Resting Heart Rate and In-Hospital Mortality in Acute Ischemic Stroke Patients With and Without Atrial Fibrillation

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Background: The prognostic role of resting heart rate (RHR) on mortality in acute ischemic stroke (AIS) patients including atrial fibrillation (AF) is unclear. This study evaluated the relationship between RHR and in-hospital mortality among all AIS patients with and without AF.

Methods and Results: The study enrolled 3,447 AIS patients from December 2013 to May 2014 across 22 hospitals in Suzhou City. Patients were divided into 2 groups based on median baseline RHR (<76 and ≥ 76 beats/min). Cox proportional hazard regression models were used to estimate the effects of RHR on all-cause in-hospital mortality. During hospitalization, 124 patients (3.6%) died from all causes. A multivariable model adjusted for potential covariates showed that higher RHR (≥ 76 beats/min) was associated with an increase in the risk of in-hospital mortality among AIS patients (hazard ratio [HR] 1.63; 95% confidence interval [CI] 1.09–2.45; $P=0.018$). This relationship was consistent in a subgroup analysis of patients without AF (HR 2.39; 95% CI 1.29–4.45; $P=0.006$). However, there was no significant association between higher RHR and in-hospital mortality among patients with AF ($P=0.654$). Similar findings were confirmed in analyses with heart rate as a continuous variable.

Conclusions: Higher RHR at admission was independently associated with in-hospital mortality in AIS patients without AF.

Key Words: Acute ischemic stroke; Atrial fibrillation; In-hospital mortality; Prognosis; Resting heart rate

Previous epidemiological and clinical studies demonstrated that high resting heart rate is significantly associated with increased mortality in the general population, as well as in patients with coronary artery disease, heart failure, hypertension, and stroke.^{1–9} High resting heart rate is a risk factor for long-term (24 months) and short-term (in-hospital or 3 months) mortality after ischemic stroke,^{7–10} as well as hemorrhage stroke.¹¹ However, most of these studies were restricted to patients experiencing acute ischemic stroke (AIS) or transient ischemic attack (TIA) without a history of atrial fibrillation (AF).^{7–11} AF is one of the most important risk factors for ischemic stroke, accounting for 10–25% of all ischemic strokes and associated with high mortality and morbidity.^{12–15} Among AF patients, study findings on the relationship between

heart rate and mortality are conflicting. One study reported that high heart rate is associated with increased mortality in acute myocardial infarction patients with AF,¹⁶ whereas another study indicated a J-shaped relationship between heart rate and mortality in patients with permanent AF.¹⁷ Currently, there is a paucity of data on the prognostic role of heart rate on outcomes of ischemic stroke patients with a history of AF. The aim of this study was to evaluate the possible association between high heart rate and in-hospital mortality in AIS patients with and without AF.

Methods

Study Participants

From December 2013 to May 2014, patients with AIS or

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TIA were recruited from 22 hospitals in Suzhou, China. Patients aged ≥ 18 years with a clinical diagnosis of AIS or TIA were considered eligible for the study. A diagnosis of ischemic stroke was made according to World Health Organization-defined criteria based on patient history, clinical data, and neuroimaging results (computed tomography or magnetic resonance imaging). A team of investigators, including neurologists, reviewed the eligibility of study participants. Exclusion criteria were a diagnosis of TIA and time from onset to admission >7 days. In all, 3,450 patients were potentially eligible for inclusion in the present study. Of these, 3 patients were excluded because of lack of heart rate data on admission. A flowchart of participant selection is shown in **Figure 1**.

Ethics Statement

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Soochow University, as well as ethics committees at the participating hospitals. Written consent was obtained from all study participants or their immediate family members.

Data Collection and Outcome Assessment

Baseline information was collected, including patient demographics, vascular risk factors, stroke severity (National Institutes of Health Stroke Scale [NIHSS] score and modified Rankin Scale score), medication use, imaging data, and diagnosis-related information. Vascular risk factors included a history of stroke, hypertension, diabetes mellitus, AF, or coronary artery disease, current or previous smoking status, and alcohol consumption. Information on these factors was obtained by interviews with patients or their family members (if patients were not able to communicate). Current smoking was defined as having smoked at least 1 cigarette per day for 1 year or more. Data on the amount and type of alcohol consumed during the past year were collected. Alcohol consumption was defined as having consumed at least 1 alcoholic drink per day during the past year. Hypertension was defined as having a systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg or the use of antihypertensive medications. Diabetes mellitus was defined as having fasting glucose ≥ 7.0 mmol/L (126 mg/dL), non-fasting glucose ≥ 11.1 mmol/L (200 mg/dL) with classic symptoms of hyperglycemia or hyperglycemic crisis or the use of glucose-lowering drugs. AF was defined as having a history of AF, confirmed by ≥ 1 electrocardiogram (ECG) or the presence of arrhythmia during hospitalization. Blood samples were collected within 24 h of hospital admission. Laboratory variables were assayed at local laboratories. Participants' resting heart rate was recorded from a 12-lead ECG or electrocardiographic monitoring, which was conducted at the time of hospital admission by a nurse with the patient lying in a supine position. The primary endpoint for the present study was all-cause in-hospital mortality.

Statistical Analysis

For the main analysis, resting heart rate was assessed as a dichotomous variable, divided according to median heart rate (<76 and ≥ 76 beats/min). Continuous variables are expressed as the mean $\pm$ SD or median value with interquartile range (IQR) and were compared using independent Student's *t*-test or the Wilcoxon rank-sum test. Categorical variables are expressed as frequencies and percentages and were compared using the Chi-squared test.

The cumulative risk of all-cause mortality among the 2 groups was estimated using Kaplan-Meier curves and compared by the log-rank test. Cox proportional hazards regression models were used to evaluate associations between heart rate and all-cause in-hospital mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) of death were calculated for heart rate ≥ 76 beats/min with heart rate <76 beats/min as the reference, adjusted for important confounding factors including age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of AF, history of stroke, antihypertensive medication, estimated glomerular filtration rate, body temperature, stroke subtype (stroke syndromes), thrombolysis treatment, and baseline NIHSS score (<4 vs. ≥ 4). To assess the robustness of the association between baseline heart rate and in-hospital mortality, we assessed baseline heart rate as a continuous variable (by 10-beats/min increases) for sensitivity analyses. We further evaluated the potential role of AF on the relationship between heart rate and in-hospital mortality using interaction terms; the heterogeneity between subgroups was estimated by adding an interaction term to the model. All *P*-values are 2-tailed, and significance was set at $P < 0.05$. All analyses were conducted using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 3,450 AIS patients who met the diagnosis criteria in the present study, of whom 3 (0.08%) were excluded due to missing heart rate data. Complete data on conventional risk factors and heart rate at admission were available for 3,447 patients. The mean ($\pm$ SD) patient age was 68.6 ± 12.9 years, and the median baseline NIHSS score was 4.0 (IQR 2.0–7.0). Compared with participants with a lower heart rate (<76 beats/min), those with higher heart rate (≥ 76 beats/min) were more likely to be female, have higher systolic and diastolic BP, higher blood glucose, and more severe stroke (as indicated by higher NIHSS scores),

Table 1. Baseline Patient Characteristics by Resting Heart Rate

	Resting heart rate at baseline (beats/min)		P-value
	<76	≥76	
No. subjects	1,699	1,748	
Demographics			
Age (years)	68.6±12.4	68.5±13.3	0.881
Male sex	1,017 (59.9)	974 (55.7)	0.014
Cigarette smoking	387 (22.8)	302 (17.3)	<0.001
Alcohol consumption	196 (11.5)	142 (8.1)	0.001
Clinical features			
Time from onset to hospital (h)	24.0 [6.0–72.0]	24.0 [5.0–48.0]	0.005
Hospital stay (days)	10.0 [8.0–14.0]	11.0 [8.0–14.0]	0.256
Systolic BP (mmHg)	151.1±22.7	153.8±22.8	0.001
Diastolic BP (mmHg)	83.8±12.8	87.2±13.6	<0.001
Resting heart rate (beats/min)	67.5±5.9	85.9±11.3	<0.001
TG (mmol/L)	1.2 [0.9–1.7]	1.2 [0.8–1.7]	0.229
TC (mmol/L)	4.6 [3.9–5.3]	4.5 [3.9–5.3]	0.822
LDL-C (mmol/L)	2.7 [2.1–3.3]	2.7 [2.1–3.3]	0.743
HDL-C (mmol/L)	1.2 [1.0–1.4]	1.2 [1.0–1.4]	0.366
FPG (mmol/L)	5.9 [5.0–6.8]	5.9 [5.1–7.5]	<0.001
Body temperature (°C)	36.5 [36.2–36.7]	36.5 [36.2–36.8]	0.031
eGFR (mL/min/1.73 m ²)	98.1±32.1	98.0±36.3	0.925
NIHSS score	3.0 [2.0–6.0]	4.0 [2.0–8.0]	<0.001
Medical history			
Hypertension	1,323 (77.9)	1,377 (78.8)	0.518
Diabetes mellitus	416 (24.5)	476 (27.2)	0.066
Coronary artery disease	89 (5.2)	104 (5.9)	0.364
AF	221 (13.0)	311 (17.8)	<0.001
Stroke	377 (22.2)	395 (22.6)	0.774
Medication history			
Antihypertensive therapy	986 (58.0)	1,028 (58.8)	0.644
Antiplatelet therapy	121 (7.1)	131 (7.5)	0.675
Anticoagulation therapy	19 (1.1)	18 (1.0)	0.801
Antiglycemic therapy	306 (18.0)	343 (19.6)	0.226
Statin therapy	49 (2.9)	55 (3.1)	0.653
Thrombolysis treatment	36 (2.1)	49 (2.8)	0.195
Stroke syndrome (OCSP classification)			0.001
TACS	139 (8.2)	203 (11.6)	
PACS	835 (49.1)	892 (51.0)	
POCS	422 (24.8)	383 (21.9)	
LACS	303 (17.8)	270 (15.4)	

Continuous variables are expressed as the mean±SD or as the median [interquartile range]. Categorical variables are expressed as n (%). AF, atrial fibrillation; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LACS, lacunar syndrome; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; TC, total cholesterol; TG, triglycerides.

and tended to have lower rates of smoking and alcohol consumption, higher rates of a history of AF, and a shorter time from onset to hospital (**Table 1**).

During hospitalization, 124 patients (3.6%) died from any cause. The cumulative incidence rates of all-cause mortality for patients with higher and lower heart rate (<76 and ≥76 beats/min) were 4.9% and 2.2%, respectively. **Figure 2** presents the Kaplan-Meier curves for the cumulative incidence rate of all-cause mortality by heart rate status (log-rank $P<0.001$). In the unadjusted Cox model, in-hospital mortality was significantly increased among study participants with a higher (≥76 beats/min) than lower (<76 beats/min) heart rate (HR 2.18; 95% CI 1.49–3.19;

$P<0.001$). After adjusting for age, sex, time from onset to admission, baseline NIHSS score (<4 vs. ≥4), stroke subtype, and other traditional risk factors, the mortality HR for patients with a higher heart rate at admission was 1.63 (95% CI 1.09–2.45; $P=0.018$) (**Table 2**). The association between heart rate and in-hospital mortality remained significant (adjusted HR 1.13; 95% CI 1.02–1.24; $P=0.014$, for every 10-beats/min increase) with resting heart rate as a continuous variable (**Table 2**).

There was heterogeneity in the effect of heart rate on in-hospital mortality by AF status (unadjusted $P_{\text{interaction}}=0.041$; adjusted $P_{\text{interaction}}=0.040$), indicating that the effect of heart rate on in-hospital mortality differed according to

a patient's AF status. Therefore, multivariate models were built to separately assess the effects of heart rate in patients with and without AF separately (Table 3).

There were 2,915 patients without AF and 532 patients with AF. Of the patients without AF, 58 (2.0%) died from all causes, compared with 66 patients with AF (12.4%). Figure 3 presents the Kaplan-Meier curves for the cumulative incidence of all-cause mortality by heart rate group in patients with (log-rank $P=0.302$; Figure 3B) and without (log-rank $P<0.001$; Figure 3A) AF. After adjusting for traditional risk factors, compared with lower heart rate (<76 beats/min) at admission, the HR for mortality for patients with a higher heart rate (≥ 76 beats/min) at admission was 2.39 (95% CI 1.29–4.45; $P=0.006$; Table 3) in patients without AF. However, there was no significant association between heart rate and in-hospital mortality in patients with AF after adjusting for potential confounders (HR 1.13; 95% CI 0.65–1.97; $P=0.654$). The heterogeneous effect of heart rate on in-hospital mortality in patients with or without AF was also confirmed in analyses with heart rate as a continuous variable (Table 3).

Discussion

The present study of 3,447 patients investigated the relationship between resting heart rate on admission and the in-hospital mortality in AIS patients. We found that a higher resting heart rate at admission is associated with 1.63-fold increased risk of in-hospital mortality in AIS patients. In addition, the prognostic effect of resting heart rate appeared to differ in ischemic stroke patients by AF status. In patients without AF, there was 2.39-fold increased in-hospital mortality in patients with a heart rate ≥ 76 beats/min compared with patients with a heart rate <76 beats/min. However, no independent relationship between heart rate and in-hospital mortality was observed in AIS patients with AF. Similar findings were confirmed in sensitivity analyses with heart rate as a continuous variable.

A growing body of evidence suggests that having higher heart rate at admission is associated with increased mortality after stroke.^{7–11} Data from the Prevention Regimen for Effectively Avoiding Second Stroke trial (PROFESS) of 20,165 ischemic stroke patients indicated that high heart rate is a risk indicator for all-cause or vascular mortality at 3 months.⁷ The Virtual International Stroke Trials Archive (VISTA) study of 5,606 AIS patients showed that higher heart rate (>86 beats/min) is significantly linked to mortality, heart failure, and a higher degree of dependence after 90 days.⁹ Erdur et al also reported that high heart rate on admission is independently associated with in-hospital

Figure 2. Cumulative incidence curves of in-hospital mortality, according to resting heart rate at admission (<76 vs. ≥ 76 beats/min).

mortality in 1,335 AIS patients.⁸ However, most of these studies were restricted to patients without AF. Consistent with prior studies, the present analyses of 3,447 AIS patients (including those with AF) demonstrated an independent relationship between high heart rate (≥ 76 beats/min) at admission and in-hospital mortality, after adjusting for age, sex, time from onset to admission, baseline NIHSS score, and other conventional risk factors.

In contrast with ischemic stroke patients without AF, the relationship between heart rate and in-hospital mortality was not significant in patients with AF. These results, together with those of previous studies,^{16–18} could suggest that the prognostic effect of heart rate may vary in AF patients according to the types of comorbidities. Data from the OMEGA trial including 211 acute myocardial infarction patients with AF on admission indicated that a high HR (≥ 95 beats/min) on admission was associated with increased risk of 1-year mortality.¹⁶ The study of Steinberg et al of 2,812 US outpatients with permanent AF demonstrated a J-shaped relationship between heart rate and mortality.¹⁷ Subgroup analysis of patients with concurrent diabetes mellitus and AF in the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial indicated no significant association between heart rate and all-cause mortality.¹⁸ In the present study, the rate of in-hospital mortality of 12.4%

Table 2. Associations Between Resting Heart Rate and In-Hospital All-Cause Mortality in Ischemic Stroke Patients

	No. cases (%)	Unadjusted		Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Heart rate (beats/min)							
<76	38/1,699 (2.2)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
≥ 76	86/1,748 (4.9)	2.18 (1.49–3.19)	<0.001	2.10 (1.43–3.08)	<0.001	1.63 (1.09–2.45)	0.018
Per 10-beats/min increase		1.42 (1.30–1.55)	<0.001	1.37 (1.26–1.50)	<0.001	1.13 (1.02–1.24)	0.014

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of AF, history of stroke, eGFR, body temperature, antihypertensive medication, stroke syndrome, thrombolysis treatment, and baseline NIHSS score (<4 vs. ≥ 4). CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Table 3. Associations Between Resting Heart Rate and In-Hospital All-Cause Mortality in Ischemic Stroke Patients With and Without Atrial Fibrillation							
	No. cases (%)	Unadjusted		Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Without AF			0.041 ^a		0.029 ^a		0.040 ^a
Resting heart rate at baseline (beats/min)							
<76	15/1,478 (1.0)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
≥76	43/1,437 (3.0)	2.95 (1.64–5.32)	<0.001	2.97 (1.65–5.35)	<0.001	2.39 (1.29–4.45)	0.006
Per 10-beats/min increase		1.61 (1.41–1.84)	<0.001	1.55 (1.36–1.77)	<0.001	1.20 (1.03–1.38)	0.018
With AF							
Resting heart rate at baseline (beats/min)							
<76	23/221 (10.4)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
≥76	43/311 (13.8)	1.30 (0.79–2.16)	0.307	1.26 (0.76–2.10)	0.365	1.13 (0.65–1.97)	0.654
Per 10-beats/min increase		1.14 (1.01–1.29)	0.032	1.14 (1.00–1.29)	0.036	1.07 (0.94–1.21)	0.326

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of stroke, eGFR, body temperature, antihypertensive medication, stroke syndrome, thrombolysis treatment, and baseline NIHSS score (<4 vs. ≥4). ^aP-value for interaction between AF and heart rate. Abbreviations as in Tables 1,2.

in AF patients was markedly higher than that of patients without AF (2.0%). The AF patients were more likely to be older^{19,20} and have increased stroke severity,^{14,19} which are factors leading to increased rates of mortality in both heart rate groups. The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) trial showed that strict heart rate control (<80 beats/min) did not decrease the mortality risk in patients with permanent AF,²¹ and this may be another possible reason for the observed lack of effect of high heart rate on mortality rates in patients with AF. Several mechanisms possibly explain the association between high heart rate and increased risk of in-hospital mortality in patients without AF. First, high heart rate may reflect sympathetic nervous overactivity. Sympathetic nervous overactivity was associated with high night-time blood pressure²² and inflammatory response,²³ which are

known predictors of mortality in stroke.^{22,24,25} Second, blood glucose is higher in patients with a high heart rate, and this is significantly associated with mortality and poor outcome.^{26,27} A strength of this study is the relatively large, well-characterized patient population. To the best of our knowledge, the present study is the first to investigate the prognostic effect of heart rate in ischemic stroke patients with and without AF. However, there are still some potential limitations that merit consideration. First, this cohort included some patients whose time from onset to admission exceeded 48 h; therefore, the heart rate at admission may not accurately reflect the heart rate at stroke onset. Second, we did not have detailed information on the use of medications that could have altered the heart rate and/or rhythm at baseline (e.g., β -blockers). Third, the heart rate of some patients was derived from electrocardiograph monitoring. In addition, we did not collect post-baseline

heart rate, heart rate variability, and prestroke disability data, which may also be associated with in-hospital mortality. Finally, we did not have information on the cause of death, which would improve our understanding of the underlying causes for the heart rate variations, although the most common reason for in-hospital mortality after AIS was the ischemic stroke itself.

Conclusions

The results of this study showed that high resting heart rate at admission was significantly associated with an increased risk of all-cause in-hospital mortality in AIS patients, particularly in those without AF. The findings suggest that high resting heart rate could be a useful marker for the prediction of in-hospital mortality and present a potential treatment target in AIS patients without AF.

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Conflict of Interest

None declared.

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-19-0946>