

Decreased Nighttime Heart Rate Variability Is Associated With Increased Stroke Risk

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Background and Purpose—Prediction of stroke in healthy individuals is challenging and there is a diurnal variation of stroke onset. We hypothesized that heart rate variability with a focus on nighttime heart rate variability will predict the risk of stroke in apparently healthy middle-age and elderly subjects.

Methods—The population-based cohort of the Copenhagen Holter Study, consisting of 678 healthy subjects between age 55 and 75 years with no history of cardiovascular disease or stroke, was evaluated. All underwent 48-hour ambulatory electrocardiogram monitoring. The SD of normal-to-normal RR intervals (SDNN) was selected as the method of measuring heart rate variability. Nighttime SDNN was measured between 02:00 and 02:15 AM and could be evaluated in 653 subjects. Median follow-up was 76 months.

Results—Nighttime SDNN was lower in women than in men ($P=0.0008$), and in diabetics than nondiabetics ($P=0.03$). However, smoking, cholesterol, systolic blood pressure, and age were not associated with nighttime SDNN. The risk of stroke was significantly associated with nighttime SDNN in a univariate analysis (HR, 0.66; 95% CI, 0.50–0.88; $P=0.004$) and after adjustment for conventional risk factors (HR, 0.67; 95% CI, 0.51–0.89; $P=0.005$) per 10 ms increments of SDNN. Eighty-one percent of all strokes (21/26) occurred in 330 subjects with the lower half of nighttime SDNN (≤ 38 ms; HR, 4.31; 95% CI, 1.62–11.42; $P=0.003$).

Conclusions—Nocturnal heart rate variability is a strong marker for the development of stroke in apparently healthy subjects. The mechanism is unknown, but reduced parasympathetic activity may increase the risk of stroke by increasing the risk of arrhythmias. (*Stroke*. 2011;42:3196-3201.)

Key Words: nighttime heart rate variability ■ SDNN ■ atrial fibrillation ■ risk factors ■ stroke

Worldwide, stroke is one of the major causes of disability and death.¹ In Denmark (5.5 million inhabitants), stroke affects more than 15 000 people annually, and the incidence is steadily increasing.² Thirty percent of all stroke cases are believed to be cardioembolic, and atrial fibrillation accounts for half of all cardioembolic strokes.^{2,3} A circadian variation in stroke onset has been previously shown. There appears to be a lack of diurnal variation of hemostatic factors or platelet activation among patients with atrial fibrillation, thus suggesting influence of the autonomic nervous system in the diurnal variation of a stroke.⁴

Heart rate is controlled by the autonomic nervous system, and heart rate variability (HRV) reflects the influence of both the sympathetic and parasympathetic systems.^{5,6} Several studies have revealed that autonomic dysfunction and reduced HRV are associated with increased all-cause and cardiovascular mortality.^{7–12} A weak parasympathetic control may be responsible for increased risk of cardiovascular events.^{13,14} Stroke survivors have impaired function of the autonomic nervous system, and disturbances in sympathovagal balance may predict survival after the acute phase of

stroke.^{15,16} Survival after stroke correlates with reduced HRV.^{16,17} An autonomic imbalance and reduced HRV have been identified prior to paroxysms of atrial fibrillation in some studies.^{18–21}

It is believed that decreased vagal tone correlates with development of paroxysmal atrial fibrillation.^{22,23}

HRV may be influenced by physical activity and mental stress. Study subjects were assumed to sleep at night; therefore, nighttime HRV could be free from incidental influences. The value of nighttime HRV is measured more easily and may be more reproducible than is 24-hour HRV.

We hypothesized that in apparently healthy middle-aged and elderly subjects, reduced HRV is predictive of stroke, and that nighttime HRV is a better predictive tool than is 24-hour HRV.

Methods

The Copenhagen Holter Study

This study is part of the Copenhagen Holter Study, which was aimed at addressing the value of 24-hour Holter recording in the risk assessment of middle-aged and elderly men and women in relation to other risk factors. The Copenhagen Holter Study is the largest Holter

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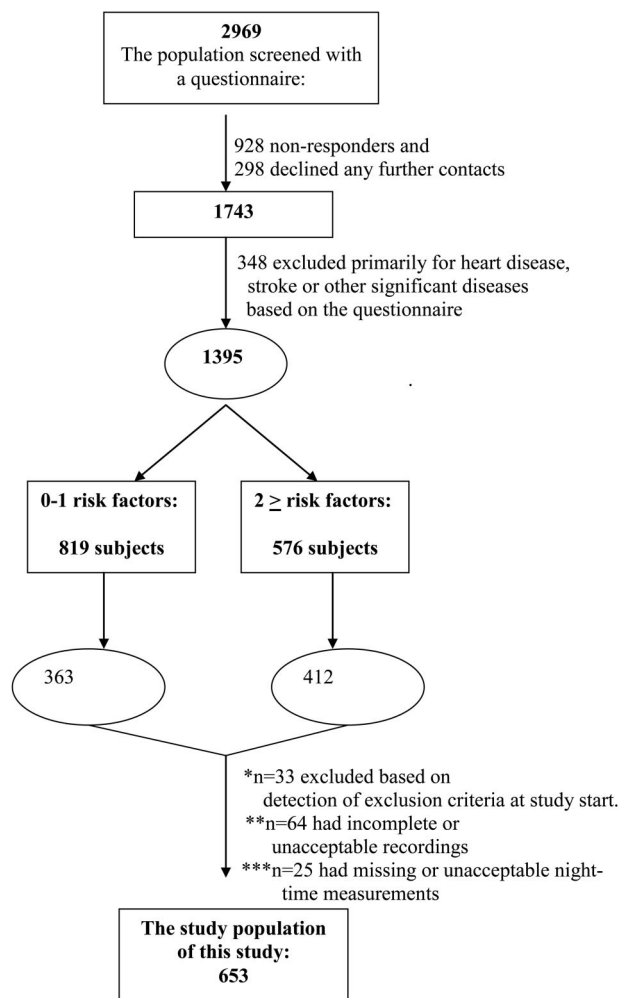


Figure 1. Flow diagram.

study in apparently healthy subjects, and was conducted from 1998 to 2000. The study protocol and selection procedures have been previously published.²⁴

Recruitment

Every person in Denmark is identified by a unique number in the Central Personal Register of the Ministry of the Interior. This number enabled us to perform an epidemiological survey of subjects living within 2 well-defined postal regions in Copenhagen. Every man age 55 years, and all men and women age 60, 65, 70, and 75 years, received a questionnaire ($n=2969$) about cardiovascular risk factors, use of medications, and medical history. These subjects were ranked according to the number of the following self-reported risk factors: hypertension, diabetes mellitus, smoking habits, familial history of cardiac disease (sudden death or acute myocardial infarction in a parent or sibling before the age of 60 years), and obesity (body mass index >30) or known hypercholesterolemia.

Exclusion criteria for this study were: manifest ischemic heart disease, eg, history of acute myocardial infarction, coronary revascularization, or angina pectoris; other manifest cardiac diseases, eg, congestive heart failure, valvular heart disease, congenital heart disease, arrhythmic heart disease (including permanent atrial fibrillation), or medical treatment for any heart disease; history of stroke; cancer; other significant or life-threatening diseases, such as hepatic cirrhosis, renal insufficiency requiring dialysis, and chronic lung disease requiring home oxygen therapy; and technical reasons, (eg, interrupted recording or poor quality recording). Figure 1 shows the study population at different exclusion steps. Altogether, 653 sub-

jects participated in this study and had acceptable Holter monitoring, including nighttime HRV analyses. All participants were subject to a physician-based interview, physical examination including anthropometric measurements, fasting laboratory testing, and 48-hour Holter monitoring. The study started in April 1998 and the last subject was included in June 2000. The follow-up was performed in April 2005. Selection criteria were as demonstrated in Figure 1.

Recording Device

The study has up-to-48-hour Holter monitoring in 678 subjects.²¹ More than 98% of the study population had more than 24 hours of recording. Nighttime HRV was available for study in 653 subjects (96%).

Holter recording for up to 48 hours was carried out by the use of 2-channel SpaceLabs tape recorders (9025, SpaceLabs, Inc). From the 48-hour Holter recording, the first 24 hours were selected for analyses (the second to the 25th hour). The primary editing and analyses were performed by experienced personnel and supervised by a responsible cardiologist. All Holter analyses were performed blinded to other patient data. An analysis of HRV was done using an FT3000 Medical Analysis and Review Station. The quality of the analyses has previously been described in detail, and interobserver variability shows κ values between 0.91 and 0.94.²⁵ Reproducibility was tested by a blinded reanalysis of 50 tapes, and the Spearman's rank correlation coefficient between the measurements was 0.95 to 0.97.

To examine the reproducibility of the HRV variables over time, we compared HRV measurements in another cohort of patients (40 subjects) for 2 consecutive days and found a Spearman's correlation coefficient between 0.72 and 0.85 for different HRV variables.

The range of technically acceptable recording and analysis time was 17.2 to 49.2 hours. The median value was 44.1 hours (Q1 and Q3, 41.4–45.5 hours).

Definitions

The simplest time domain measures of HRV were used for this study: SDNN, which is defined as SD for the mean value of all normal-to-normal (NN) QRS intervals.⁷ Nighttime SDNN was calculated over a period of 15 minutes from 02:00 AM to 02:15 AM, and 24-hour SDNN was calculated for a 24-hour period. The calculations were performed after the laboratory technician had edited the recordings and artifacts, and abnormal complexes and arrhythmias were defined.

Mean_{NN}, which stands for mean value for the time between normal complexes, was used as a measure of the mean 24-hour heart rate. Nighttime Mean_{NN} was analyzed between 2:00 AM and 2:15 AM, whereas 24-hour Mean_{NN} was calculated for an entire 24-hour period. The Mean_{NN} for each period reflects the mean heart rate during that period ($60\,000/\text{Mean}_{\text{NN}} = \text{heart rate in beats/s}$).

End Points

Primary End Points

Combined end point of stroke or death based on all-cause mortality or first event of stroke.

Secondary End Points

Secondary end points were stroke alone, all-cause mortality alone, and admissions for atrial fibrillation. All stroke cases were classified according to TOAST criteria.^{26,27}

In Denmark, all deaths, hospital admissions, and discharges are reported to the national central registry within 2 weeks. Data on stroke, death, and atrial fibrillation were obtained through this registry, but had to be confirmed. Discharge letters from hospital admissions and necessary cases patient files were reviewed. Discharge summaries were also used to identify patients with potential episodes of clinically relevant atrial fibrillation, and documentation was available from hospital records. The diagnosis of stroke was based on the anamnestic history of neurological deficits and had to be verified with computed tomography or magnetic resonance imaging scanning of the cerebrum. Only verified ischemic stroke were accepted for this study. All cases of strokes in our study are of

Table 1. Baseline Characteristics for Subjects With Nighttime SDNN and Subjects With Low Nighttime SDNN Compared With Normal Nighttime SDNN

Baseline Variables	Total	Nighttime SDNN <38	Nighttime SDNN >38	<i>P</i>
No. of Cases	653	330	323	
Age, y, mean±SD	64.1±6.8	64.8±6.9	63.9±6.6	0.0539
Female sex, n (%)	276 (42)	154 (46.7)	122 (37.8)	<0.00001
Current smoker, n (%)	305 (46.7)	163 (49.4)	142 (43.9)	0.16
Diabetes mellitus, n (%)	71 (10.9)	45 (13.6)	26 (8.0)	0.02
SBP, mm Hg, mean±SD	157±24	157±25.1	156±23.5	0.69
DBP, mm Hg, mean±SD	91±11	91.1±11.3	90.8±10.6	0.74
Total cholesterol, mmol/L, mean±SD	6.1±1.04	6.07±1.11	6.06±0.98	0.80
Triglyceride, mmol/L, median (Q1-Q3)	1.25 (0.92–1.83)	1.32 (0.97–1.95)	1.21 (0.88–1.74)	0.04
Glucose, mmol/L, mean±SD	5.8±1.7	5.9±1.87	5.7±1.55	0.097
HbA _{1c} , median (Q1-Q3)	0.061 (0.057–0.063)	0.061 (0.058–0.064)	0.060 (0.057–0.063)	0.047
hs-C-Reactive Protein μL/mL, median (Q1-Q3)	3 (3–5)	3 (3–5)	3 (3–4)	0.022
Low level of physical activity, n (%)	169 (25.9)	93 (28.2)	76 (23.5)	0.29
BMI, kg/m ² , mean±SD	26.1±4.2	26.11±4.26	26.16 (4.14)	0.88
Alcohol, units/week, mean±SD	18±20.4	18.02±21.3	18.01±19.5	0.99
Aspirin usage, n (%)	93 (14.2)	51 (15.4)	42 (13.0)	0.37
Betablocker usage, n (%)	31 (4.7)	15 (4.5)	16 (4.9)	0.81
Diuretic usage, n (%)	117 (19.9)	65 (19.7)	52 (16.1)	0.23
ACE inhibitor usage, n (%)	32 (4.9)	18 (5.4)	14 (4.3)	0.51
Statin usage, n (%)	14 (2.1)	7 (2.1)	7 (2.2)	0.97
Nighttime SDNN, ms, median (Q1-Q3)	38 (27–55)	27 (21–33)	55 (45–68)	<0.00001

ACE indicates angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; HbA_{1c}, Hemoglobin A_{1c}; SBP, systolic blood pressure; SD, standard deviation.

the ischemic type, while subjects diagnosed with hemorrhagic strokes were excluded from statistical analysis. All medications were registered at baseline and no participants were on warfarin, although antiplatelet therapy was common (14.2%).

Ethics

Written informed consent was obtained from all study subjects. The Regional Ethical Committee approved the study and the Declaration of Helsinki was followed.

Statistical Analysis

For normally distributed variables, mean and SD are presented; otherwise median value and quartiles (Q1–Q3) are presented.

Univariate associations between SDNN and other baseline parameters were evaluated by either Spearman's rank correlation or Kruskal-Wallis rank test, as appropriate. Moreover, a Wilcoxon rank sum and a paired *t* test were performed. Two-tailed tests of significance are reported and probability values of less than 0.05 are considered significant. Additional adjustments for the other variables associated with nighttime SDNN with *P*≤0.05 at baseline were also performed.

Regression analyses (logistic or linear) were performed to evaluate the covariate-adjusted association of the variable of interest. Cox proportional hazard models were used to evaluate the risk-factor-adjusted associations of nighttime SDNN and 24-hour SDNN with the primary and secondary end points. Both univariate and multivariate analyses were conducted. Adjustments were performed for age and sex alone, and together with other conventional risk factors, such as smoking, diabetes mellitus, systolic blood pressure, and total cholesterol. Further analyses were performed with all of the abovementioned conventional risk factors and the following variables: high sensitive-C reactive protein (hs-CRP), N-terminal prohormone B-type natriuretic peptide (NT-proBNP), and triglyceride. The conditions for Cox

models were met ie, model assumptions—the linearity of continuous variables, the proportional-hazard assumption, and the lack of interactions—were tested and found to be valid unless otherwise indicated. HRs are given per 10 ms change in SDNN and Mean_{NN} in all analyses. STATA/IC for Windows 10 was used to create the statistical analysis.

Results

Characteristics at baseline for the study population are listed in Table 1, which shows that subjects in the lower half of nighttime SDNN were older compared with the rest of the study subjects, and had higher blood pressure and more diabetes. In addition, hemoglobin A_{1c}, triglyceride, and hs-CRP levels were higher compared with those in subjects with higher nighttime values (probability values 0.047, 0.04, and 0.022, respectively). Nighttime HRV was lower in women (39.5±20 ms) than in men (46.2±25.1 ms; *P*=0.001) and in diabetics (39.8±23.9 ms) than in nondiabetics (43.8±23.2 ms; *P*=0.03) in multiple regression analyses. Triglyceride and hs-CRP were inversely related to nighttime HRV, *P*=0.002 and *P*=0.004, respectively. However, smoking, cholesterol, systolic blood pressure, and age were not associated with nighttime HRV (data not shown).

Follow-Up and End Points

Median follow-up was 76 months (Q1 and Q3, 74–78 months). During the follow-up period, 87 subjects died, 26 subjects developed ischemic strokes, and 20 subjects were admitted to the hospital with atrial fibrillation. Eighty sub-

Table 2. Cox Regression Models With the Combined Primary End Point (All-Cause Mortality and Stroke) and Secondary End Points (Stroke, All-Cause Mortality, and Atrial Fibrillation)

	Nighttime SDNN (ms)		Nighttime Mean _{NN} (ms)		24-Hour SDNN (ms)		24-Hour Mean _{NN} (ms)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All causes of mortality and stroke								
Univariate	0.836 (0.748–0.935)	0.002	0.696 (0.566–0.855)	0.001	0.682 (0.55–0.847)	0.001	0.769 (0.62–0.953)	0.016
Age and sex adjusted	0.830 (0.744–0.925)	0.001	0.600 (0.485–0.743)	<0.0001	0.652 (0.522–0.814)	<0.0001	0.640 (0.51–0.803)	<0.0001
Multivariable*	0.861 (0.774–0.956)	0.005	0.697 (0.554–0.877)	0.002	0.749 (0.597–0.94)	0.013	0.729 (0.577–0.923)	0.009
Stroke								
Univariate	0.669 (0.509–0.88)	0.004	0.853 (0.577–1.261)	0.425	0.768 (0.509–1.158)	0.207	0.892 (0.594–1.34)	0.583
Age and sex adjusted	0.666 (0.508–0.873)	0.003	0.751 (0.501–1.124)	0.164	0.734 (0.483–1.115)	0.147	0.769 (0.504–1.175)	0.225
Multivariable	0.675 (0.513–0.888)	0.005	0.867 (0.566–1.33)	0.514	0.866 (0.563–1.333)	0.514	0.832 (0.535–1.3)	0.418
All causes of mortality								
Univariate	0.881 (0.784–0.99)	0.033	0.680 (0.541–0.855)	0.001	0.661 (0.51–0.841)	0.001	0.767 (0.605–0.972)	0.028
Age and sex adjusted	0.875 (0.781–0.98)	0.02	0.587 (0.464–0.744)	<0.0001	0.629 (0.49–0.806)	<0.0001	0.640 (0.498–0.823)	0.001
Multivariable*	0.911 (0.818–1.015)	0.092	0.686 (0.533–0.883)	0.003	0.723 (0.56–0.933)	0.013	0.738 (0.57–0.954)	0.021
Atrial fibrillation								
Univariate	0.991 (0.816–1.204)	0.929	0.982 (0.631–1.529)	0.937	0.817 (0.516–1.295)	0.390	1.249 (0.817–1.91)	0.304
Age and sex adjusted	1.008 (0.833–1.22)	0.936	0.979 (0.614–1.559)	0.928	0.840 (0.523–1.349)	0.470	1.232 (0.789–1.922)	0.359
Multivariable*	1.010 (0.833–1.226)	0.915	1.019 (0.635–1.637)	0.936	0.910 (0.561–1.477)	0.703	1.223 (0.783–1.92)	0.373

SDNN indicates standard deviation of normal-to-normal RR intervals; Mean_{NN}, mean time between normal complexes; HR, hazard ratio; CI, confidence interval. *Age, sex, smoker, diabetes mellitus, systolic blood pressure, total cholesterol.

jects were identified in the group of the combined end point of all-cause mortality and stroke.

Death or Stroke

Nighttime SDNN was strongly correlated with the primary end point of death or stroke in univariate, age- and sex-adjusted, and fully adjusted models (HR, 0.861; 95% CI, 0.774–0.956; P=0.005) after adjustments for age, sex, smoking, diabetes mellitus, systolic blood pressure, and total cholesterol (Table 2). In addition, adjustments for triglyceride, hs-CRP, and NT-proBNP did not significantly change the demonstrated association (data not shown). Similarly, 24-hour SDNN, 24-hour Mean_{NN}, and nighttime Mean_{NN} were also associated with the combined end point of death and stroke (Table 2). Figure 2 shows the time course of

event (death or stroke) rates according to the quartiles of nighttime SDNN.

Stroke

The risk of stroke was significantly associated with nighttime SDNN in a univariate analysis (HR, 0.669; 95% CI, 0.509–0.88; P=0.004), after adjustment for sex and age (HR, 0.666; 95% CI, 0.508–0.873; P=0.003) and in a fully adjusted model (HR, 0.675; 95% CI, 0.513–0.888; P=0.005). Nighttime Mean_{NN}, 24-hour SDNN, and 24-hour Mean_{NN} were not associated with stroke in univariate or adjusted models (Table 2). The association between nighttime SDNN and stroke remained significant even after additional adjustment for heart rate and relevant biomarkers such as triglycerides, hs-CRP, and NT-pro BNP (data not shown). Of the 26 subjects who experienced an event of stroke, 81% (21/26) of all cases were in the lower half of nighttime SDNN, thus reflecting a strong association with nighttime SDNN below this level (HR, 4.31; 95% CI, 1.62–11.42; P=0.003). TOAST classification was performed retrospectively in all stroke patients. Eight subjects were classified as undetermined etiology (TOAST class 10), 8 subjects as possible or probable lacunar infarctions (TOAST class 5 OR 6), 7 subjects as probable or possible atherosclerosis (TOAST class 1 or 2), and 3 subjects as possible or probable cardioembolic stroke (TOAST class 3 or 4). Nighttime HRV was not significantly different among the groups. Figure 3 shows the risk of admissions for stroke in all subjects according to the quartiles of nighttime SDNN.

All-Cause Mortality

Nighttime SDNN was associated with all-cause mortality in a univariate analysis and after adjustment for age and sex, but not in fully adjusted models (Table 2). Nevertheless, 24-hour Mean_{NN}, nighttime Mean_{NN}, and 24-hour SDNN were all

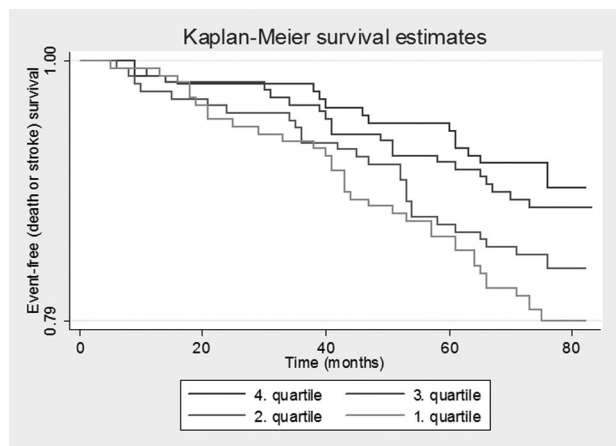


Figure 2. A Kaplan-Meier survival curve showing the time course of events (death or stroke) according to the quartiles of nighttime heart rate variability.

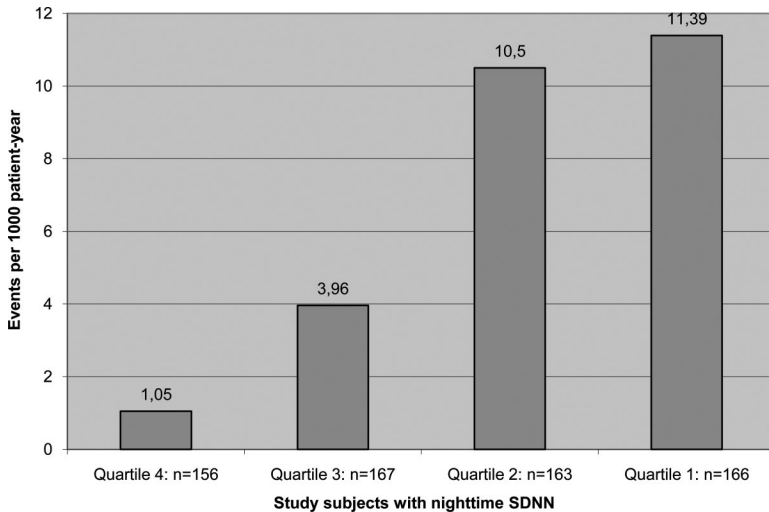


Figure 3. Incidence of admissions for stroke per 1000 patient-years in relations to nighttime SDNN in quartiles.

strongly associated with all-cause mortality, both in univariate and adjusted models (Table 2).

Admissions for Atrial Fibrillation

Admission for atrial fibrillation as an end point was not associated with any of the 4 different variables studied, neither in univariate nor in adjusted models (Table 2).

Discussion

The major finding of this study is that reduced nighttime HRV is associated with increased stroke risk in apparently healthy subjects with no previous history of stroke or cardiovascular disease. Twenty-four-hour SDNN and Mean_{NN} were associated with all-cause mortality, but not with stroke. The observed increased risk associated with low nighttime HRV seems to be beyond conventional risk factors. This in particular is of importance because reduced HRV has been demonstrated to be associated with many risk factors for atherosclerosis, including inflammatory markers.²⁴ No previous study has evaluated the prognostic value of nighttime HRV or heart rate in relation to stroke.

The underlying mechanisms of pathogenesis and etiology of decreased nighttime HRV in relation to stroke are not completely resolved and remain unclear; however, several mechanisms may be involved, with hypertension most probably being one of them. Some studies have found a strong correlation between HRV and blood pressure.^{2,13,28,29} Reduced HRV, elevation in the heart rate and cardiac output, as well as increased levels of norepinephrine, characterize a hyperkinetic state that may delineate a transition state between borderline hypertension and high-resistant hypertension.¹³ Other complications that are unrelated to blood pressure are increased hematocrit, tachycardia, obesity, and insulin resistance.¹³ Sympathetic activity probably stimulates enlargement of the left ventricle, thereby causing ventricular hypertrophy and stiffness of the arteries. Conversely, this causes increasing vascular resistance.¹³

Reduced parasympathetic tone may enhance hypercoagulation or increase blood viscosity, possibly triggering episodes of bradycardia and inducing arrhythmias.¹³ Variation

in heart rate has an impact on hypertension, atherosclerosis, and cardiovascular morbidity and mortality.^{13,14,28,29}

Impairment of the autonomic nervous system and the consequent sinus node derangement may enhance wall stress in the atrium. It has been suggested that this may induce episodes of paroxysmal atrial fibrillation, and even a tendency toward thromboembolism.¹⁵ We did not find any association between HRV and admissions for atrial fibrillation. Even so, admissions for atrial fibrillation most likely only compose a small part of the total burden of atrial fibrillation.

Limitations

The study population was exclusively middle-aged and elderly white patients. Therefore, the application of these data for other ethnic groups should be undertaken with caution. A selection bias cannot be excluded because not all eligible subjects were able to or willing to participate. We were only able to evaluate admissions for atrial fibrillation in this study; many cases of paroxysmal atrial fibrillation may have gone undiscovered. The number of admissions for atrial fibrillation during follow-up was also relatively low; hence, any associations between HRV and admissions for atrial fibrillation in this study must be considered with caution. Even though we have adjusted for conventional risk factors, and the use of the usual medication does not seem to be different among the various groups, there may still be residual confounding that contributes to the presence of the demonstrated associations.

It is assumed that the study population were sleeping during nighttime, though the subjects did not keep a diary of their sleep times.

Conclusions

Nighttime HRV is strongly associated with stroke, whereas 24-hour HRV is associated with all-cause mortality. The observed associations are shown to be beyond conventional risk factors.

Author Contributions

We state that all authors had access to the data and their role in writing the manuscript was as follows: Zeynep Binici: I participated

in preparing the first draft, data analyses, and in writing the manuscript. I have approved the final version. Mette Rauhe Mouridsen: I participated in validation and interpretation of data. I have approved the final version. Lars Køber: I have interpreted the data and reviewed the manuscript. I have approved the final version. Ahmad Sajadieh: I am the principal investigator of this study and participated in the initiation and coordination of the study, and in preparing the manuscript. I have approved the final version.

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Disclosures

None.

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