Association Between Heart Rate and Subclinical Cerebrovascular Disease in the Elderly

Koki Nakanishi, MD; Zhezhen Jin, PhD; Shunichi Homma, MD; Mitchell S.V. Elkind, MD, MS; Tatjana Rundek, MD, PhD; Seitetz C. Lee, MD; Aylin Tugcu, MD; Mitsuhiro Yoshita, MD; Charles DeCarli, MD; Clinton B. Wright, MD, MS; Ralph L. Sacco, MD, MS; Marco R. Di Tullio, MD

Background and Purpose—Although increased heart rate (HR) is a predictor of cardiovascular events and mortality, its possible association with subclinical cerebrovascular disease, which is prevalent in the elderly, has not been evaluated. This study aimed to investigate the association of daytime, nighttime, 24-hour HR, and HR variability with subclinical cerebrovascular disease in an elderly cohort without history of stroke.

Methods—The study cohort consisted of 680 participants (mean age, 73±7 years; 42% men) in sinus rhythm who underwent 24-hour ambulatory blood pressure and HR monitoring, 2-dimensional echocardiography, and brain magnetic resonance imaging as part of the CABL study (Cardiac Abnormalities and Brain Lesion). Subclinical cerebrovascular disease was defined as silent brain infarcts and white matter hyperintensity volume (WMHV). The relationship of HR measures with the presence of silent brain infarct and upper quartile of log WMHV (log WMHV4) was analyzed.

Results—Presence of silent brain infarct was detected in 93 participants (13.7%); mean log WMHV was −0.92±0.93 (median, −1.05; min, −5.88; max, 1.74). Multivariate analysis showed that only nighttime HR (adjusted odds ratio, 1.29 per 10 bpm; 95% confidence interval, 1.03–1.61; P=0.026) was significantly associated with log WMHV4, independent of traditional cardiovascular risk factors, ambulatory systolic blood pressure, and echocardiographic parameters. No similar association was observed for daytime HR and HR variability. There was no significant association between all HR measures and silent brain infarct.

Conclusions—In a predominantly elderly cohort, elevated nighttime HR was associated with WMHV, suggesting an independent role of HR in subclinical cerebrovascular disease. **(*Stroke*. 2018;49:319-324. DOI: 10.1161/STROKEAHA.117.019355.)**

Key Words: echocardiography ■ heart rate ■ magnetic resonance imaging ■ multivariate analysis ■ odds ratio

A significant association between increased heart rate (HR) and all-cause and cardiovascular mortality has been reported in numerous epidemiological studies.[1–5] Recent studies also demonstrated that nighttime HR has better prognostic value compared with resting and daytime HR.[6,7] Faster HR is a possible manifestation of an altered autonomic nervous tone that can be associated with increased vascular resistance and high blood pressure (BP), thus predisposing to the development of adverse cardiovascular outcomes. There is accumulating evidence that increased sympathetic nervous activity might be an important element in protecting the brain from excessive increases in perfusion pressure during BP increases[8,9] and flow during rapid eye movement sleep.[10,11] However, the association between HR and stroke remains unclear, and the studies on the topic have provided conflicting results.[12–17] In addition, most of prior studies have considered only a single measurement of HR during daytime.

In population-based studies, the prevalence of asymptomatic vascular brain lesions is substantially higher than that of clinically overt disease. Silent brain infarcts (SBIs) and white matter hyperintensities (WMHs), both manifestations of subclinical cerebrovascular disease primarily caused by small-vessel disease, are commonly seen on brain magnetic resonance imaging (MRI) of elderly adults and carry an increased risk of subsequent stroke, cognitive impairment, dementia, and death.[18–21] However, the association between HR measures and subclinical cerebrovascular disease is not established. The aim of the present study was to assess the

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From the Department of Medicine (K.N., S.H., S.C.L., A.T., M.R.D.T.), Department of Biostatistics (Z.J.), and Departments of Neurology and Epidemiology (M.S.V.E.), Columbia University, New York, NY; Department of Neurology (T.R., C.B.W., R.L.S.), Department of Public Health Sciences (T.R., C.B.W., R.L.S.), and Department of Human Genetics (R.L.S.), Miller School of Medicine, University of Miami, FL; Department of Neurology, Hokuriku National Hospital, Nanto, Japan (M.Y.); and Department of Neurology, University of California at Davis (C.D.).

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Correspondence to Marco R. Di Tullio, MD, Columbia University College of Physicians and Surgeons, PH 3-342, 622 W 168th St, New York, NY 10032. E-mail md42@cumc.columbia.edu

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association of daytime, nighttime, 24-hour HR, and HR variability with subclinical cerebrovascular disease in an elderly sample of the general population without history of stroke.

Methods

Study Population

The data that support the findings of this study are available from the corresponding author on reasonable request. The study population was derived from the CABL study (Cardiovascular Abnormalities and Brain Lesions), which is a community-based epidemiological study designed to investigate the cardiovascular predictors of silent cerebrovascular disease. CABL based its recruitment on the NOMAS (Northern Manhattan Study), a population-based prospective study that enrolled 3298 participants from the community living in northern Manhattan between 1993 and 2001. The study design and recruitment details of NOMAS have been described previously.[22] Beginning in 2003, NOMAS participants were invited to participate in an MRI substudy if they (1) were at least 55 years of age, (2) had no contraindications to MRI, and (3) did not have a previous diagnosis of stroke. From September 2005 to July 2010, NOMAS MRI participants who voluntarily agreed to undergo a more extensive cardiovascular evaluation including transthoracic echocardiography were included in CABL. A total of 1004 participants were included in CABL, 828 of whom underwent 24-hour ambulatory BP monitoring with simultaneous HR measurement. Of those, 53 participants with atrial fibrillation and 95 participants under the age of 60 years were excluded. Therefore, the cohort of the present study consisted of 680 participants. Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Boards of Columbia University Medical Center and the University of Miami.

Risk Factor Assessment

Cardiovascular risk factors were ascertained through direct examination and interviews conducted by trained research assistants. Among the variables used in the analysis, hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg (mean of 2 readings obtained in sitting position), or antihypertensive medication use. Diabetes mellitus was defined by current use of insulin or hypoglycemic agents, or a fasting glucose of ≥126 mg/dL, tested on ≥2 occasions. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dL, or the use of lipid-lowering medications. Body mass index was calculated using height and weight (kg/m^2).

Ambulatory HR Measurement

Ambulatory HR measures were obtained from ambulatory BP monitoring. The methods of ambulatory BP monitoring have been previously published.[23] In brief, the participants were asked to follow their usual routine and to note their activities at the time of each BP/HR reading in a diary, as well as their sleep onset and wake-up times. Ambulatory BP/HR reading was automatically taken and recorded every 15 minutes during waking hours and every 30 minutes during sleeping hours for 24 hours. The mean HRs and BPs were calculated for the 24-hour period and separately for daytime (awake) and nighttime (sleep) periods, defined by subjects' diary reports of actual asleep and awake times. HR variability was also calculated based on the coefficient of variation in the 24 hours.

Two-Dimensional Echocardiographic Examination

Echocardiographic examination was performed using a commercially available system (iE 33; Philips, Andover, MA) by a trained, registered cardiac sonographer blinded to the participant's clinical information according to a standardized protocol. The dimensions of the cardiac chambers were measured in the standard manner.[24] Left ventricular (LV) ejection fraction was obtained by using the Simpson method from apical 4- and 2-chamber views.[24] LV mass was calculated with a validated method[25] and indexed for the participant's body surface area. Left atrial (LA) anteroposterior diameter was measured at the level of the aortic valve according to a leading edge-to-leading edge convention. LA diameter was also indexed by the body surface area.

Image Acquisition and Interpretation of Brain MRI

A detailed description of the assessment of subclinical cerebrovascular lesions has been published previously.[26,27] In brief, brain imaging was performed on a 1.5-T MRI system (Philips Medical Systems). SBIs were defined as either a cavitation on the fluid-attenuated inversion recovery sequence of at least 3 mm in size, distinct from a vessel (owing to the lack of signal void on T2 sequence), and of equal intensity to cerebrospinal fluid in the case of lacunar infarction, or a wedge-shaped cortical or cerebellar area of encephalomalacia with surrounding gliosis consistent with infarction attributable to distal arterial branch occlusion. Interobserver agreement for SBI detection was 93.3%.[27] WMH volume (WMHV) analysis was based on a fluid-attenuated inversion recovery image and performed by using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. WMHV was expressed as proportion of total cranial volume corrected for head size and log-transformed (log WMHV) to achieve a normal distribution for analysis as a continuous variable. The upper quartile of log WMHV (log WMHV4) was used as the dependent variable in the categorical analyses. All measurements were performed blinded to participant clinical information.

Statistical Analysis

Categorical variables are presented as numbers and percentages and continuous variables are expressed as mean±SD. Univariate and multivariate logistic regression analyses were used to evaluate the association between HR measures and subclinical cerebrovascular disease. Multivariate models were adjusted for age, sex, significant potential cofactors (variables associated to silent cerebrovascular disease with $P<0.1$ in the univariate analysis), and use of β-blockers in 3 sequential models as follows: model 1: adjustment for age and sex; model 2: adjustment for age, sex, hypertension, ambulatory systolic BP (at the corresponding time of the day); and model 3: additional adjustment for the use of β-blockers and echocardiographic parameters associated with subclinical cerebrovascular disease (LV mass index and LA diameter index). Odds ratios with their 95% confidence interval were reported. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Clinical characteristics of the study population are shown in Table 1. Mean age of the study participants was 72.6±7.3 years, and 282 (41.5%) were male. Mean daytime HR was 74.8±9.9 bpm, nighttime HR was 65.5±8.9 bpm, and 24-hour HR was 71.4±9.0 bpm.

Presence of SBI was detected in 93 participants (13.7%); mean log WMHV was −0.92±0.93 (median, −1.05; min, −5.88; max, 1.74; also Table 1). In univariate analysis, only nighttime HR was significantly associated with log WMHV4, whereas other HR measures were not associated with log WMHV4 or SBI (Table 2). Table 3 shows the univariate association of clinical and echocardiographic variables with log WMHV4. Age, hypertension, ambulatory systolic BP, LV mass index, and LA diameter index were associated with log WMHV4.

Both nighttime and 24-hour HR were associated with log WMHV4 in age- and sex-adjusted models (Table 4, model 1), whereas daytime HR and HR variability were not. In the multivariable analyses adjusted for hypertension and

Table 1. Characteristics of the Study Population

n=680	
Age, y	72.6±7.3
Male sex, n (%)	282 (41.5)
Race/ethnicity	
White, n (%)	81 (11.9)
Black, n (%)	103 (15.1)
Hispanic, n (%)	482 (70.9)
Other, n (%)	14 (2.1)
Hypertension, n (%)	547 (80.4)
Diabetes mellitus, n (%)	212 (31.2)
Hypercholesterolemia, n (%)	484 (71.2)
Body mass index, kg/m^2	28.1±4.7
Coronary artery disease, n (%)	43 (6.3)
β-Blocker use, n (%)	172 (25.3)
Daytime heart rate, bpm	74.8±9.9
Nighttime heart rate, bpm	65.5±8.9
24-h heart rate, bpm	71.4±9.0
Heart rate variability	9.2±3.1
Daytime SBP, mm Hg	128.9±14.6
Nighttime SBP, mm Hg	119.7±16.5
24-h SBP, mm Hg	125.6±14.5
Echocardiography	
LV end-diastolic diameter, mm	44.6±4.6
LV end-systolic diameter, mm	28.3±4.7
LV ejection fraction, %	63.8±7.0
LV mass index, g/m^2	102.9±25.5
LA diameter index, mm/m^2	22.3±3.0
Brain MRI	
SBI	93 (13.7)
Log WMHV	−0.92±0.93

Values are mean±SD or n (%). LA indicates left atrium; LV, left ventricle; MRI, magnetic resonance imaging; SBI, silent brain infarcts; SBP, systolic blood pressure; and WMHV, white matter hyperintensity volume.

corresponding ambulatory systolic BP, only nighttime HR remained significant (Table 4, model 2). Even after adjustment for use of β-blockers and for pertinent echocardiographic parameters (LV mass index and LA diameter index), nighttime HR remained significantly associated with log WMHV4 (adjusted odds ratio, 1.29 per 10 bpm; 95% confidence interval, 1.03–1.61; P=0.026).

Discussion

Our study demonstrates that nighttime HR is significantly associated with WMHV, a manifestation of subclinical brain disease, independently of traditional cardiovascular risk factors, systolic BP recorded at the same time of the day, and echocardiographic parameters in an elderly general population sample without history of stroke. On the other hand, daytime HR and HR variability showed no association with subclinical cerebrovascular disease.

Table 2. Univariate Association of Heart Rate Measures With SBI and Upper Quartile of Log WMHV

	SBI		Log WMHV4	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Daytime heart rate	0.95 (0.76–1.19)	0.676	1.02 (0.85–1.21)	0.855
Nighttime heart rate	0.98 (0.76–1.26)	0.875	1.23 (1.01–1.49)	0.041
24-h heart rate	0.94 (0.74–1.20)	0.619	1.09 (0.90–1.32)	0.377
Heart rate variability	0.89 (0.71–1.11)	0.289	0.96 (0.81–1.14)	0.620

Odds ratio for each increase of 10 bpm and for increase of 0.04 heart rate variability. CI indicates confidence interval; SBI, silent brain infarcts; and WMHV, white matter hyperintensity volume.

Numerous epidemiological studies have shown that increased HR is associated with the development of cardiovascular events and mortality.[1–5] Recent studies also demonstrated that nighttime HR has better prognostic value compared with resting and daytime HR.[6,7] Johansen et al[7] demonstrated that nighttime HR was the only parameter associated with cardiovascular events after multivariable adjustment for cardiovascular risk factors in 653 middle-aged subjects with no apparent heart disease. However, the association between HR and stroke remains unclear. The reports that have examined this relationship are conflicting

Table 3. Univariate Logistic Regression Analysis for Upper Quartile of Log WMHV

	Odds Ratio (95% CI)	P Value
Age, y	1.12 (1.09–1.15)	<0.001
Sex, male	0.76 (0.53–1.08)	0.127
Hypertension	3.39 (1.89–6.08)	<0.001
Diabetes mellitus	0.96 (0.66–1.40)	0.849
Hypercholesterolemia	0.83 (0.57–1.21)	0.329
Body mass index, kg/m^2	0.98 (0.94–1.01)	0.216
Coronary artery disease	1.49 (0.77–2.89)	0.239
β-Blocker use	1.37 (0.92–2.04)	0.122
Daytime SBP, mm Hg	1.03 (1.02–1.05)	<0.001
Nighttime SBP, mm Hg	1.03 (1.02–1.04)	<0.001
24-h SBP, mm Hg	1.04 (1.02–1.05)	<0.001
LV end-diastolic diameter, mm	0.97 (0.94–1.01)	0.183
LV end-systolic diameter, mm	0.98 (0.94–1.02)	0.245
LV ejection fraction, %	1.00 (0.98–1.03)	0.811
LV mass index, g/m^2	1.01 (1.01–1.02)	<0.001
LA diameter index, mm/m^2	1.09 (1.03–1.16)	0.003

CI indicates confidence interval; LA, left atrium; LV, left ventricle; SBP, systolic blood pressure; and WMHV, white matter hyperintensity volume.

Table 4. Association of HR Measures With Upper Quartile of Log WMHV

	Daytime HR		Nighttime HR		24-h HR		HR Variability	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Model 1	1.17 (0.97–1.42)	0.109	1.35 (1.09–1.67)	0.005	1.27 (1.02–1.56)	0.029	1.00 (0.84–1.20)	0.968
Model 2	1.15 (0.94–1.40)	0.169	1.30 (1.04–1.61)	0.019	1.24 (0.99–1.54)	0.053	1.05 (0.88–1.26)	0.579
Model 3	1.16 (0.95–1.43)	0.146	1.29 (1.03–1.61)	0.026	1.25 (0.99–1.56)	0.052	1.09 (0.91–1.30)	0.378

Model 1: age and sex adjusted. Model 2: adjusted for age, sex, hypertension, and corresponding systolic blood pressure. Model 3: adjusted for variables as in model 2, use of β-blocker, LV mass index, and LA diameter index. Odds ratio for each increase of 10 bpm and for increase of 0.04 HR variability. CI indicates confidence interval; HR, heart rate; LA, left atrium; , left ventricle; and WMHV, white matter hyperintensity volume.

and mostly based on a single measurement of daytime HR. Mao et al[14] showed that high resting HR increased the risk of stroke in 169 871 general Chinese adults ≥40 years. Similarly, data from patients with stable coronary artery disease and hypertension demonstrated that high resting HR was associated with an increased risk of stroke.[15,16] More recently, the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) investigators found in 24 730 participants without history of stroke that each 10 bpm HR increase was associated with a 10% increase in the risk of stroke.[17] In contrast, reports from the general French population[12] and from the Women's Health Initiative Study[13] did not show an association between resting HR and stroke.

MRI-defined SBIs and WMHs are commonly present in elderly adults and are important markers of cerebral small-vessel disease. Although SBIs and WMHs are not typically associated with overt, clinical stroke symptoms, they are not entirely silent or benign, as they are often associated with subtle neurological symptoms, increased risk of stroke, cognitive impairment, dementia, and death.[18–21] In this study, we found an independent association of nighttime HR with WMHV. The underlying mechanisms of this association are not entirely clear, but we hypothesize several potential explanations. First, arterial compliance and distensibility may be impaired in individuals with elevated HR. Mangoni et al[28] observed that pacing-induced tachycardia led to reductions in carotid artery compliance and distensibility in a rat model. Large epidemiological studies also showed that an elevated HR was associated with arterial stiffness.[29,30] In the Multi-Ethnic Study of Atherosclerosis, Whelton et al[30] demonstrated that carotid and aortic distensibility decreased with increasing HR (P for trend <0.001 and 0.009, respectively). Second, faster HR may also increase the risk of thromboembolism through increased blood viscosity, platelet activation, and a procoagulant state.[31] Finally, increased HR may contribute to endothelial dysfunction by the upregulation of inflammatory cytokines.[32] Interestingly, the association between HR and WMHs in our study was not observed during daytime, but at nighttime. This may be partially explained by the fact that HR during sleep is more stable than HR during waking hours, which is influenced by physical activities or emotional triggers.[33] Moreover, an elevated nighttime HR can also represent persistent sympathetic overactivity and is a better reflection of the mechanical stress on the arterial wall than daytime HR.[34] In addition, the presence of a sleep disorder may also affect the association between increased nighttime HR and WMHs. In fact, sleep apnea syndrome is associated with elevated nighttime HR[35] and carotid atherosclerosis[36] and WMHs.[37] It should be noted that, although hypertension is considered a major determinant of increased SBI and WMHV, our results were adjusted for ambulatory BP values obtained at the corresponding time of the day, suggesting that the association between nighttime HR and increased WMHV is not merely a marker of a parallel BP increase. Elevated BP directly impairs cerebrovascular reactivity[38] causing increased risk of WMHs.[39] In addition, elevated BP also induces LV hypertrophy and renal dysfunction, both of which are risk factors for WMHs.[40,41] These mechanisms cannot be involved in the association between elevated HR and WMHs, which may instead be mediated by impaired arterial distensibility, increased blood viscosity, platelet activation, and endothelial dysfunction via upregulation of inflammatory cytokines, as mentioned above.

In our study, no significant association was observed between any HR measure and SBI. Although the reason for the discordance in the association of HR measures with SBI and with WMHV is unclear, different pathophysiological mechanisms between SBI and WMHV may be involved in explaining the results. SBIs may reflect more focal areas of infarct, presumed to result from the occlusion of a small perforating artery supplying the subcortical areas of the brain,[42] whereas WMHs are considered areas of leukoaraiosis because of chronic hypoperfusion and disruption of the blood–brain barrier, leading to chronic leakage of plasma into the white matter.[43] In addition, considering the strong association between HR and sympathetic nervous activity, WMHV may be more strongly associated with a dysfunction of the autonomic nervous system than SBI. Indeed, previous studies demonstrated the association of autonomic dysfunction with WMHV.[44,45] Because WMHs carry an increased risk of subsequent stroke, closer follow-up may be needed in subjects with high nighttime HR. Furthermore, HR-lowering therapy and more intensive risk factor control might have beneficial effect on subclinical cerebrovascular disease in subjects with high nighttime HR. Those concepts, however, require testing in prospective large controlled trials. Our study also encourages further investigations on the underlying pathophysiological mechanisms between HR and subclinical cerebrovascular disease.

Study Limitations

The study sample included elderly participants, with large Hispanic representation and high prevalence of cardiovascular risk factors, which might not allow generalization of the results to cohorts with different demographic composition

and risk profiles. Because of the cross-sectional design of our study, we are not able to establish a cause–effect relationship between HR and subclinical cerebrovascular disease. Finally, although we accounted for several confounders and performed multivariate analyses adjusted for variables associated with subclinical cerebrovascular disease, we cannot exclude the possibility of unmeasured confounders playing a role in the observed associations.

Conclusions

In an elderly sample of the general population, higher nighttime HR was independently associated with increased risk of WMHs, suggesting a role nighttime HR in the development of subclinical cerebrovascular disease.

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