

## Association Between Heart Rate and Subclinical Cerebrovascular Disease in the Elderly

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**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  $-0.92\pm 0.93$  (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;49:00-00. 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.<sup>1–5</sup> Recent studies also demonstrated that nighttime HR has better prognostic value compared with resting and daytime HR.<sup>6,7</sup> 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<sup>8,9</sup> and flow during rapid eye movement sleep.<sup>10,11</sup> However, the association between HR and stroke remains unclear, and the studies

on the topic have provided conflicting results.<sup>12–17</sup> 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.<sup>18–21</sup> 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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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.<sup>22</sup> 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  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg (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  $\geq 126$  mg/dL, tested on  $\geq 2$  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 ( $\text{kg}/\text{m}^2$ ).

### Ambulatory HR Measurement

Ambulatory HR measures were obtained from ambulatory BP monitoring. The methods of ambulatory BP monitoring have been previously published.<sup>23</sup> 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.<sup>24</sup> Left ventricular (LV) ejection fraction was obtained by using the Simpson method from apical 4- and 2-chamber views.<sup>24</sup> LV mass

was calculated with a validated method<sup>25</sup> 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.<sup>26,27</sup> 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%.<sup>27</sup> 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 $\pm$ 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  $\beta$ -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  $\beta$ -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  $72.6 \pm 7.3$  years, and 282 (41.5%) were male. Mean daytime HR was  $74.8 \pm 9.9$  bpm, nighttime HR was  $65.5 \pm 8.9$  bpm, and 24-hour HR was  $71.4 \pm 9.0$  bpm.

Presence of SBI was detected in 93 participants (13.7%); mean log WMHV was  $-0.92 \pm 0.93$  (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 <sup>2</sup>	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 <sup>2</sup>	102.9±25.5
LA diameter index, mm/m <sup>2</sup>	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,

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

	SBI		Log WMHV4	
	Odds Ratio (95% CI)	<i>P</i> Value	Odds Ratio (95% CI)	<i>P</i> 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.

daytime HR and HR variability showed no association with subclinical cerebrovascular disease.

Numerous epidemiological studies have shown that increased HR is associated with the development of cardiovascular events and mortality.<sup>1–5</sup> Recent studies also demonstrated that nighttime HR has better prognostic value compared with resting and daytime HR.<sup>6,7</sup> Johansen et al<sup>7</sup> 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)	<i>P</i> 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 <sup>2</sup>	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 <sup>2</sup>	1.01 (1.01–1.02)	<0.001
LA diameter index, mm/m <sup>2</sup>	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)	<i>P</i> Value	Odds Ratio (95% CI)	<i>P</i> Value	Odds Ratio (95% CI)	<i>P</i> Value	Odds Ratio (95% CI)	<i>P</i> 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  $\beta$ -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; LV, left ventricle; and WMHV, white matter hyperintensity volume.

and mostly based on a single measurement of daytime HR. Mao et al<sup>14</sup> showed that high resting HR increased the risk of stroke in 169 871 general Chinese adults  $\geq 40$  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.<sup>15,16</sup> 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.<sup>17</sup> In contrast, reports from the general French population<sup>12</sup> and from the Women's Health Initiative Study<sup>13</sup> 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.<sup>18–21</sup> 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<sup>28</sup> 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.<sup>29,30</sup> In the Multi-Ethnic Study of Atherosclerosis, Whelton et al<sup>30</sup> 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.<sup>31</sup> Finally, increased HR may contribute to endothelial dysfunction by the upregulation of inflammatory cytokines.<sup>32</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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<sup>35</sup> and carotid atherosclerosis<sup>36</sup> and WMHs.<sup>37</sup> 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<sup>38</sup> causing increased risk of WMHs.<sup>39</sup> In addition, elevated BP also induces LV hypertrophy and renal dysfunction, both of which are risk factors for WMHs.<sup>40,41</sup> 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,<sup>42</sup> 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.<sup>43</sup> 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.<sup>44,45</sup> 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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## References

- Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J*. 1987;113:1489–1494.
- Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J*. 1991;121(1 pt 1):172–177.
- Greenland P, Daviglius ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol*. 1999;149:853–862.
- Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate: a risk factor for cardiovascular death in elderly men. *Arch Intern Med*. 1999;159:585–592.
- Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50:823–830. doi: 10.1016/j.jacc.2007.04.079.
- Hansen TW, Thijs L, Boggia J, Li Y, Kikuya M, Björklund-Bodegård K, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of ambulatory heart rate revisited in 6928 subjects from 6 populations. *Hypertension*. 2008;52:229–235. doi: 10.1161/HYPERTENSIONAHA.108.113191.
- Johansen CD, Olsen RH, Pedersen LR, Kumarathurai P, Mouridsen MR, Binici Z, et al. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. *Eur Heart J*. 2013;34:1732–1739. doi: 10.1093/eurheartj/ehs449.
- Heistad DD, Marcus ML. Effect of sympathetic stimulation on permeability of the blood-brain barrier to albumin during acute hypertension in cats. *Circ Res*. 1979;45:331–338.
- Cassaglia PA, Griffiths RI, Walker AM. Sympathetic nerve activity in the superior cervical ganglia increases in response to imposed increases in arterial pressure. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R1255–R1261. doi: 10.1152/ajpregu.00332.2007.
- Loos N, Grant DA, Wild J, Paul S, Barfield C, Zoccoli G, et al. Sympathetic nervous control of the cerebral circulation in sleep. *J Sleep Res*. 2005;14:275–283. doi: 10.1111/j.1365-2869.2005.00464.x.
- Cassaglia PA, Griffiths RI, Walker AM. Cerebral sympathetic nerve activity has a major regulatory role in the cerebral circulation in REM sleep. *J Appl Physiol (1985)*. 2009;106:1050–1056. doi: 10.1152/jappphysiol.91349.2008.
- Benetos A, Rudnicki A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. *Hypertension*. 1999;33:44–52.
- Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, Hendrix SL, et al; Women's Health Initiative Research Group. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. *BMJ*. 2009;338:b219. doi: 10.1136/bmj.b219.
- Mao Q, Huang JF, Lu X, Wu X, Chen J, Cao J, et al. Heart rate influence on incidence of cardiovascular disease among adults in China. *Int J Epidemiol*. 2010;39:1638–1646. doi: 10.1093/ije/dyq119.
- Julius S, Palatini P, Kjeldsen SE, Zanchetti A, Weber MA, McInnes GT, et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. *Am J Cardiol*. 2012;109:685–692. doi: 10.1016/j.amjcard.2011.10.025.
- Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, et al. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol*. 2014;103:149–159. doi: 10.1007/s00392-013-0644-4.
- O'Neal WT, Qureshi WT, Judd SE, Meschia JF, Howard VJ, Howard G, et al. Heart rate and ischemic stroke: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Int J Stroke*. 2015;10:1229–1235. doi: 10.1111/ijss.12620.
- Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34:1126–1129. doi: 10.1161/01.STR.0000068408.82115.D2.
- Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222. doi: 10.1056/NEJMoa022066.
- Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr; Cardiovascular Health Study Collaborative Research Group. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*. 2004;35:1821–1825. doi: 10.1161/01.STR.0000132193.35955.69.
- Liebetrau M, Steen B, Hamann GF, Skoog I. Silent and symptomatic infarcts on cranial computerized tomography in relation to dementia and mortality: a population-based study in 85-year-old subjects. *Stroke*. 2004;35:1816–1820. doi: 10.1161/01.STR.0000131928.47478.44.
- Sacco RL, Khatri M, Rundek T, Xu Q, Gardener H, Boden-Albala B, et al. Improving global vascular risk prediction with behavioral and anthropometric factors. The multiethnic NOMAS (Northern Manhattan Cohort Study). *J Am Coll Cardiol*. 2009;54:2303–2311. doi: 10.1016/j.jacc.2009.07.047.
- Iwata S, Jin Z, Schwartz JE, Homma S, Elkind MS, Rundek T, et al. Relationship between ambulatory blood pressure and aortic arch atherosclerosis. *Atherosclerosis*. 2012;221:427–431. doi: 10.1016/j.atherosclerosis.2012.01.010.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1.e14–39.e14. doi: 10.1016/j.echo.2014.10.003.
- Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation*. 1977;55:613–618.
- Wright CB, Paik MC, Brown TR, Stabler SP, Allen RH, Sacco RL, et al. Total homocysteine is associated with white matter hyperintensity volume: the Northern Manhattan Study. *Stroke*. 2005;36:1207–1211. doi: 10.1161/01.STR.0000165923.02318.22.
- Willey JZ, Moon YP, Paik MC, Yoshita M, Decarli C, Sacco RL, et al. Lower prevalence of silent brain infarcts in the physically active: the Northern Manhattan Study. *Neurology*. 2011;76:2112–2118. doi: 10.1212/WNL.0b013e31821f4472.

28. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. *J Hypertens*. 1996;14:897–901.
29. Park BJ, Lee HR, Shim JY, Lee JH, Jung DH, Lee YJ. Association between resting heart rate and arterial stiffness in Korean adults. *Arch Cardiovasc Dis*. 2010;103:246–252. doi: 10.1016/j.acvd.2010.03.004.
30. Whelton SP, Blankstein R, Al-Mallah MH, Lima JA, Bluemke DA, Hundley WG, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension*. 2013;62:477–484. doi: 10.1161/HYPERTENSIONAHA.113.01605.
31. Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. *J Hum Hypertens*. 1997;11 (suppl 1):S19–S27.
32. Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol*. 2010;56:1973–1983. doi: 10.1016/j.jacc.2010.09.014.
33. Palatini P, Reboldi G, Beilin LJ, Eguchi K, Imai Y, Kario K, et al. Predictive value of night-time heart rate for cardiovascular events in hypertension. The ABP-International study. *Int J Cardiol*. 2013;168:1490–1495. doi: 10.1016/j.ijcard.2012.12.103.
34. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyrn M. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med*. 2007;167:2116–2121. doi: 10.1001/archinte.167.19.2116.
35. Ozeke O, Güngör M, Hızal SB, Aydın D, Ertürk O, Celenk MK, et al. Influence of the severity of obstructive sleep apnea on nocturnal heart rate indices and its association with hypertension. *Anadolu Kardiyol Derg*. 2011;11:509–514. doi: 10.5152/akd.2011.135.
36. Gunnarsson SI, Peppard PE, Korcarz CE, Barnet JH, Aeschlimann SE, Hagen EW, et al. Obstructive sleep apnea is associated with future subclinical carotid artery disease: thirteen-year follow-up from the Wisconsin sleep cohort. *Arterioscler Thromb Vasc Biol*. 2014;34:2338–2342. doi: 10.1161/ATVBAHA.114.303965.
37. Kim H, Yun CH, Thomas RJ, Lee SH, Seo HS, Cho ER, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. *Sleep*. 2013;36:709B–715B. doi: 10.5665/sleep.2632.
38. Hajjar I, Zhao P, Alsop D, Novak V. Hypertension and cerebral vasoreactivity: a continuous arterial spin labeling magnetic resonance imaging study. *Hypertension*. 2010;56:859–864. doi: 10.1161/HYPERTENSIONAHA.110.160002.
39. Zhao P, Alsop DC, Abduljalil A, Selim M, Lipsitz L, Novak P, et al. Vasoreactivity and peri-infarct hyperintensities in stroke. *Neurology*. 2009;72:643–649. doi: 10.1212/01.wnl.0000342473.65373.80.
40. Khatri M, Wright CB, Nickolas TL, Yoshita M, Paik MC, Kranwinkel G, et al. Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). *Stroke*. 2007;38:3121–3126. doi: 10.1161/STROKEAHA.107.493593.
41. Nakanishi K, Jin Z, Homma S, Elkind MS, Rundek T, Tugcu A, et al. Left ventricular mass-geometry and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. *Am Heart J*. 2017;185:85–92. doi: 10.1016/j.ahj.2016.11.010.
42. Bamford JM, Warlow CP. Evolution and testing of the lacunar hypothesis. *Stroke*. 1988;19:1074–1082.
43. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701. doi: 10.1016/S1474-4422(10)70104-6.
44. Galluzzi S, Nicosia F, Geroldi C, Alicandri A, Bonetti M, Romanelli G, et al. Cardiac autonomic dysfunction is associated with white matter lesions in patients with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci*. 2009;64:1312–1315. doi: 10.1093/gerona/glp105.
45. Nakagawa T, Hasegawa Y, Uekawa K, Ma M, Katayama T, Sueta D, et al. Renal denervation prevents stroke and brain injury via attenuation of oxidative stress in hypertensive rats. *J Am Heart Assoc*. 2013;2:e000375. doi: 10.1161/JAHA.113.000375.



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