Heart Rate Variability and Incident Stroke
The Atherosclerosis Risk in Communities Study

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Background and Purpose—Low heart rate variability (HRV), a marker of cardiac autonomic dysfunction, has been associated with increased all-cause and cardiovascular mortality. We examined the association between reduced HRV and incident stroke in a community-based cohort.

Methods—The Atherosclerosis Risk in Communities (ARIC) study measured HRV using 2-minute ECG readings in 12,550 middle-aged adults at baseline (1987–1989). HRV indices were calculated using the SD of RR intervals (SDNN), the mean of all normal RR intervals (meanNN), the root mean square of successive differences of successive RR intervals (RMSSD), low (LF) and high (HF) frequency power, and the LF/HF ratio. All HRV measures were categorized into quintiles. Incident stroke was adjudicated through 2011. Cox regression was used to estimate hazard ratios (HRs) with the lowest HRV quintile as the reference, with and without stratification by prevalent diabetes mellitus.

Results—Over a median follow-up of 22 years, 816 (6.5%) participants experienced incident stroke. After covariate adjustment, there was no strong evidence of association between HRV and stroke risk. In stratified analyses, the lowest HRV quintile was associated with higher stroke risk compared with the highest quintile for SDNN (HR, 2.0; 95% confidence interval, 1.1–4.0), RMSSD (HR, 1.7; 95% confidence interval, 0.9–3.2), LF (HR, 1.5; 95% confidence interval, 0.8–3.0), and HF (HR, 1.7; 95% confidence interval, 0.9–3.0) only among people with diabetes mellitus. Conclusions—Lower HRV was associated with higher risk of incident stroke among middle-aged adults with prevalent diabetes mellitus but not among people without diabetes mellitus. (Stroke. 2016;47:1452-1458. DOI: 10.1161/STROKEAHA.116.012662.)

Key Words: autonomic nervous system ■ diabetes mellitus ■ follow-up studies ■ heart rate ■ stroke

Stroke is the most severe form of cerebrovascular disease with 795,000 cases in the United States each year. Stroke is the fourth leading cause of death in the United States, leaving 50% of survivors disabled. In 2008, the United States spent $18.8 billion on health care for strokes, and $15.5 billion was lost in productivity. Numerous studies have identified risk factors for incident stroke—the most prominent being older age, male sex, black versus white race, hypertension, diabetes mellitus, obesity, and smoking. More recently, autonomic nervous system (ANS) dysfunction has been associated with increased poststroke morbidity and mortality. Proposed mechanisms include the influence of the ANS on cerebral circulatory autoregulation, blood pressure, and essential hypertension.

Heart rate variability (HRV) is a commonly examined marker for ANS dysfunction. Heart rate is regulated by a balance between the sympathetic and parasympathetic nervous systems; consequently, ANS dysfunction leads to measurable differences in heart rate and HRV. Low HRV has been positively associated with cardiovascular disease risk factors and multiple cardiovascular outcomes, including cardiovascular mortality and incident coronary heart disease among others. The association between HRV and cardiovascular outcomes has been shown to be stronger in people with diabetes mellitus.

A previous study has identified an association between low HRV and the risk of all-cause mortality and cardiovascular mortality in older stroke survivors. Another study reported an association between low nighttime HRV and increased risk of incident ischemic stroke but was limited by small sample size and few stroke events. The clinical value of HRV for identifying people at high risk of stroke is unknown; no
studies have evaluated daytime HRV as would be assessed in a routine clinic visit. These unresolved questions have clinical and public health implications as HRV may represent a target for stroke prevention through medication or lifestyle changes that improve or preserve ANS function.14 Furthermore, identification of high-risk groups could prove valuable for stroke prevention. We analyzed data from the Atherosclerosis Risk in Communities (ARIC) cohort study to estimate the association between HRV and primary incident stroke.

Methods

Study Population

The ARIC study is a longitudinal prospective cohort study initiated in 1987–1989. Originally, 15,792 men and women aged 45 to 64 years were recruited from 4 US communities: suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina. Four follow-up visits were conducted: visit 2 (1990–1992), visit 3 (1993–1995), visit 4 (1996–1998), and visit 5 (2011–2013).15 At each visit, visit participants underwent extensive clinical examinations; visits 1 and 4 included ECG assessment of HRV. Written informed consent was collected from all study participants, and all affiliated Institutional Review Boards approved the study protocol.

HRV Assessment

The Task Force of the European Society of Cardiology and others have documented standards and procedures for HRV measurement.23 In short, heart rate is measured from the intervals between R waves of successive heartbeats (RR interval); HRV reflects the magnitude of RR interval variation over time.8,10 Protocols for data processing and analysis in ARIC have been previously published (Tables I and II in the online-only Data Supplement).10,17 Briefly, ARIC measured HRV twice: (1) 2-minute ECG readings at visit 1 and (2) 6-minute ECG readings at visit 4. All data were collected on resting participants in a supine position, reflect short-term daytime HRV, and were analyzed using ECG software (time domain) or a previously developed computer algorithm (frequency domain).9,10,17,18 Our primary analysis used visit 1 HRV measures, with secondary analyses using visit 4 HRV measures and participants who remained stroke free at that examination. HRV indices are commonly divided into time- and frequency-domain measurements. Time-domain measures are calculated directly from heart rate or the duration between successive RR intervals. Frequency-domain measures are calculated from spectral imaging of the ECG recording. We evaluated 3 time-domain measures of HRV: (1) the SD of all normal-to-normal (NN) RR intervals (SDNN), which characterizes overall HRV, (2) the mean of all RR intervals (meanNN), and (3) the root mean square of successive differences in RR intervals, which is thought to reflect parasympathetic nervous system activity. We also evaluated 3 frequency-domain measures of HRV: (1) low frequency power (0.04–0.15 Hz), considered to include both sympathetic and parasympathetic nervous system activities, (2) high frequency power (0.15–0.40 Hz), thought to reflect parasympathetic nervous system activity, and (3) low/high frequency power ratio, which estimates the balance between sympathetic and parasympathetic nervous system activity.8

Incident Stroke Ascertainment

Stroke events were identified between visit 1 (1987–1989) and December 31, 2011.19 Annual telephone calls to study participants assessed hospitalizations and deaths possibly attributed to strokes in the previous year. In addition, hospital discharge summaries were reviewed for International Classification of Diseases, 9th Revision, codes 430 to 436, which are indicative of cerebrovascular events, and state death registries were reviewed for cerebrovascular-related mortality. Study personnel documented whether hospital discharge International Classification of Diseases, 9th Revision, codes included cerebrovascular disease if cerebrovascular disease was noted in the discharge summary or a cerebrovascular finding was referenced in the neuroimaging report study. Study staff then abstracted, from the hospital record, stroke signs and symptoms and findings from cerebrovascular imaging (computed tomography or magnetic resonance). On the basis of National Survey of Stroke criteria,20 a computer algorithm and study physician categorized all possible incident stroke events; an additional study reviewer adjudicated discrepancies. For the present analysis, incident stroke included ischemic and hemorrhagic strokes defined by the presence of an acute infarction or hemorrhage respectively on neurological imaging or autopsy.

Covariates

Sociodemographic and lifestyle variables in our primary (visit 1) and secondary (visit 4) analyses included ARIC field site, sex, age in years at the clinic examination, sex, race (black and white), total years of education (less than completed high school, completed high school or equivalent, and at least some college), cigarette smoking and alcohol consumption (both coded as current, former, and never), and physical activity (score of leisure time sports activity). Clinical variables included body mass index, systolic blood pressure (SBP), diastolic blood pressure, self-reported current use of antihypertensive medication, blood lipids, and diabetes mellitus (fasting glucose, ≥216 mg/dL, nonfasting glucose, ≥200 mg/dL, currently taking medication for diabetes mellitus, or self-reported physician diagnosis of diabetes mellitus).15 SBP, diastolic blood pressure, and use of antihypertensive medication were excluded as covariates in sensitivity analyses.

Exclusions and Missing Data

Of the 15,792 participants at visit 1, we excluded individuals for the following reasons: (1) racial identification of Asian, American Indian, other, or black race from the predominantly white ARIC field sites (n=2033); (2) taking medication known to affect HRV (β-blockers, antiarrhythmics, calcium-channel blockers, or digoxin; n=2259); (3) prevalent stroke at the baseline examination (n=204); and (4) prevalent coronary heart disease or heart failure (n=676). Our final sample size was 12,550 observations. An additional 2667 individuals would have been included because of missing HRV data at baseline. To preserve sample size and minimize the possibility of selection bias, we used multiple imputation by chained equations with 100 repetitions to impute missing data for the 2667 people who would have been excluded in a complete case analysis based on missing HRV data.21

Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) for the relationship between each HRV measure and incident stroke. Person-time was calculated as the number of years from the visit 1 examination to date of incident stroke or censoring (either death, loss to follow-up, or administrative censoring on December 31, 2011). Because of nonlinear trends observed in preliminary descriptive analyses and a restricted cubic spline analysis, we categorized each HRV measure into quintiles (highest category serving as the reference for all comparisons). In the primary analysis, we fit 2 adjusted models: (1) model 1 adjusted for baseline age, sex, and race and (2) model 2 additionally adjusted for other baseline lifestyle and clinical covariates (model 1+education, smoking, alcohol consumption, physical activity, body mass index, SBP, diastolic blood pressure, blood lipids, prevalent diabetes mellitus, antihypertensive medication, and heart rate [except meanNN]). We excluded heart rate from models for the mean RR interval (meanNN) because of collinearity. Because of concerns that hypertension could be a possible mediator between HRV and stroke, we performed a sensitivity analysis, excluding SBP, diastolic blood pressure, and antihypertensive use. Results were nearly identical; we included blood pressure variables in our models to address any possibility of confounding effects of blood pressure on the relationship.
between HRV and risk of incident stroke. Previous studies examining the association between HRV and heart disease reported effect modification by diabetes mellitus status.\textsuperscript{10,11} Therefore, we evaluated statistical evidence for interaction in the full model and estimated stratified associations by diabetes mellitus prevalence at baseline. All results for our primary analysis incorporate imputed data using multiple imputation by chained equations.

In secondary analyses, we evaluated the association between 6-minute HRV measured at visit 4 and subsequent stroke; we examined statistical evidence for interaction and estimated stratified associations by prevalent diabetes mellitus status. The latter analysis was restricted to cohort members who were stroke free at their visit 4 examination because results between the complete case analysis and nonimputed data set in our primary analysis (visit 1) were similar, we did not perform multiple imputation by chained equations for our sensitivity analysis for visit 4. We tested all models and detected no evidence of violation of the proportional hazard assumption. We used Stata version 14 and R for data management and statistical analyses.\textsuperscript{22,23}

**Results**

Of the 12,550 ARIC participants included in our analysis at visit 1, 6.5% (n=816) experienced a stroke during follow-up. Table 1 shows descriptive statistics for baseline variables presented separately by SD\textsubscript{NN} quintile. In general, groups with lower SD\textsubscript{NN} values tended to have higher proportions of women, lower education, and higher blood pressure, heart rate, and proportions of people with hypertension and taking antihypertensive medication. Groups with lower SD\textsubscript{NN} tended to have higher proportions of people with prevalent diabetes mellitus, with a strikingly higher proportion in the lowest SD\textsubscript{NN} quintile. Crude cumulative stroke incidence was consistent with higher risk in the lowest HRV quintiles (Figure I in the online-only Data Supplement). Ranges for all HRV measurements by quintile are reported in Table III in the online-only Data Supplement.

**Table 1. Baseline (Visit 1) Characteristics for Study Sample by SD\textsubscript{NN} Quintile, Atherosclerosis Risk in Communities, 1987–1989 (n=12,550)**

<table>
<thead>
<tr>
<th>Category</th>
<th>SD\textsubscript{NN} Quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Range, ms</td>
<td>0.5–23.4</td>
</tr>
<tr>
<td>n (Total)</td>
<td>2519</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Women, %</td>
<td>61</td>
</tr>
<tr>
<td>Black race, %</td>
<td>28</td>
</tr>
<tr>
<td>Education (total years), %</td>
<td></td>
</tr>
<tr>
<td>Less than completed high school</td>
<td>25</td>
</tr>
<tr>
<td>Completed high school or equivalent</td>
<td>41</td>
</tr>
<tr>
<td>At least some college</td>
<td>34</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>27</td>
</tr>
<tr>
<td>Former</td>
<td>30</td>
</tr>
<tr>
<td>Never</td>
<td>44</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>54</td>
</tr>
<tr>
<td>Former</td>
<td>19</td>
</tr>
<tr>
<td>Never</td>
<td>27</td>
</tr>
<tr>
<td>Sport PA, score, mean (SD)</td>
<td>2.4 (0.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2), mean (SD)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg, mean (SD)</td>
<td>124 (21)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg, mean (SD)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>Heart rate, bpm, mean (SD)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>HDL, mg/dL, mean (SD)</td>
<td>53 (19)</td>
</tr>
<tr>
<td>LDL, mg/dL, mean (SD)</td>
<td>139 (43)</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>25</td>
</tr>
<tr>
<td>Prevalent hypertension, %</td>
<td>35</td>
</tr>
<tr>
<td>Prevalent diabetes mellitus, %</td>
<td>17.1</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PA, physical activity; and SD\textsubscript{NN}, SD of all normal-to-normal RR intervals.
In Cox regression analysis for the full cohort (Tables 2 and 3), people in the lowest HRV quintiles showed higher risk of stroke compared with the reference group in demographic-adjusted models, but these associations were attenuated after full covariate adjustment. Only the interaction between prevalent diabetes mellitus and SDNN was statistically significant (Tables 4 and 5). Stratified analyses restricted to people with diabetes mellitus consistently showed higher stroke risk associated with the lowest HRV quintiles for SDNN (HR, 2.0; 95% confidence interval [CI], 1.1–4.0), root mean square of successive differences of successive RR intervals; and SDNN, root mean square of all normal-to-normal RR intervals.

**Table 2. Time-Domain Heart Rate Variability at Visit 1 and Stroke Risk; Total n=12550; Split Into ≈2510 Observations per Quintile for Each Heart Rate Variability Measure; Total Patients With Strokes, n=816**

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDNN</td>
<td>MeanNN</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>1.4 (1.1–1.7)</td>
<td>1.7 (1.3–2.1)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>1.0 (0.8–1.3)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>1.1 (0.9–1.4)</td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>1.0 (0.7–1.2)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and race. Model 2: model 1+education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressures, blood lipids, prevalent diabetes mellitus, antihypertensive use, and heart rate (except for meanNN). Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference). CI indicates confidence interval; HR, hazard ratio; Ref, reference quintile; RMSSD, root mean square of successive differences of successive RR intervals; and SDNN, SD of all normal-to-normal RR intervals.

In this prospective population-based analysis of ARIC participants, we found some evidence of increased risk of stroke among diabetic participants in the lowest quintile of HRV relative to those in the highest quintile. We observed little evidence of an association between low HRV and incident stroke among nondiabetic participants. These results were consistent across most, but not all, of the time- and frequency-domain HRV measures.

One previous study reported a positive association between low nighttime HRV (15-minute recording) and incident ischemic stroke. Although informative, this study was limited by a small sample size, few stroke events, and examination of time-domain HRV measures only. We have expanded on this work by using a large prospective biracial cohort, time- and frequency-domain HRV indices, and by evaluating potential effect modification by diabetes mellitus status.

Individuals with type 2 diabetes mellitus are known to have an elevated risk of cardiovascular disease; previous studies have found positive associations between elevated fasting glucose levels and incident stroke. In this study, we found that low HRV was associated with increased risk of stroke among diabetic participants.

**Discussion**

In this prospective population-based analysis of ARIC participants, we found some evidence of increased risk of stroke among diabetic participants in the lowest quintile of HRV relative to those in the highest quintile. We observed little evidence of an association between low HRV and incident stroke among nondiabetic participants. These results were consistent across most, but not all, of the time- and frequency-domain HRV measures.

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Individuals with type 2 diabetes mellitus are known to have an elevated risk of cardiovascular disease; previous studies have found positive associations between elevated fasting glucose levels and incident stroke. In this study, we found that low HRV was associated with increased risk of stroke among diabetic participants.
closely regulated. It is unknown how HRV affects changes are physiologically controlled, whereas fast changes are not.

The sympathetic nervous system plays a critical role in circulatory autoregulation; slow pressure and blood flow changes in cerebral vascular pressure; it is possible that low HRV association of HRV and incident stroke include circulatory autoregulation and blood pressure. The onset and progression between blood pressure and blood flow in the cerebral vessels, circulatory autoregulation, are essential for brain health. The primary mechanisms providing insight into a possible association of HRV and incident stroke include circulatory autoregulation and blood pressure. First, the dynamics of hypertension are a result of elevated sympathetic tone. Furthermore, arterial stiffness and left ventricular hypertrophy (LVH) are a result of increased ANS activity; both increase vascular resistance, a known contributor to hypertension. We were initially concerned that blood pressure variables were possible mediators in the association between HRV and incident stroke. Simultaneously, hypertension is an established risk factor for incident stroke and is known to be associated with autonomic dysfunction. We performed a sensitivity analysis examining results with blood pressure variables excluded from the models. The results from the sensitivity and main analyses were quite similar. To be conservative, we retained blood pressure variables in our models to address any potential confounding effects of blood pressure on the relationship between HRV and risk of incident stroke. Finally, despite the fact that we did not find an association between low HRV and incident stroke in our primary analyses, these mechanisms may become physiologically relevant when other disease processes, such as diabetes mellitus, are present. Previous studies report that low HRV precedes coronary heart disease and mortality postmyocardial infarction.

### Table 4. Time-Domain Heart Rate Variability at Visit 1 and Stroke Risk for People Without (n=11 237) and With (n=1196) Prevalent Diabetes Mellitus; Total Patients With Strokes, n=816

<table>
<thead>
<tr>
<th></th>
<th>SD(<em>{\text{nnm}}) Mean(</em>{\text{nnm}}) RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>HR (95% CI) HR (95% CI) HR (95% CI)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>0.9 (0.6–1.2) 2.0 (1.1–4.0) 1.1 (0.9–1.5)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>1.0 (0.7–1.3) 1.7 (0.9–3.4) 1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>0.9 (0.7–1.2) 1.1 (0.5–2.4) 1.1 (0.8–1.4)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>Ref Ref Ref</td>
</tr>
</tbody>
</table>

### Table 5. Frequency-Domain Heart Rate Variability at Visit 1 and Stroke Risk for People Without (n=11 237) and With (n=1196) Prevalent Diabetes Mellitus; Total Patients With Strokes, n=816

<table>
<thead>
<tr>
<th></th>
<th>Low Frequency</th>
<th>High Frequency</th>
<th>Low Frequency/High Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>0.9 (0.7–1.3)</td>
<td>1.5 (0.8–3.0)</td>
<td>1.7 (0.9–3.0)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>1.1 (0.8–1.4)</td>
<td>1.5 (0.8–2.9)</td>
<td>1.2 (0.6–2.2)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>1.0 (0.7–1.3)</td>
<td>1.2 (0.6–2.4)</td>
<td>1.2 (0.7–2.3)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>1.1 (0.8–1.5)</td>
<td>1.0 (0.5–2.2)</td>
<td>0.9 (0.7–1.2)</td>
</tr>
</tbody>
</table>

All results from model 2: adjusted for age, sex, race, education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressure, blood lipids, prevalent diabetes mellitus, antihypertensive use, and heart rate (except for mean\(_{\text{nn}}\)). Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference). CI indicates confidence interval; HR, hazard ratio; and Ref, reference quintile.
These same studies have hypothesized that low HRV may be an early indicator of declining health. If low HRV reflects poor general health, it is possible that autonomic dysfunction has more effects on populations already at risk (ie, type 2 diabetes mellitus).

Strengths of this study include the use of a prospective design with long-term follow-up, a large sample size, and multiple imputation methods to minimize the possibility of selection bias. In addition, the present study used a community-based biracial cohort, measurement of multiple time and frequency-domain HRV indices, and comprehensive collection of cardiovascular risk factors for confounding adjustment. HRV and incident stroke were both objectively measured for all analyses. Secondary analyses using 6-minute ECG recordings at visit 4 (Table IV in the online-only Data Supplement) yielded nearly identical results to the primary analysis (Tables 4 and 5). There are many limitations of this study. First, HRV was measured using 2-minute and 6-minute ECGs at visits 1 and 4, respectively. Collection of long-term (>18 hours) Holter ECG recordings is generally preferred to short-term (=5 minutes) ECG recordings because length of ECG recording affects measurement variability. Our results, however, did not change using 2-minute (visit 1) and 6-minute (visit 4) ECG data giving confidence to minimal measurement error. Furthermore, previous studies have demonstrated that 2-minute, 15-minute, and 24-hour HRV indices are correlated (most ≥0.75). A more robust measurement of HRV (24-hour Holter ECG) could have yielded a more accurate measure of HRV. Second, it should be noted that our data reflect daytime HRV and may not represent the overall variations of sympathetic and parasympathetic activity that occur in a 24-hour period. Third, although losses to follow-up are relatively small in ARIC, the possibility of selection bias exists; the association we report may not be generalizable. Fourth, there is considerable imprecision in many of our HRs, and studies with more events may help estimate the associations more accurately. Finally, despite our attempts to statistically adjust for known confounders, residual confounding may be present.

Implications
Identification of new indicators that contribute to incident stroke provides the opportunity to identify individuals at high risk and develop protocols for early intervention. Although newer guidelines for HRV assessment in diabetics have been proposed, current guidelines recommend measuring HRV in 2 situations: (1) to measure risk of mortality in individuals post myocardial infarction and (2) to examine possible autonomic neuropathy in individuals with diabetes mellitus. Since these guidelines were published ~2 decades ago, lower HRV has consistently been found to predict cardiovascular disease morbidity and mortality. Expanding the clinical scope and relevance of HRV may be warranted.

Summary/Conclusions
In conclusion, in this large community-based biracial cohort, lower HRV was associated with a modest risk of incident stroke in people with diabetes mellitus, independent of traditional cardiovascular risk factors. Further studies are warranted, and additional exploration of the causes of cardiac autonomic dysfunction and stroke in individuals with diabetes mellitus may be beneficial.

Acknowledgments
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Disclosures
None.

References


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/6/1452

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/05/04/STROKEAHA.116.012662.DC1
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ONLINE SUPPLEMENT
Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study
### eTable I. Detailed description of heart rate variability (HRV) methodology; the Atherosclerosis Risk in Communities (ARIC) Study.

<table>
<thead>
<tr>
<th></th>
<th>Time-Domain</th>
<th>Frequency-Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Collection</strong></td>
<td>• Participants rested supine, comfortably for ≥ 20 minutes.</td>
<td>• Coders electronically marked all R-peaks (procedure performed in duplicate).</td>
</tr>
<tr>
<td></td>
<td>• ARIC B-mode ultrasound and arterial distensibility studies.</td>
<td>• Abnormal beats flagged; two subsequent intervals excluded.</td>
</tr>
<tr>
<td></td>
<td>• 3 ECG leads placed on epigastrium.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dedicated computer and software continuously collected ECG data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Visit 1: 2-minute recordings collected; Visit 4: 6-minute recordings collected.</td>
<td></td>
</tr>
<tr>
<td><strong>Data Processing</strong></td>
<td>• Software converted R-interval data to beat-to-beat heart rate data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Computer algorithm imputed beat-to-beat heart data and performed smoothing.</td>
<td></td>
</tr>
<tr>
<td><strong>Data Analysis</strong></td>
<td>• Linear interpolation used on neighboring data points.</td>
<td>• Software calculated R-R interval duration on the basis of difference between coordinates.</td>
</tr>
<tr>
<td></td>
<td>• Neighboring data points used to fit a quadratic least squares model to obtain residuals.</td>
<td>• Software calculated mean of duplicate R-R interval measurements.</td>
</tr>
<tr>
<td></td>
<td>• Fast Fourier Transformation applied to residuals to compute power spectral density (PSD).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• From PSD curve, low and high frequency spectral powers were calculated using a rectangular method.</td>
<td></td>
</tr>
</tbody>
</table>
eTable II: Clinical implications of HRV assessment; the Atherosclerosis Risk in Communities (ARIC) Study.

<table>
<thead>
<tr>
<th>HRV Parameter</th>
<th>Units</th>
<th>Description</th>
<th>ANS Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-domain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>ms</td>
<td>Standard deviation of all NN RR intervals</td>
<td>Overall ANS variability</td>
</tr>
<tr>
<td>RMSSD</td>
<td>ms</td>
<td>Root mean square of successive differences in NN RR intervals</td>
<td>PNS</td>
</tr>
<tr>
<td>MeanNN</td>
<td>ms</td>
<td>Mean of all NN intervals</td>
<td>-</td>
</tr>
<tr>
<td>Frequency-domain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>ms(^2)</td>
<td>Low frequency power</td>
<td>SNS &amp; PNS</td>
</tr>
<tr>
<td>HF</td>
<td>ms(^2)</td>
<td>High frequency power</td>
<td>PNS</td>
</tr>
<tr>
<td>LF:HF</td>
<td>-</td>
<td>Ratio low:high frequency power</td>
<td>Balance between SNS &amp; PNS</td>
</tr>
</tbody>
</table>

Abbreviations: Normal-to-normal, NN; interval between R waves of successive heartbeats, RR interval; autonomic nervous system, ANS; parasympathetic nervous system, PNS; sympathetic nervous system, SNS; milliseconds, ms; milliseconds squared, ms\(^2\).

*All ECG recordings obtained under standardized conditions to minimize external stimuli on autonomic function.
†Used primarily to calculate other HRV parameters.

eTable III: HRV quintile ranges for visit 1; the Atherosclerosis Risk in Communities (ARIC) Study.

<table>
<thead>
<tr>
<th>HRV Parameter</th>
<th>Time-domain*</th>
<th>Frequency-domain†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDNN</td>
<td>RMSSD</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>0.5-23.4</td>
<td>0.0 - 15.1</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>23.5-30.4</td>
<td>15.2 - 21.0</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>30.5-38.0</td>
<td>21.1 - 27.8</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>38.1-49.5</td>
<td>27.9 - 39.0</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>49.6-394</td>
<td>39.1 - 652.4</td>
</tr>
</tbody>
</table>

Abbreviations: Standard deviation of all NN intervals, SD\(_{NN}\); root mean square of successive differences in NN RR intervals, RMSSD; mean of all NN intervals, Mean\(_{NN}\); low frequency power, LF; high frequency power, HF; ratio low:high frequency power, LF:HF.

*Time-domain units: milliseconds, ms.
†Frequency-domain units: milliseconds squared, ms\(^2\) (except LF:HF, a ratio).
**eTable IV:** Time-domain (top) and frequency-domain (bottom) heart rate variability at visit 4 and stroke risk for people without \((n = 6951)\) and with \((n = 1090)\) prevalent diabetes; total strokes \(n = 372\).

<table>
<thead>
<tr>
<th>Time Domain</th>
<th><strong>SD(_{NN})</strong></th>
<th><strong>Mean(_{NN})</strong></th>
<th><strong>RMSSD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No diabetes</strong></td>
<td><strong>Diabetes</strong></td>
<td><strong>No diabetes</strong></td>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td><strong>Quintile 1</strong></td>
<td>(0.8\ (0.5, 1.2))</td>
<td>(1.8\ (0.8, 3.8))</td>
<td>(1.2\ (0.8, 1.7))</td>
</tr>
<tr>
<td><strong>Quintile 2</strong></td>
<td>(0.8\ (0.6, 1.2))</td>
<td>(1.7\ (0.8, 3.6))</td>
<td>(1.4\ (1.0, 2.1))</td>
</tr>
<tr>
<td><strong>Quintile 3</strong></td>
<td>(0.7\ (0.5, 1.1))</td>
<td>(1.9\ (0.9, 4.0))</td>
<td>(1.2\ (0.8, 1.7))</td>
</tr>
<tr>
<td><strong>Quintile 4</strong></td>
<td>(0.8\ (0.5, 1.1))</td>
<td>(1.4\ (0.6, 3.3))</td>
<td>(0.9\ (0.6, 1.4))</td>
</tr>
<tr>
<td><strong>Quintile 5</strong></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>(p_{\text{interaction}})</td>
<td>0.31</td>
<td>0.62</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency Domain</th>
<th><strong>Low frequency</strong></th>
<th><strong>High frequency</strong></th>
<th><strong>Low frequency/High frequency</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No diabetes</strong></td>
<td><strong>Diabetes</strong></td>
<td><strong>No diabetes</strong></td>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td><strong>Quintile 1</strong></td>
<td>(1.2\ (0.8, 1.8))</td>
<td>(1.7\ (0.9, 3.3))</td>
<td>(1.0\ (0.7, 1.5))</td>
</tr>
<tr>
<td><strong>Quintile 2</strong></td>
<td>(1.1\ (0.7, 1.7))</td>
<td>(1.1\ (0.5, 2.3))</td>
<td>(1.0\ (0.6, 1.4))</td>
</tr>
<tr>
<td><strong>Quintile 3</strong></td>
<td>(1.3\ (0.9, 1.9))</td>
<td>(1.7\ (0.8, 3.6))</td>
<td>(1.1\ (0.8, 1.7))</td>
</tr>
<tr>
<td><strong>Quintile 4</strong></td>
<td>(1.0\ (0.7, 1.6))</td>
<td>(1.0\ (0.5, 2.2))</td>
<td>(0.8\ (0.6, 1.3))</td>
</tr>
<tr>
<td><strong>Quintile 5</strong></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>(p_{\text{interaction}})</td>
<td>0.80</td>
<td>0.99</td>
<td>0.25</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio; CI = Confidence Interval; Ref = Reference quintile.
Visit 4 HRV measurements used 6-minute ECG recordings.
All results from Model 2: adjusted for age, sex, race, education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressure, blood lipids, prevalent diabetes, antihypertensive use, and heart rate (except for Mean\(_{NN}\)).
Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference).
**Figure.** Unadjusted cumulative incidence of stroke (%, 95% CI) by HRV quintiles at: (A) visit 1, and (B) visit 4 in The Atherosclerosis Risk in Communities Study (ARIC).

(A) Visit 1

(B) Visit 4
REFERENCES:
1. The ARIC Manuals of Operation, No. 6, “Ultrasound Assessment.”
   https://www2.cscc.unc.edu/aric/cohort-manuals
背景及目的：心率变异性和卒中的相关性。未发现有力证据证明心率变异性降低与卒中风险之间的相关性。分层分析中，仅在合并糖尿病的参与者中发现，与 HRV 最高五等分组相比，HRV 最低五等分组与更高的卒中风险相关 [SD NN, HR = 2.0, 95% CI 1.1~4.0; RMSSD, HR = 1.7, 95% CI 0.9~3.2; LF, HR = 1.5, 95% CI 0.8~3.0; HF, HR = 1.7, 95% CI 0.9~3.0]。

结论：在合并糖尿病的中年人中，心率变异性降低与更高的卒中事件风险相关，但在不合并糖尿病的人群中无相关性。

关键词：自主神经系统；糖尿病；随访研究；心率；卒中

卒中是最严重的脑血管疾病。在美国，每年有 795,000 例患者罹患卒中。卒中是美国第四大死因，50% 生存者遗留残疾。2008 年，美国因卒中产生的医疗花费达 188 亿美元，且造成 156 亿美元的生产力损失。诸多研究发现最重要的卒中事件危险因素包括老年、男性、黑色人种、高血压、糖尿病、肥胖和吸烟。新近发现，自主神经系统 (autonomic nervous system, ANS) 功能障碍与卒中后残疾率和死亡率升高相关。可能的机制包括 ANS 影响脑血流自动调节功能、血压和原发性高血压。心率变异性 (heart rate variability, HRV) 是常用的 ANS 功能障碍评估指标。心率由交感和副交感神经系统之间的平衡进行调节。因此，AVS 功能障碍导致心率和 HRV 的显著变异。HRV 降低与心血管疾病死亡率相关，且与多种心血管病预后明显相关，如心血管疾病死亡率和冠心病发病率。HRV 与心血管病预后之间的相关性在糖尿病人群中更显著。未解决的问题有着临床和公共卫生意义。此外，识别高风险人群对于卒中预防是至关重要的。我们通过分析动脉粥样硬化风险社区队列研究 (the Atherosclerosis Risk in Communities, ARIC) 的数据，评估 HRV 与卒中事件的相关性。

方法

研究人群


HRV 评估

欧洲心脏病学会特别小组和其他组织已经阐明了 HRV 测量的标准和流程。与此同时，心率通过相邻心跳的 R 波间期（RR 间期）测量获
得: HRV 反应了 RR 间隔随时间变化的大小程度。ARIC 研究的数据处理和分析方案此前已发表 (在线补充数据的表 I 和 II)。简言之，ARIC 研究 2 次测量了 HRV：(1) 随访 1 的 2 min ECG 数据，(2) 随访 4 的 6 min ECG 数据。所有的数据收集于参与者仰卧位休息时, 反映短时白天 HRV。数据分析使用 ECG 分析软件 (时域) 或先前开发的计算机算法 (频域)。首次分析使用随访 1 的 HRV 数据，再次分析使用随访 4 时仍未有卒中事件的参与者 HRV 数据。HRV 指标通过 RR 间期随时间变异的大小程度 (standard deviation of all normal-to-normal(RR)intervals, SDNN)，反应整体 HRV；(2) RR 间隔的平均值 (the mean of all RR intervals, meanNN)，(3) 相邻 RR 间隔差值的均方根 (the root mean square of successive differences in RR intervals, RMSSD)，反应副交感神经系统活动。我们也评价了 3 项 HRV 频域指标：(1) 低频功率 (0.04~0.15 Hz)，反应交感和副交感神经系统活动；(2) 高频功率 (0.15~0.40 Hz)，反应副交感神经系统活动；(3) 高低频功率比值，反应交感和副交感神经系统活动之间的平衡。卒中事件确定：卒中事件的观察时间段为随访 1 (1987-1989 年) 和 2011 年 12 月 31 日之间。每年通过电话访问研究参与者以调查上一年度可能出现的卒中事件和死亡。另外，对国际疾病分类 (9 版) 编码 430-436 (代表脑血管事件) 的出院小结和脑血管相关的国家死亡登记进行回顾。根据出院小结中记录有脑血管疾病或神经影像报告中提及脑血管异常发现，研究人员记录出院国际疾病分类 (9 版) 编码是否包括了脑血管疾病。然后，研究人员从医院记录，卒中症状体征和脑血管影像学发现 (计算机断层扫描或磁共振) 中提取数据。根据卒中全国性调查标准，通过计算机运算和研究医师对所有可能的卒中事件分类；另一个研究者对差异进行裁定。目前，卒中事件包括缺血性卒中和出血性卒中，根据在神经影像或尸检中发现急性梗死或出血确定。协变量：在首次 (随访 1) 和再次 (随访 4) 分析中，社会人口学和生活方式因素包括 (ARIC) 研究地点、进行临床检查时的年龄、性别、种族 (黑人和白人)、总教育年限 (高中未毕业、高中毕业或同等学历、大学及以上学历)、吸烟和饮酒 (均分为现在、先前和从不) 和体力活动。表 1 根据 SDNN 五分等分的研究样本基线资料 (随访 1)，动脉粥样硬化风险社区研究，1987-1989 年 (n=12550)。

<table>
<thead>
<tr>
<th>分类</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>范围，ms</td>
<td>0.5-23.4</td>
<td>23.5-30.4</td>
<td>30.5-38.0</td>
<td>38.1-49.5</td>
<td>49.6-394</td>
</tr>
<tr>
<td>n (总)</td>
<td>2519</td>
<td>2512</td>
<td>2510</td>
<td>2504</td>
<td>2505</td>
</tr>
<tr>
<td>年龄，岁，平均值 (SD)</td>
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<td>54(6)</td>
<td>54(6)</td>
<td>53(6)</td>
<td>53(6)</td>
</tr>
<tr>
<td>女性，%</td>
<td>61</td>
<td>59</td>
<td>56</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>黑种人，%</td>
<td>28</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>教育（总年数），%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>高中未毕业</td>
<td>25</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>高中毕业或同等学历</td>
<td>41</td>
<td>41</td>
<td>42</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>大学及以上</td>
<td>34</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>吸烟，%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>现在</td>
<td>27</td>
<td>26</td>
<td>25</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>以前</td>
<td>30</td>
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<td>33</td>
<td>32</td>
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<tr>
<td>从不</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>饮酒，%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>现在</td>
<td>54</td>
<td>59</td>
<td>56</td>
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<td>59</td>
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<tr>
<td>以前</td>
<td>19</td>
<td>15</td>
<td>18</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>从不</td>
<td>27</td>
<td>26</td>
<td>26</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>体重指数，kg/m²，平均值 (SD)</td>
<td>27(6)</td>
<td>27(6)</td>
<td>27(6)</td>
<td>27(5)</td>
<td>27(5)</td>
</tr>
<tr>
<td>收缩压，mmHg，平均值 (SD)</td>
<td>124(21)</td>
<td>121(19)</td>
<td>120(18)</td>
<td>119(19)</td>
<td>118(19)</td>
</tr>
<tr>
<td>舒张压，mmHg，平均值 (SD)</td>
<td>75(12)</td>
<td>74(11)</td>
<td>73(12)</td>
<td>73(12)</td>
<td>72(12)</td>
</tr>
<tr>
<td>心率，bpm，平均值 (SD)</td>
<td>74(12)</td>
<td>68(10)</td>
<td>67(9)</td>
<td>65(9)</td>
<td>62(9)</td>
</tr>
<tr>
<td>HDL，mg/dL，平均值 (SD)</td>
<td>53(19)</td>
<td>54(18)</td>
<td>53(18)</td>
<td>53(18)</td>
<td>52(18)</td>
</tr>
<tr>
<td>LDL，mg/dL，平均值 (SD)</td>
<td>139(43)</td>
<td>137(42)</td>
<td>136(42)</td>
<td>137(41)</td>
<td>135(41)</td>
</tr>
<tr>
<td>降压药物，%</td>
<td>25</td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>高血压，%</td>
<td>35</td>
<td>26</td>
<td>24</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>糖尿病，%</td>
<td>17.1</td>
<td>9.8</td>
<td>7.9</td>
<td>7.2</td>
<td>6.5</td>
</tr>
</tbody>
</table>

注: SDNN: 正常 RR 间隔的标准差; SD: 标准差; HDL: 高密度脂蛋白; LDL: 低密度脂蛋白。
表 2 随访 1 心率变异性时域分析和卒中风险: 总数 n=12 550; 每个心率变异性指标五等分,每组≈ 2510; 总卒中事件患者 n=816

<table>
<thead>
<tr>
<th></th>
<th>模型 1</th>
<th>模型 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDNN</td>
<td>MeanNN</td>
</tr>
<tr>
<td>组 1</td>
<td>1.4 (1.1-1.7)</td>
<td>1.7 (1.3-2.1)</td>
</tr>
<tr>
<td>组 2</td>
<td>1.0 (0.8-1.3)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>组 3</td>
<td>1.1 (0.9-1.4)</td>
<td>1.2 (0.9-1.5)</td>
</tr>
<tr>
<td>组 4</td>
<td>1.0 (0.7-1.2)</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>组 5</td>
<td>参照</td>
<td>参照</td>
</tr>
</tbody>
</table>

模型 1: 校正年龄、性别和种族。模型 2: 模型 1+ 教育、吸烟、饮酒、体力活动、体重指数、收缩压、舒张压、血脂、糖尿病、降压药物使用和心率 (除外 meanNN); 风险比定义为组 1、2、3、4 分别与组 5 (参照) 对比。注: CI: 可信区间; HR: 风险比; RMSSD: 相邻 RR 间期差值的均方差; SDNN: 正常 RR 间期的标准差; meanNN: 正常 RR 期间的平均值。
最小组糖尿病患病率尤其高。HRV 最低组的原始累计卒中风险最高（在线补充数据图Ⅰ）。所有 HRV 指标的范围见在线补充数据表Ⅲ。

全队列 Cox 回归分析显示（表 2 和 3），在人口统计学校正模型中，HRV 最低组人群较参照组人群出现卒中的风险更高，但这种相关性经全协变量校正后减弱。只有糖尿病和 SDNN 之间的相互性具有统计学意义（表 4 和表 5）。限于糖尿病人群的分层分析同样显示更高的卒中风险与最低 HRV 相关 \[SDNN, HR=2.0, 95\% CI 1.1~4.0; RMSSD, HR=1.7, 95\% CI 0.9~3.2; \] 低频功率，HR=1.5, 95% CI 0.8~3; 高频功率, HR=1.7, 95% CI 0.9~3.0]。重要的是，大部分指标的分组间具有很大的变异性（表 4 和 5）。在糖尿病人群中，meanNN 或低/高频功率比值没有明显相关性，而在非糖尿病人群中，所有的 HRV 指标和卒中发作均无相关性。尽管事实上并不是所有的结果均有统计学意义，但在糖尿病人群中，大多数 HRV 指标最低值与卒中风险增加密切相关的。

重要的是，HRV 和卒中事件相关性的主要机制可能包括循环自动调节功能和血压。首先，血压和脑血管血流之间的动力学变化、循环自动调节是大脑健康的关键。交感神经系统在循环自动调节中起到关键作用；缓慢的压力和血流变化可得到生理性控制，而对于快速的变化并不能进行严密调节。目前尚不清楚 HRV 如何影响脑血管的压力变化；可能的机制是：HRV 降低触发脑血管压力的快速变化，使得调节发生障碍，并影响血管健康，导致卒中风险。其次，高血压是介导 HRV 与卒中的另一种可能机制。高血压的发生和发展是交感神经张力升高的结果，并影响血管健康。另外，动脉硬化和左心室肥厚（left ventricular hypertrophy, LVH）是 ANS 活性增加的结果；两者增加了血管阻力，对高血压的发生作出贡献。我们最初担心血压可能是 HRV 和卒中之间的关联因素。同时，高血压是卒中的一个已知危险因素，并且与自主神经功能障碍有关。我们进行了将血压变量排除在外的敏感性分析；所有结果来自于模型 2：校正年龄、性别和种族、教育、吸烟、饮酒、体力活动、体重指数、收缩压、舒张压、血脂、糖尿病、降压药物和心率（除外 meanNN）。风险比定义为组 1、2、3、4 分别和组 5（参照）对比。注：CI: 可信区间; HR: 风险比; RMSSD; 根据 RR 间期差值的均方差; SDNN; 正常 RR 间期差值; meanNN; 正常 RR 期间的平均值。

### 表 4 随访 1 心率变异性时域分析和卒中风险分层分析（糖尿病人群 n=11 237；非糖尿病人群 n=1196）；总卒中事件患者 n=816

<table>
<thead>
<tr>
<th></th>
<th>SDNN</th>
<th>MeanNN</th>
<th>RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>对比</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>组 1</td>
<td>0.9 (0.6~1.2)</td>
<td>2.0 (1.1~4.0)</td>
<td>11.0 (9.0~15)</td>
</tr>
<tr>
<td>组 2</td>
<td>0.9 (0.7~1.2)</td>
<td>12.0 (6.2~4)</td>
<td>10.0 (6.0~14)</td>
</tr>
<tr>
<td>组 3</td>
<td>1.0 (0.7~1.3)</td>
<td>17.0 (9.0~14)</td>
<td>9.0 (0.5~16)</td>
</tr>
<tr>
<td>组 4</td>
<td>0.9 (0.7~1.2)</td>
<td>11.0 (6.2~4)</td>
<td>7.0 (0.3~13)</td>
</tr>
<tr>
<td>组 5</td>
<td>参照</td>
<td>参照</td>
<td>参照</td>
</tr>
</tbody>
</table>

所有结果来自于模型 2：校正年龄、性别和种族、教育、吸烟、饮酒、体力活动、体重指数、收缩压、舒张压、血脂、糖尿病、降压药物和心率（除外 meanNN）。风险比定义为组 1、2、3、4 分别和组 5（参照）对比。注：CI: 可信区间; HR: 风险比; meanNN: 正常 RR 期间的平均值。

### 表 5 随访 1 糖尿病人群 (n=11 237) 和非糖尿病人群 (n=1196) 心率变异性频域分析和卒中风险；总卒中事件患者 n=816

<table>
<thead>
<tr>
<th></th>
<th>低频</th>
<th>高频</th>
<th>低频/高频</th>
</tr>
</thead>
<tbody>
<tr>
<td>对比</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>组 1</td>
<td>0.9 (0.7~1.3)</td>
<td>15.0 (8.0~30)</td>
<td>1.0 (0.8~14)</td>
</tr>
<tr>
<td>组 2</td>
<td>1.1 (0.8~14)</td>
<td>15.0 (8.0~29)</td>
<td>0.8 (0.6~11)</td>
</tr>
<tr>
<td>组 3</td>
<td>1.0 (0.7~13)</td>
<td>12.0 (6.2~24)</td>
<td>1.0 (0.7~13)</td>
</tr>
<tr>
<td>组 4</td>
<td>1.1 (0.8~15)</td>
<td>1.0 (0.5~22)</td>
<td>0.9 (0.7~12)</td>
</tr>
<tr>
<td>组 5</td>
<td>参照</td>
<td>参照</td>
<td>参照</td>
</tr>
</tbody>
</table>

所有结果来自于模型 2：校正年龄、性别和种族、教育、吸烟、饮酒、体力活动、体重指数、收缩压、舒张压、血脂、糖尿病、降压药物和心率（除外 meanNN）。风险比定义为组 1、2、3、4 分别和组 5（参照）对比。注：CI: 可信区间; HR: 风险比; meanNN: 正常 RR 期间的平均值。

## 讨论

本项基于 ARIC 数据的前瞻性人群研究中，我们发现了一些证据表明糖尿病人群 HRV 最低五等分组相较于最高五等分组的卒中风险增加。而在非糖尿病人群，HRV 降低与卒中事件的关联证据很少。这些结果在大多数指标中是一致的，但不是所有的 HRV 时域和频域指标。

### 2 型糖尿病患者心血管疾病风险升高；此前研究发现，空腹胰岛素升高或 2 型糖尿病与 ANS 功能障碍呈正相关。我们的结果与此前研究结果一致，在 ARIC 人群中糖尿病是一种影响因素：在糖尿病参与者中，HRV 最低组相比与最高组，冠心病事件的风险升高；在无糖尿病参与者未观察到相关性。11

HRV 和卒中事件相关性的主要机制可能包括循环自动调节功能和血压。首先，血压和脑血管血流之间的动力学变化、循环自动调节是大脑健康的关键。交感神经系统在循环自动调节中起到关键作用；缓慢的压力和血流变化可得到生理性控制，而对于快速的变化并不能进行严密调节。目前尚不清楚 HRV 如何影响脑血管的压力变化；可能的机制是：HRV 降低触发脑血管压力的快速变化，使得调节发生障碍，并影响血管健康，导致卒中风险。其次，高血压是介导 HRV 与卒中的另一种可能机制。高血压的发生和发展是交感神经张力升高的结果，并影响血管健康。另外，动脉硬化和左心室肥厚（left ventricular hypertrophy, LVH）是 ANS 活性增加的结果；两者增加了血管阻力，对高血压的发生作出贡献。我们最初担心血压可能是 HRV 和卒中之间的关联因素。同时，高血压是卒中的一个已知危险因素，并且与自主神经功能障碍有关。我们进行了将血压变量排除在外的敏感性分析；所有结果来自于模型 2：校正年龄、性别和种族、教育、吸烟、饮酒、体力活动、体重指数、收缩压、舒张压、血脂、糖尿病、降压药物和心率（除外 meanNN）。风险比定义为组 1、2、3、4 分别和组 5（参照）对比。注：CI: 可信区间; HR: 风险比; meanNN: 正常 RR 期间的平均值。
模型。敏感性分析结果与主体分析结果非常相似，但有些指标
在模型中保持了血压变化对 HRV 与卒中风险之间关系的影响。
尽管如此，我们在初步分析中没有发现 HRV 降低与卒中事件的
相关性，但当合并在其他疾病时，这些机制可能
变得相关，例如糖尿病。之前的研究报道，HRV 降低预测冠心病
和心肌梗死死亡率。这些证据提示 HRV 降低可能是健康下降的早期
指标。如果 HRV 降低反映了一般健康状况较差，自主神经功能障碍
可能在已存在风险的人群中产生更大的影响（例如，2 型糖尿病）。

参考文献