differences in survival by quartiles of HF power (Figure, A) were minor and nonsignificant ($P=0.09$), participants in quartile 1 (lowest quartile) of the distributions of both LF power (Figure, B) and SDNN (Figure, C) experienced significantly ($P=0.0002$ and $P=0.0008$, respectively) less diabetes-free survival time than participants in the highest quartile (quartile 4). Diabetes-free survival was lowest among participants with higher heart rates ($P<0.0001$).

All models of HRV and incident diabetes were adjusted for heart rate. When the highest quartile was used as the referent, there was no evidence of a dose-response relationship between any HRV index and incident diabetes. Rather, an elevated risk was detected only when the lowest quartile of HRV (quartile 1) was contrasted with the highest quartile. Thus, Table 2 displays only the association between the extreme quartiles (quartile 1 versus quartile 4) of HRV.

In minimally adjusted models, reduced LF power (<7.7 ms^2) was associated with an ≈30% increased risk of developing diabetes that varied slightly with adjustment for demographic characteristics (age, race, sex, study center, and education) and confounders (current alcohol drinking, current smoking, and prevalent CHD). When further adjusted for physical activity and BMI, the strength of the association was attenuated but remained statistically significant. The finding was the same when waist circumference was used in place of or in addition to BMI. We did not observe any association between HF power or SDNN and incident diabetes.

In contrast to the clear threshold effect between HRV indices and diabetes, the association between heart rate and diabetes risk was graded, so in addition to quartile comparisons (quartile 4 versus quartile 1), we also examined the association as heart rate increased continuously (Table 2). High (>73 bpm) versus low (≤60 bpm) heart rate at baseline was associated with nearly a doubling in the risk of developing diabetes with multivariate adjustment. Adjustment for physical activity and BMI yielded a 61% increased risk (95% CI 1.3–1.9). The risk of developing diabetes was 18% to 24% greater per 9.7-bpm increase in baseline heart rate in models with varying degrees of multivariate adjustment (models 1 through 3).

The previously reported relation between antihypertensive medication use and the development of diabetes in this



Kaplan-Meier estimates of diabetes-free survival by quartiles of heart rate variability and heart rate (n=8185), 1987 to 1998.

TABLE 2. Adjusted* Relative Risk (95% CIs) of Diabetes by HRV and Heart Rate

	HF Power: Q1 (<3.9 ms²) vs Q4 (≥19.4 ms²)		LF Power: Q1 (<7.7 ms²) vs Q4 (≥38.9 ms²)		SDNN: Q1 (<25.5 ms) vs Q4 (≥46.1 ms)		Heart Rate: Q4 (>72.7 bpm) vs Q1 (≤60.1 bpm)		Heart Rate per SD Increase (9.7 bpm)	
Model	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Total sample (n=8185)										
1	1.03	0.87–1.22	1.40	1.18–1.67	1.06	0.89–1.27	1.66	1.40–1.98†	1.21	1.14–1.28†
2	1.05	0.88–1.26	1.31	1.09–1.57	1.01	0.84–1.22	1.87	1.56–2.24	1.24	1.17–1.32
3	0.97	0.81–1.16	1.20	1.00–1.44	1.00	0.82–1.21	1.61	1.34–1.94	1.18	1.11–1.26
4	1.04	0.87–1.24	1.17	0.97–1.40	1.05	0.87–1.27	1.23	1.03–1.48	1.06	1.00–1.13
Persons who did not use antihypertensive medications over follow-up (n=4461)‡										
1	1.02	0.76–1.36	1.52	1.12–2.06	1.20	0.88–1.65	1.48	1.09–2.01	1.20	1.08–1.33
2	1.07	0.78–1.46	1.58	1.15–2.16	1.21	0.87–1.68	1.85	1.34–2.55	1.29	1.16–1.43
3	1.07	0.78–1.46	1.48	1.08–2.03	1.10	0.79–1.53	1.50	1.08–2.09	1.21	1.08–1.35
4	1.05	0.76–1.45	1.39	1.01–1.91	1.13	0.82–1.57	1.09	0.79–1.51	1.06	0.95–1.19
Sample with normal fasting glucose (glucose <110 mg/dL) at baseline (n=7192)										
1	0.92	0.74–1.16	1.29	1.01–1.63	1.12	0.87–1.43	1.43	1.13–1.80†	1.14	1.05–1.24†
2	0.99	0.78–1.25	1.18	0.93–1.52	1.08	0.84–1.40	1.57	1.23–2.00	1.18	1.09–1.28
3	0.91	0.72–1.16	1.11	0.87–1.43	1.07	0.83–1.39	1.39	1.09–1.77	1.13	1.04–1.22

*Models adjusted for the following parameters: model 1, heart rate; model 2, model 1 plus age, race, study center, education (less than high school, high school), current alcohol drinking, current smoking, and prevalent CHD; model 3, model 2 plus physical activity and body mass index; and model 4, model 3 plus baseline glucose.

†Crude association.

‡β-Blockers, ACE inhibitors, calcium channel blockers, diuretics, or other antihypertensive medication.

cohort[21] prompted us to exclude persons using antihypertensive medications and to test the association between HRV or heart rate and incident diabetes. In the subset of persons who did not use any antihypertensive medications over follow-up (n=4461), the associations between LF power, heart rate, and incident diabetes remained significant even after adjustment for physical activity and BMI.

Because we expected a strong association between baseline glucose levels and the risk of developing diabetes, we restricted the full sample (including persons who used antihypertensive medications) to participants with normal fasting glucose (glucose <6.1 mmol/L) at baseline (n=7192) and replicated the analyses. A similar pattern was observed, but the magnitude of association between both low LF power and high heart rate and diabetes was slightly attenuated (Table 2), although it remained significant for heart rate. We observed a similar attenuation in strength for both LF and heart rate when the sample was restricted to participants with fasting serum insulin below the 90th percentile (insulin <19 μU/mL, n=7379) at baseline. Again, low LF power was associated with a nonsignificantly elevated risk of incident diabetes, and heart rate was directly and significantly associated with diabetes risk (data not shown).

In our final model (model 4), we evaluated whether HRV and heart rate continued to predict incident diabetes after adjustment for baseline glucose. In the full sample, LF power remained moderately inversely associated with incident diabetes but was attenuated to nonsignificance. Similarly, the strength of the association between higher heart rate and incident diabetes decreased, but in contrast to LF power, it retained statistical significance. In the sample of participants who did not use antihypertensive medications during follow-up, higher heart rates no longer predicted diabetes once baseline glucose was accounted for, but the association of lower LF power and diabetes remained moderately strong and was statistically significant. Additionally, we adjusted for fasting insulin at baseline and observed a similar attenuation in the strength of the effect, but estimates retained statistical significance in the full model for both LF power (RR=1.2, 95% CI 1.0–1.4, quartile 1 versus quartile 4) and heart rate (RR=1.4, 95% CI 1.2–1.7, quartile 4 versus quartile 1; RR=1.13, 95% CI 1.1–1.2 per 9.7 bpm).

Discussion

In this population sample of healthy adults, participants with reduced LF power HRV, a marker of decreased parasympathetic input, and high resting heart rate, a global marker of poor autonomic nervous system modulation and poor physical fitness, were at an increased risk for developing type 2 diabetes. Although persons with low LF power and higher heart rates had demographic and clinical characteristics commonly associated with an increased risk of developing diabetes (data not shown), statistical adjustment for these characteristics weakened but did not eliminate the observed associations. There was evidence that low levels of physical activity, overall adiposity, and central adiposity played a large role in this association; however, autonomic nervous system dysfunction remained independently associated with the development of diabetes. As expected, glucose levels at baseline accounted for a large proportion of this finding, because persons with higher glucose levels at baseline would be at increased risk of crossing the cutpoint for later diabetes

diagnosis. However, even at comparable levels of baseline glucose, heart rate remained a significant predictor of diabetes risk. These results suggest that autonomic nervous system dysfunction may contribute to the development of diabetes in healthy adults.

Temporal Sequence

CHD risk is directly associated with glucose concentrations in persons without diabetes.[22] Previous research indicates that autonomic dysfunction, an indicator of microvascular disease, demonstrates a similar pattern of association with glucose in persons without diabetes.[2,3,8] If, as suspected, insulin resistance precedes hyperglycemia and a clinical diagnosis of diabetes, it is plausible that diabetic neuropathy is associated with insulin resistance, not hyperglycemia after frank diabetes, as previously thought.[23] One proposed mechanism is that increased sympathetic activation, a hallmark of autonomic dysfunction, leads to enhanced catecholamine release and consequent increases in circulating free fatty acids and the potential for increased insulin resistance.[24]

Previous research supports this hypothesis and demonstrates stronger cross-sectional associations between autonomic dysfunction and insulin than glucose. In the Insulin Resistance and Atherosclerosis Study, heart rate was inversely associated with insulin sensitivity and directly associated with the acute insulin response to glucose and proinsulin concentration after adjustment for demographic characteristics, glucose tolerance status, and smoking.[7] Additionally, in a previous ARIC study, the inverse association of HRV and fasting insulin remained significant after adjustment for cigarette smoking, hypertension, total cholesterol, and heart rate, whereas the same relationship with glucose did not.[2] In a clinical study of 162 adults with normal fasting glucose, impaired baroreflex sensitivity, another marker of autonomic cardiac control, was associated with higher levels of fasting plasma insulin, independent of BMI, physical activity, or blood pressure. In contrast, there was no multivariable association between fasting glucose and baroreflex sensitivity in this sample.[25] These results support the hypothesis that autonomic dysfunction is present with impaired insulin function before the development of hyperglycemia, but they do not identify the temporal sequence between autonomic impairment and insulin resistance.

What Does Heart Rate Measure?

It is possible that the association between high heart rate and incident diabetes in the present study merely reflects an association between physical fitness and glucose metabolism. Resting heart rate is dependent on the level of physical fitness; as fitness increases, resting heart rates are lower.[26] Fitness, assessed by maximum heart rate on a treadmill test, was shown to be an independent predictor of impaired fasting glucose and type 2 diabetes in adult men.[27] Heart rate is the sum of fitness, neurohormonal factors, and autonomic nervous system function. Thus, it is possible that poor physical fitness leads to poor autonomic nervous system function,[26] which in turn negatively affects glucose metabolism, circulating glycated hemoglobin,[28] and insulin sensitivity.[9] Despite our attempts to statistically adjust for physical activity, we may have done so incompletely because of our tool to measure activity and our inability to objectively measure fitness.

Estimation of Autonomic Nervous System Function

In the present study, LF power was the only HRV index to demonstrate a modest association with incident diabetes in multivariate models. Although it was surprising that HF power was not associated with incident diabetes, the presence and strength of association between HRV indices and cardiovascular morbidity and mortality varied as well.[29–32] This can be attributed to the unique components of autonomic function represented by each index.[33]

The absence of an effect by HF power may reflect the role of the sympathetic nervous system.[16,17] HF has been identified as an estimate of parasympathetic modulation of variability at rest with pharmacological blockade of parasympathetic function. In contrast, LF comprises both parasympathetic and sympathetic inputs. Because HRV reflects fluctuations in autonomic inputs to the heart, and not the average input, both the absence of autonomic input and high sympathetic modulation lead to diminished HRV.[16,33] Thus, persons with low HRV and correspondingly low LF power can have considerable resting sympathetic input. If, as previously reported,[34] sympathetic impairment develops after parasympathetic impairment, enhanced sympathetic modulation, marked by low LF power, may be a better marker than parasympathetic modulation of autonomic dysfunction leading to metabolic derangement.

Study Limitations

This study must be interpreted in light of some limitations. First, without direct measures of insulin resistance, we were unable to evaluate whether autonomic nervous system dysfunction acted on insulin action or was a consequence of hyperglycemia (in the nondiabetic range). As a result, we demonstrate a temporal relation between autonomic nervous system function and an outcome (diabetes) but are unable to determine the causal pathway and temporal sequence. Second, supine HRV captures resting autonomic modulation of heart rate but does not describe the extent of autonomic dysfunction, specifically whether sympathetic fibers are also involved. A measure of HRV with physical or mental stimulation to elicit sympathetic activation could provide more detailed information on the type of dysfunction associated with diabetes risk. Third, because persons who developed diabetes may have had higher levels of glucose at baseline, the diagnosis of diabetes may reflect participants who moved slightly over the cutpoint for diabetes. We attempted to overcome this by conducting secondary analyses in the subset of participants who had normal fasting glucose at baseline in one set of models and adjusting for baseline glucose levels in another. Despite the potential for overadjustment and an artificial reduction in the relative hazard associated with adjusting for a measure (baseline glucose) that is along the causal pathway for developing clinically elevated glucose and a diagnosis of diabetes, our primary findings persisted.

Conclusions

This research suggests for the first time that autonomic influences on metabolism are associated with the development of diabetes in healthy persons. Further research is needed to confirm these findings and determine whether autonomic dysfunction is a consequence or cause of insulin resistance.

Acknowledgments

Dr Carnethon was supported in part by a career development award from the National Heart, Lung, and Blood Institute (1 K01 HL73249-01). The authors thank the staff and participants in the ARIC study for their important contributions.

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